Volume 119/Issue 11 June 1, 2013 Pages 2083–2202 Cancer Supplement ISSN 0008-543X

Volume 119 / Issue 11
June 1, 2013
www.canceronlinejournal.com

Cancer

Interdisciplinary International Journal of the American Cancer Society

Supplement to Cancer

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

American Cancer Society

WILEY

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

Guest Editors

Vittorio Mattioli, MD
Kevin Stein, PhD

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders", and through intramural funding of the American Cancer Society's Behavioral Research Center.

Cancer

Volume 119/Issue 11
June 1, 2013
Supplement

Contents

INTRODUCTION

FOREWORD

PREFACE

ORIGINAL ARTICLES

(Continued)

Cancer

Volume 119/Issue 11
June 1, 2013
Supplement

Contents

(Continued)

Cancer
Volume 119/Issue 11
June 1, 2013
Supplement

Contents

Cancer
Volume 119/Issue 11
June 1, 2013
Supplement

Editorial Board

INSTRUCTIONS FOR AUTHORS

The instructions for authors are available at http://www.canceronlinejournal.com
Please refer to these instructions in the preparation of manuscript submissions and for journal policies.

Cancer

Volume 119/Issue 11
June 1, 2013
Supplement

Editorial Board

CANCER (Print ISSN: 0008-543X; Online ISSN: 1097-0142) is published semi-monthly on behalf of the American Cancer Society by Wiley Subscription Services, Inc., a Wiley Company, 111 River St., Hoboken, NJ 07030-5774. Periodical Postage Paid at Hoboken, NJ and additional offices. Postmaster: Send all address changes to CANCER, Journal Customer Services, John Wiley & Sons Inc., 350 Main St., Malden, MA 02148-5020.

Printed in the USA by Cenveo Publisher Services.

Information for subscribers: CANCER is published in 24 issues per year. Institutional subscription prices for 2013 are: Print & Online: US$1,097 (US), US$1,337 (Rest of World), €890 (Europe), £704 (UK). Prices are exclusive of tax. Asia-Pacific GST, Canadian GST and European VAT will be applied at the appropriate rates. For more information on current tax rates, please go to www.wileyonlinelibrary.com/tax-vat. The price includes online access to the current and all online back files to January 1st 2009, where available. For other pricing options, including access information and terms and conditions, please visit www.wileyonlinelibrary.com/access. **Change of Address:** Please forward to the subscriptions address listed above 6 weeks prior to move; enclose present mailing label with change of address. **Claims for Missing Issues:** Claims for missing issues must be submitted within 6 months of the publication date. **Cancellations:** Subscription cancellations will not be accepted after the first issue has been mailed. Opinions expressed by the authors are their own and not necessarily those of the American Cancer Society or the publisher, Wiley-Liss, Inc.

Delivery Terms and Legal Title: Where the subscription price includes print issues and delivery is to the recipient's address, delivery terms are Delivered At Place (DAP); the recipient is responsible for paying any import duty or taxes. Title to all issues transfers FOB our shipping point, freight prepaid. We will endeavour to fulfil claims for missing or damaged copies within six months of publication, within our reasonable discretion and subject to availability.

Back Issues: Single issues from current and prior year volumes are available at the current single issue price from cs-journals@wiley.com. Earlier issues may be obtained from Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA. Tel: +1 518 537 4700, Fax: +1 518 537 5899, Email: psc@periodicals.com

Advertising: Advertising inquiries should be directed to: Stephen Donohue, John Wiley & Sons, Inc.,350 Main Street, Malden, MA 02148; (781) 388-8511; fax: (781) 338-8511.

Production Editor: Karen Harmon (E-mail: cncrprod@wiley.com).

Journal Customer Services: For ordering information, claims and any enquiry concerning your journal subscription please go to www.wileycustomerhelp.com/ask or contact your nearest office: **Americas:** E-mail cs-journals@wiley.com; Tel: +1 781 388 8598 or +1 800 835 6770 (toll free in the USA & Canada). **Europe, Middle East and Africa:** E-mail: cs-journals@ wiley.com; Tel: +44 (0) 1865 778315. **Asia Pacific:** E-mail: cs-journals@wiley.com; Tel: +65 6511 8000. **Japan:** For Japanese speaking support, E-mail: cs-japan@wiley.com; Tel: +65 6511 8010 or Tel (toll free) 005 316 50 480. **Visit our Online Customer Get-Help** available in 6 languages at www.wileycustomerhelp.com

View this journal online at wileyonlinelibrary.com/journal/CNCR

Indexed by: Biological Abstracts®(Thomson ISI), BIOSIS Previews® (Thomson ISI), CAB Abstracts® (CABI), Cambridge Scientific Abstracts (CSA/CIG), Chemical Abstracts Service/SciFinder (ACS), CINAHL©: Cumulative Index to Nursing & Allied Health Literature, CSA Biological Sciences Database (CSA/CIG), Current Awareness in Biological Sciences (Elsevier), Current Contents®/Clinical Medicine (Thomson ISI), Current Contents®/Life Sciences (Thomson ISI), Current Index to Statistics (ASA/IMS), EMBASE (Elsevier), EORTC Database (European Organisation for Research and Treatment of Cancer), Index Medicus/MEDLINE/PubMed (NLM), Journal Citation Reports/Science Edition (Thomson ISI), PASCAL Database (INIST/CNRS), Reference Update (Thomson ISI), Science Citation Index Expanded™ (Thomson ISI), Science Citation Index® (Thomson ISI), SCOPUS (Elsevier), SIIC Databases (Sociedad Iberoamericana de Información Científica), Web of Science® (Thomson ISI).

Acknowledgements

The Guest Editors Vittorio Mattioli, MD, and Kevin Stein, PhD, would first of all like to thank all the authors for having accepted this unique challenge and for giving us their authoritative contribution.

The contributions of the former European Commissioner for Health and Consumer Policy, John Dalli, and the American Cancer Society's Chief Executive Officer, John R. Seffrin, PhD, are particularly appreciated, as they represent an institutional commitment to supporting research, programmatic, and health care policy efforts to address the physical and psychosocial issues of cancer survivors.

A special thanks also goes to John Daniel, Scientific Editor for Intramural Research at the American Cancer Society and Caroline Oakley, from the International Relations Office at NCRC Bari, for their invaluable assistance with author correspondence and manuscript editing.

Authors	Affiliation	Country
Denis Horgan, LLM, MSC	Office of the Executive Director, European Alliance for Personalized Medicine, Brussels	Belgium
John Dalli	European Commissioner for Health and Consumer Policy, European Commission, Brussels	Belgium
Susanne O. Dalton, MD, PhD	Survivorship, Danish Cancer Society Research Center, Copenhagen	Denmark
Anja Mehnert, PhD	Section of Psychosocial Oncology, Department of Medical Psychology and Medical Sociology, University Medical Center Leipzig, Leipzig; Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg	Germany
Uwe Koch-Gromus, MD, PhD	Medical University Center Hamburg-Eppendorf, Hamburg	Germany
Gil Goldzweig, PhD	Department of Psychology, School of Behavioral Sciences, Tel-Aviv-Yaffo Academic College, Tel-Aviv	Israel
Alessio Molfino, MD, PhD	Department of Clinical Medicine, Sapienza University of Rome, Rome	Italy
Angelo Paradiso, MD, PhD	National Cancer Research Center Istituto Tumori "Giovanni Paolo II", Bari; Education and Training, Organization of European Cancer Institutes, Brussels, Belgium	Italy
Claudia Cormio, PhD	Experimental Unit of Psycho-Oncology, Department of Critical Area and Surgery, National Cancer Research Center Istituto Tumori "Giovanni Paolo II", Bari	Italy
Daniela Cardinale, MD, PhD	Cardioncology Unit, European Institute of Oncology, Milan	Italy
Francesca Romito, PhD	Experimental Unit of Psycho-Oncology, Department of Critical Area and Surgery, National Cancer Research Center Istituto Tumori "Giovanni Paolo II", Bari	Italy
Francesco De Lorenzo, MD	European Cancer Patient Coalition (ECPC), Brussels, Belgium; Italian Federation of Voluntary Associations in Oncology (FAVO), Rome	Italy
Maurizio Muscaritoli, MD, FACN	Department of Clinical Medicine, Sapienza University of Rome, Rome	Italy
Stefano Oliva, MD	Cardiology Unit, National Cancer Research Center Istituto Tumori "Giovanni Paolo II", Bari	Italy
Vittorio Mattioli, MD	Department of Critical Area and Surgery, National Cancer Research Center "Giovanni Paolo II", Bari	Italy
Jon Håvard Loge, MD, PhD	National Resource Center for Late Effects After Cancer Treatment, The Norwegian Radium Hospital, Oslo University Hospital, Oslo; University of Oslo, Oslo	Norway
Sophie D. Fosså, MD, PhD	National Resource Center for Late Effects After Cancer Treatment, The Norwegian Radium Hospital, Oslo University Hospital, Oslo; University of Oslo, Oslo	Norway
Lars Hjorth, MD, PHD	Pediatric Oncology and Hematology, Department of Pediatrics, Skane University Hospital, Clinical Sciences, Lund University, Lund	Sweden
Yvonne Wengstrom, MD	Department of Neurobiology, Care Science and Society, Division of Nursing, Karolinska Institute, Stockholm	Sweden
Angela de Boer, PhD	Coronel Institute of Occupational Health, Academic Medical Center, Amsterdam	The Netherlands
Floortje Mols, PhD	Center of Research on Psychology in Somatic Diseases (CoRPS) Tilburg University, Tilburg; Comprehensive Cancer Center South (CCCS), Eindhoven Cancer Registry, Eindhoven	The Netherlands
Jan-Willem W. Coebergh, MD, PhD	Comprehensive Cancer Center South (CCCS), Eindhoven Cancer Registry, Eindhoven; Department of Public Health, Erasmus University Medical Center, Rotterdam	The Netherlands
Lonneke Van de Poll-Franse, PhD	Center of Research on Psychology in Somatic Diseases (CoRPS) Tilburg University, Tilburg; Comprehensive Cancer Center South (CCCS), Eindhoven Cancer Registry, Eindhoven	The Netherlands
Mariët Hagedoorn, PhD	Health Psychology Section, Department of Health Sciences, University of Groningen, University Medical Center Groningen, Groningen	The Netherlands
Martine M. Goedendorp, PhD	Expert Centre for Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen	The Netherlands
Melissa S.Y. Thong, PhD	Center of Research on Psychology in Somatic Diseases (CoRPS) Tilburg University, Tilburg; Comprehensive Cancer Center South (CCCS), Eindhoven Cancer Registry, Eindhoven	The Netherlands

Authors	Affiliation	Country
Wim H. van Harten, MD, PhD	Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam; Organization of European Cancer Institutes, Brussels, Belgium	The Netherlands
Adam Glaser, MD	Paediatric and Adolescent Oncology Program, Leeds Teaching Hospitals NHS Trust, Leeds National Cancer Survivor Initiative, Department of Health, London	United Kingdom
Fiona Cramp, PhD	Musculoskeletal Health, Faculty of Health and Life Sciences, University of the West of England, Bristol	United Kingdom
Gill Hubbard, PhD	Cancer Care Research Center, School of Nursing, Midwifery, and Health, University of Stirling, Highland Campus, Centre for Health Science, Inverness, Scotland	United Kingdom
Jane Maher, PhD, FRCP	Macmillan Cancer Support and Mount Vernon Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex	United Kingdom
Ollie Minton, PhD, FRCP	Division of Population Health Sciences and Education, St. George's University of London, London	United Kingdom
Patrick Stone, MA, MD, FRCP	Palliative Medicine, Division of Population Health Sciences and Education, St. George's University of London, London	United Kingdom
Sara Faithfull, PhD, MSc BSc (Hons)	Faculty of Health and Medical Sciences, University of Surrey, Stag Hill, Guildford, Surrey	United Kingdom
Wendy Makin, MBChB, FRCR, FRCP	Palliative Medicine and Oncology, The Christie National Health Service Foundation Trust, Manchester	United Kingdom
Andrea Barsevick, PhD, RN, AOCN, FAAN	Fox Chase Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania	United States
Andrea Cheville, MD	Physical Medicine and Rehabilitation, Division of Cancer Rehabilitation and Lymphedema Services, Mayo Clinic, Rochester, Minnesota	United States
Ann M. Berger, PhD, APRN, AOCNS, FAAN	University of Nebraska College of Nursing, Omaha, Nebraska	United States
Barbara Andersen, PhD	Department of Psychology, The Ohio State University, Columbus, Ohio	United States
Catherine M. Alfano, PhD	Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH)/Department of Health and Human Services (DHHS), Bethesda, Maryland	United States
Daniel Lenihan, MD	Division of Cardiovascular Medicine, Vanderbilt University, Nashville, Tennessee	United States
Eric Chow, MD, MPH	Public Health and Clinical Research Divisions, Fred Hutchinson Cancer Center, Seattle, Washington	United States
Erin Kent, PhD	Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH)/Department of Health and Human Services (DHHS), Bethesda, Maryland	United States
John Seffrin, PhD	American Cancer Society, Atlanta, Georgia	United States
Julia D. Labadie Bromberek, MSPH	Emory University, Atlanta, Georgia	United States
Julia H. Rowland, PhD	Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH)/Department of Health and Human Services (DHHS), Bethesda, Maryland	United States
Katherine Virgo, PhD, MBA	Health Services Research Program, Intramural Research Department, American Cancer Society, Atlanta, Georgia	United States
Kathryn H. Schmitz, PhD, MPH	Division of Epidemiology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania	United States
Kevin D. Stein, PhD	Behavioral Research Center, Intramural Research Department, American Cancer Society, Atlanta, Georgia; Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, Georgia	United States
Laura Forsythe, PhD, MPH	Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH)/Department of Health and Human Services (DHHS), Bethesda, Maryland	United States
Mary McCabe, RN, MA	Cancer Survivorship Program, Memorial Sloan-Kettering Cancer Center, New York, New York	United States
Michael Feuerstein, PhD, MPH, ABPP	Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland	United States

Authors	Affiliation	Country
Michael Stubblefield, MD	Rehabilitation Medicine Service, Sillerman Center for Rehabilitation, Memorial Sloan-Kettering Cancer Center, New York, New York	United States
Michelle M. Le Beau, PhD	Section of Hematology and Oncology and the Comprehensive Cancer Center, University of Chicago, Illinois, Association of American Cancer Institutes, Pittsburgh, Pennsylvania	United States
Otis W. Brawley, MD	Office of the Chief Medical Officer, American Cancer Society, Atlanta, Georgia; Emory University, Atlanta, Georgia	United States
Pamela J. Haylock, PhD, RN, FAAN	Association for Vascular Access, Medina, Texas	United States
Sandra A. Mitchell, PhD, CRNP, AOCN	Outcomes Research Branch, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland	United States
Tenbroeck Smith, MA	Behavioral Research Center, Intramural Research Department, American Cancer Society, Atlanta, Georgia	United States

Introduction

Dialogues on Cancer Survivorship: A New Model of International Cooperation

Kevin Stein, PhD[1]; and Vittorio Mattioli, MD[2]

The authors describe the rationale and background of the present supplement to *Cancer* intended to stimulate a dialogue among researchers from Europe and North America regarding important issues faced by cancer survivors. Through jointly written articles addressing various aspects of cancer survivorship, each manuscript reports on the similarities, disparities, and problems viewed from the point of view of each author's respective continent. The supplement is meant to create a springboard for increased collaboration and aid in the development of a shared care model to improve the quality of cancer care, both during and after the completion of primary treatment. We hope that this effort may represent a new model of international cooperation, which is fruitful not only for the field of scientific research but also for identifying and sharing new approaches to the care and management of cancer survivorship issues, ultimately bringing improvements to quality of life of the growing population of cancer survivors. ***Cancer*** **2013;119(11 suppl):2083-5.** © *2013 American Cancer Society.*

KEYWORDS: cancer survivorship; international cooperation.

The considerable progress in cancer care occurring over the past few decades in surgery, chemotherapy, radiotherapy, and adjuvant therapies and our ever-growing knowledge base in all areas along the cancer research continuum have undoubtedly led to greatly improved clinical outcomes. However, the growing number of individuals surviving cancer, and the facility with which modern technology allows us to communicate our thoughts, feelings, and experiences, has also meant that we have stopped viewing cancer in a purely clinical sense and have begun to develop an awareness of the human being behind the disease. More often than not, those who receive a diagnosis of cancer now no longer ask themselves how *long* they have to live, but rather how *well* they can expect to live from that moment onward. This shift in thinking from "cancer survival" to "cancer survivorship" has led to a notable increase in research on "life beyond cancer" in recent years.

This research has indicated that a significant percentage of cancer survivors experience negative physical, social, and emotional effects as the result of their cancer and its treatment. Some of these effects may present initially or during or shortly after treatment and linger in a persistent manner whereas others may develop months or even years after the completion of treatment (late effects). Regardless of their time of onset, these effects may negatively impact the quality of life of cancer survivors. Yet despite the growing body of scientific literature on cancer survivorship, many questions remain regarding how to assess, treat, and prevent survivorship-related problems. Indeed, the complex array of potential risks, problems, and long-term effects cancer survivors face and the methods to control them are just beginning to be explored and understood. Moreover, the degree to which these issues are becoming recognized varies greatly both across and within international geographic regions. Some countries are quite advanced with respect to the awareness and management of survivorship issues whereas others are just beginning to recognize and address the unique problems and concerns that cancer survivors face after the completion of their primary adjuvant treatment. Even in countries with more advanced

Corresponding author: Kevin Stein, PhD, Behavioral Research Center, American Cancer Society, 250 Williams St NE, Atlanta, GA 30303; Fax: (404) 929-6832; Kevin.Stein@cancer.org

[1]Behavioral Research Center, American Cancer Society, Atlanta, Georgia; [2]National Cancer Research Centre, "Giovanni Paolo II" Cancer Institute, Bari, Italy.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28053, **Received:** August 7, 2012; **Accepted:** September 20, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

approaches, there are few evidence-based recommendations for the management of cancer survivors, and experts have not reached consensus on the structure, content, and development of survivorship care guidelines. As a result, there are still many differences among countries regarding the research and practice in this field, which may be explained, in part, by the specific social and cultural factors that influence and shape the unique survivorship care scenarios for every country.

International differences in health care systems and delivery are also notable. Many countries in Europe, such as France, Italy, and the United Kingdom, offer free access to public health care, whereas the United States does not, potentially contributing to limitations in access to quality cancer care for poorer individuals and those without adequate health care coverage. However, compared with European countries, the commitment of patient advocacy is traditionally stronger in the United States, which has led the way in promoting the application of research findings into practice.

With increasing focus on the issues of long-term cancer survivorship in clinical care, public policy, and research initiatives, Europe and the United States are trying to respond in an even better and more targeted manner to this change in the health trajectory of patients diagnosed with cancer, with the main objective being to meet the needs of these individuals. In 2004, the report produced by the President's Cancer Panel following the first meeting of "Living Beyond Cancer: A European Dialogue," held in Lisbon, Portugal on May 27 to 28, 2003 represented the first attempt to create a dialogue between the United States and Europe.[1] The Panel stated that "a key objective of the meeting was to learn about health services and survivorship activities in diverse European nations and health systems that might benefit survivors in this country."[1] Building on this effort, since 2008 a series of scientific meetings have been sponsored by the Italian National Cancer Institutes that have brought together European and American cancer survivorship researchers to exchange ideas and foster new collaborations. The most recent of these meetings, the CME Course ESO (European School of Oncology)-OECI (Organization of European Cancer Institutes) International Symposium on Cancer Survivorship "State of the Art of Cancer Survivorship Research: Symptom Management, Psychosocial Care, and Rehabilitation" held in Bari, Italy between April 26 and 28, 2012, included representatives from 12 European nations along with distinguished scientists from Turkey and the United States.[2] A notable outcome of this meeting was the formation of the European Collaborative Group on Cancer Survivorship, which established as its initial objective to develop and share a cross-cultural plan of research, knowledge, comparison, education, and dissemination of findings to face the new challenges within the field of cancer survivorship. Similar international collaborative efforts have begun to emerge elsewhere as well, such as the Cancer and Primary Care Research International Network, which was formed in 2008 to promote international cooperation among the primary care and cancer researcher communities.

This supplement to *Cancer* was born of a desire to maintain the momentum initiated by the 2003 European Panel as well as the subsequent international meetings and collaborative groups, highlighting the potential differences and similarities that exist between American and European approaches to cancer survivorship issues and to promote an exchange of information. We hoped that by stimulating a *dialogue* among researchers from both sides of the Atlantic ocean, through jointly written articles addressing various aspects of cancer survivorship, with the similarities, disparities, and problems viewed from the point of view of each author's respective continent, we might create a springboard for increased collaboration and the development of a shared care model to improve the quality of cancer care. The task of getting authors on different continents, in different time zones, and who often spoke different primary languages to write an article together was indeed a challenge. However, these authors rose to the occasion, exchanged information and ideas, and produced articles that speak to both the similarities and differences in these cancer survivorship issues as they are approached from European and American perspectives. We hope that this may represent a new model of cooperation between the 2 sides of the Atlantic, which is fruitful not only in the field of scientific research but also in that of care, ultimately bringing improvements to the growing population of cancer survivors. Of course, we acknowledge that much survivorship research is being conducted beyond Europe and the United States, specifically in Australia, Canada, and Asia, with emerging research programs and efforts occurring in Africa, South America, and the Middle East as well. Therefore, the current effort represents just a stepping off point for international dialogue and collaboration around the issues that cancer survivors face irrespective of their locale. Indeed, although this collection of articles may only scratch the surface of a dialogue that is potentially immense, we hope to have made a small step toward the ideal of international

collaboration by presenting you, the reader, with material that makes you think, reflect, and ultimately expand your horizons.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. The President's Cancer Panel. Living Beyond Cancer: A European Dialogue. President's Cancer Panel 2003-2004 Annual Report Supplement. Bethesda, MD: National Cancer Institute, National Institutes of Health, US Department of Health and Human Services; 2004. deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp03-04rpt/Supplement.pdf. Accessed September 7, 2012.
2. Mattioli V. Cancer Survivorship: An Emerging Problem in Italy. From the American Data to the Italian Project PIO 7 [review]. National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy); 2008, Human Health Foundation Onlus, Spoleto, Italy. www.hhfonlus.org.

Foreword I: The European Perspective

John Dalli

More and more people survive cancer. Survival rates and quality of life after recovery have much improved over the last decades due to developments in screening, diagnosis, and therapy. Increasingly, integrated cancer care systems should be able to maintain an adequate quality of life for those individuals living with cancer or having recovered from their struggle against this disease.

The European Commission has kept cancer high on its agenda for over 20 years. Together with the Member States and stakeholders, the Commission supported many actions on cancer that I believe have made a difference for the millions of Europeans living with cancer.

More recently, in 2009, the Commission launched the European Partnership for Action Against Cancer to help Member States and other stakeholders in their efforts to tackle cancer. The Partnership is fostering the exchange of knowledge and developing guidelines to support Member States in implementing comprehensive cancer plans by 2014. Such plans, which are now in place in most nations within the European Union, should contribute toward reducing cancer incidence in the European Union by 15% by 2020, reducing cancer mortality and improving the quality of life of patients with cancer. Indeed, most national cancer plans include palliative care and psychooncologic services. I am therefore persuaded that activities under the Partnership will contribute further to taking such aspects forward in the future.

In the meantime, the Commission is keen to continue supporting projects in which survivorship issues, including long-term side effects, are addressed. Through its Health Programme, the Commission has cofinanced a number of projects aimed at promoting comprehensive cancer care, including defining best practices in palliative care in Europe and fostering Member States' cooperation in the area of rehabilitation.

For more and more people, there is life during and after cancer, and this is why it is important to consider how best to support "cancer survivors" in moving their lives forward, either in terms of health care or social or psychological support, or in terms of reintegrating into active society. This publication presents a number of initiatives in this area enriched by experience from both sides of the Atlantic. I wish every success to such efforts that reinforce support for cancer survivors.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The author made no disclosures.

Corresponding author: John Dalli, European Commissioner for Health and Consumer Policy, European Commission, Rue de la Loi, 170-1040, Brussels, Belgium; cab-dalli-webpage@ec.europa.eu

European Commissioner for Health and Consumer Policy, European Commission, Brussels, Belgium.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28065, **Received:** August 7, 2012; **Accepted:** September 20, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

Foreword II: The American Perspective

John R. Seffrin, PhD

Nearly 14 million people currently living in the United States have a history of cancer. That is a group that is larger than the population of a number of European countries.

Indeed, we have a nation of cancer survivors in the United States, and it is a nation that is only growing. The number of Americans with a history of cancer will swell to nearly 18 million during the next decade, thanks to an aging and growing population, and to the significant progress we are making against this disease.

We currently avert more than 400 deaths each and every day in the United States of patients who would have been lost to cancer had death rates not begun to decline in the 1990s thanks to a number of different factors, such as a declining smoking prevalence and advances in treatment and early detection. That progress also means that more people than ever before are living beyond cancer, making the health and well-being of these survivors an important concern.

At the American Cancer Society, we know that after treatment ends, the cancer experience does not. That is why we are working tirelessly to understand and address the unique needs of the survivor population. And that is why we recently released our first-ever *Cancer Treatment and Survivorship Facts and Figures* (cancer.org/Research/CancerFactsFigures/CancerTreatmentSurvivorshipFactsFigures/index), a report produced in collaboration with the National Cancer Institute to highlight the challenges and opportunities in serving cancer survivors.

We hope with this publication to help others understand the unique medical and psychosocial needs of survivors, and that there are resources to assist patients, caregivers, and health care providers in navigating the various phases of cancer survivorship.

At the American Cancer Society, we devote considerable resources to survivorship and quality-of-life research through avenues such as our Study of Cancer Survivors, which to my knowledge is one of the largest US cohorts of cancer survivors.[1,2] This nationwide, population-based research study focuses on quality of life among more than 10,000 long-term adult survivors of cancer. We are also studying the side effects of cancer treatment, such as pain, fatigue, or depression, and tracking trends in cancer symptoms and symptom management. And through a collaboration with the George Washington University Cancer Institute, we are working through the National Cancer Survivorship Resource Center (cancer.org/survivorshipcenter) to shape the future of cancer survivorship care. That work is funded through a cooperative agreement with the US Centers for Disease Control and Prevention.

We are making progress in our cancer survivorship work, and yet we still have far to go.

We know the United States is not alone in seeking to learn more about the unique challenges of cancer survivorship, and we welcome this supplement to *Cancer* as an opportunity to further the dialogue on survivorship in our nation and across Europe. We no doubt have much to learn from one another, both through this collaboration and ideally through many others around the world in years to come.

Corresponding author: John Seffrin, PhD, American Cancer Society, 250 Williams St NE, Atlanta, GA 30303; Fax: (404) 417-8017; john.seffrin@cancer.org

Chief Executive Officer, American Cancer Society, Atlanta, Georgia.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28064, **Received:** August 7, 2012; **Accepted:** September 20, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

It is only by working together that we will be able to create a world with less cancer and, as we like to say at the American Cancer Society, more birthdays and that we will help those who celebrate those birthdays live better lives. Together, we will no doubt continue to turn what was once hopeless into an experience that is today ever more hopeful.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The author made no disclosures.

REFERENCES

1. Stein K, Smith T, Kim Y, et al; American Cancer Society. The American Cancer Society's Studies of Cancer Survivors: the largest, most diverse investigation of long-term cancer survivors so far. *Am J Nurs.* 2006;106(suppl 3):83-85.
2. Smith T, Stein KD, Mehta CC, et al. The rationale, design, and implementation of the American Cancer Society's studies of cancer survivors. *Cancer.* 2007;109:1-12.

Preface

Francesco de Lorenzo, MD[1] and Pamela Haylock, PhD, RN, FAAN[2]

Cancer Survivorship: Europe—Inequalities and Actions

Francesco de Lorenzo, MD

In the European Union (EU), the burden of cancer has become so prominent in terms of social and economic implications that it is now considered to be a significant element of European societies. In the EU, life expectancy at birth has increased over the last several decades. However, disparities within the EU have also increased, and recent figures indicate that although in some countries (mainly eastern European countries) life expectancy is approximately 70 years of age, in other EU countries it is reaching or surpassing 80 years. A similar pattern has emerged with respect to cancer survival rates. Indeed, there has been a dramatic improvement in 5-year survival for individuals diagnosed with cancer. The survival rate (for all cancers combined) 5 years after a cancer diagnosis is now approximately 50%, but there are still notable differences within regions or even countries; the 5-year cancer survival rate ranges from approximately 40% to nearly 60% across European countries.

Disparities are evident in all epidemiological data: cancer prevalence rates (ie, all individuals who have had a previous cancer history) are estimated to range from 1 to 5 per 100 in the various EU populations, and from 10 to 15 per 100 in the elderly segment (those aged older than 60 years). These differences result in large variations in terms of patient needs, with the social and economic impact of cancer varying considerably across European countries. However, cancer is a continental disease. Approximately 20% to 25% of people die of cancer and, directly or indirectly, nearly all families within the EU are affected. Over the past several decades, even if the health systems have remained under the control of the individual EU Member States, the interdependence of various elements of health care politics across the EU has increased. One of the primary drivers of the EU's actions on cancer has been the influence of patient advocacy organizations. The EU Council's conclusions on reducing the burden of cancer that were adopted in June 2008 are regarded as one of the most significant achievements by patient organizations. Over the last few years, the EU Commission has recognized that cancer treatment and care should be multidisciplinary, involving the cooperation of oncologic surgery, medical oncology, radiation oncology, psychosocial support and, most importantly, rehabilitation and palliative care. Health care policymakers at a national level have been invited to take into account the psychosocial needs of cancer patients and improve their quality of life through support and palliative care, and also through rehabilitation measures aimed at facilitating an early return to work. After improving joint collaboration strategies, EU Member States are now ready to recognize the supranational role of the European Cancer Patient Coalition (ECPC) in cancer control. In this direction, considerable resources have been invested to produce EU cancer statistics so as to support the calls by the ECPC for evidence-based policy change. To meet cancer survivorship-related needs, the ECPC at the EU level and ECPC member organizations at the national level have promoted initiatives and research projects aimed at developing an EU Survivorship Care Plan, which should provide a benchmarking after the completion of primary treatment. Key priorities called for by the ECPC include the timing and

Corresponding author: Francesco de Lorenzo, MD, European Cancer Patient Coalition (ECPC), Brussels, Belgium; Fax: (011) 39 06 87462110; fdelorenzo@aimac.it

[1]European Cancer Patient Coalition (ECPC), Brussels, Belgium; [2]Association for Vascular Access, Medina, Texas.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues, *Supplement to Cancer*.

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28063, **Received:** August 7, 2012; **Accepted:** September 20, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

content of follow-up, rehabilitation, raising awareness of both short-term and long-term treatment-related effects, health maintenance, information regarding legal protections, and psychosocial support services.

The first objective has been to evaluate the different health conditions over time so that subgroups of cancer patients with different rehabilitation needs also may return to normal (or near-normal) life. In Italy, for example, the Italian Federation of Volunteer-Based Cancer Organizations (FAVO), with the collaboration of population-based cancer registries and leading cancer institutes, has performed a survey to describe the experiences of cancer patients after diagnosis to quantify cancer rehabilitation needs. Historically, cancer registries have been the primary source of cancer burden indicators, and they have been shown to be able to collect relevant data at a population level to examine rehabilitation services (civil invalidity, home assistance, and supports) obtained by cancer survivors. Another relevant example in this field is the PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry,[1] which has demonstrated the importance of rehabilitation programs in improving a patient's return to work after cancer treatment in long-term cancer survivors.[2]

In keeping with the long-term assessment of cancer survivors, another major goal for the survivorship care plan is to establish a comprehensive care summary and follow-up (to be discussed with patients) for those patients completing primary treatment. To develop appropriate recommendations, the ECPC has asked the European Society for Medical Oncology to join and called on the EU Commission to support this initiative. In Italy, the Italian Federation of Volunteer-Based Cancer Organizations (FAVO) has developed a joined initiative involving the Italian Association of Medical Oncology (AIOM), the Italian Association of Oncological Radiotherapy (AIRO), and the Italian Society of General Medicine (SIMG) to formulate recommendations providing information on long-term cancer-related and treatment-related effects, as well as tertiary prevention.

Welfare and job protection benefits will need to play a key role within cancer rehabilitation programs because they are essential to improving the quality of life for cancer survivors and to help them return to a normal life after cancer treatment. A study commissioned by the European Parliament's Committee on Employment and Social Affairs confirmed the need for patients to return to work as soon as possible, and suggested that employers can play a significant role with patient organizations. Italy's most influential governmental authorities have heeded requests from cancer organizations for legislation that addresses these issues, and as a result changes have been introduced into existing legislation. For example, in the fields of welfare and health care and public and private employment, equal treatment for all cancer patients and communication/awareness campaigns, including specific programs to be performed at the European national and local levels, have been introduced.

The ECPC is committed to documenting, at the European level, the results obtained by research studies at a national level and to undertake joint projects to develop policies to protect cancer survivors, with a special emphasis on issues of employment. The ECPC believes that increased collaboration with partners in the United States, including the American Cancer Society and the National Cancer Institute, is necessary to ensure that the health needs of cancer survivors are understood and policies are drafted to support the cancer community in responding to the health care needs of survivors. The ECPC would welcome a joint summit in the European Parliament between the US and the EU cancer communities so as to develop an EU cancer survivorship plan to be proposed in a European Parliament resolution.

Cancer Survivorship: The United States as Leaders and Learners

Pamela J. Haylock, PhD, RN, FAAN

Anyone in the United States who has followed the progress of the survivorship movement must commend Dr. de Lorenzo and his colleagues throughout Europe. Our European colleagues have in many ways already surpassed the progress in the United States, which has at least a 30-year history. Dr. de Lorenzo describes the strong collaborative efforts of governments, researchers, and clinicians throughout Europe, who in a relatively short time span have launched a vibrant and creative survivorship consortium.

Over nearly 3 decades, the United States has established a leading role in a global survivorship movement. Fitzhugh Mullan[3] introduced the notion of cancer survivorship in 1985, and the National Coalition of Cancer Survivorship (NCCS) coined and defined the terms "survivor" and "survivorship" the following year.[4] The NCCS charter defines "survivor" in this way: "From the time of discovery and for the balance of life, an individual diagnosed with cancer is a survivor."[4] Many if not most grass roots and national advocacy groups, as well as the National Cancer Institute's Office of Cancer Survivorship (OCS), use some rendition of that definition with slight

variations, such as the OCS's addition of family and caregivers as survivors.[5] Much of the work of advocacy groups, from 1986 to present, concerns collective efforts to affect public policy: advocating for increases in cancer research funding and support for the National Cancer Institute. Today, cancer-related advocacy initiatives continue to focus on public policy and access to care, but advocacy efforts also address the social, emotional, and financial challenges associated with cancer treatment; both short-term and long-term effects of the disease and its treatment; and issues imposed on survivors by the unique public/private, expensive, fragmented, and convoluted American health care system.

The US survivorship movement was initiated and is sustained by survivors who formed constituency groups and associations as a collective voice for individuals, families, and communities affected by cancer. More than a decade elapsed between the incorporation of the NCCS, its early public policy efforts, and the 1996 establishment of the OCS, which was charged with enhancing the length and quality of life of cancer survivors.[5] Another decade had passed when the US Congress asked for the review of survivorship issues that resulted in the Institute of Medicine report entitled *From Cancer Patient to Cancer Survivor: Lost in Transition,*[6] published in 2006. The American survivorship movement now encompasses nearly 3 decades of experiences, fits and starts, setbacks, disappointments, and of course moments of success and celebration. As Hewitt et al note in the preface, "...there are times when trends in medical science, health services research, and public health awareness converge to forge a new realization," expressing optimism that that convergence is finally occurring.[6]

Civil groups (the grass roots and other advocacy groups) have been and continue to be critically important in providing the face and voice of the US survivorship movement. The tendency to form associations or societies for a common action characterizes American culture, noted nearly 2 centuries ago by de Tocqueville during his 10-month stay in America.[7] American nurses were among the first survivorship advocates to bring the concept to colleagues outside the United States during the 2006 International Society of Nurses in Cancer Care conference in Toronto, Ontario, Canada[8] and the Federation of European Cancer Societies' European Cancer Conference in Barcelona, Spain in 2007.[9] What is considered by some to be a watershed event occurred in 2008, with the first "study day" on cancer survivorship in Bari, Italy, in which some of the nation's key leaders in cancer care opinion were not only present but were active participants.[10] They reflected on the US experience, considered lessons learned, and moved to advance survivorship in ways that are consistent with governmental health initiatives, health care and cancer care delivery systems, and perceived survivor needs.[10] Since that time, the cause of survivorship throughout Europe continues to gain momentum, and in many ways already surpasses the survivorship movement in the United States.

Does the concept of survivorship translate from the United States to languages and cultures of other nations and populations? Interpretation and acceptance of the term "cancer survivor" presents just 1 translation dilemma. Although far from universally accepted, the term "survivor" as used in the United States is an attempt to reflect empowerment, control, and self-advocacy among individuals affected by cancer, with the hope that the use of terms and philosophies reflecting victimization and hopelessness, including "victim," "sufferer," and even "patient," would diminish and someday disappear. Kahn et al conducted a qualitative study in the United Kingdom and found widespread rejection of the term, with its implied high risk of death, the suggestion that survival depends on personal characteristics, and assumption of an unwanted advocacy role.[11] Disputes around survivorship language continue to take place in the United States as they surely will throughout the world.

It is evident that American citizens, including cancer survivors, want a holistic approach to care; a concentration on health, wellness, and the process of healing; and self-actualization instead of the single-minded focus on the treatment of an existing ailment.[12-14] At the outset of the American survivorship movement, survivors were given not-so-subtle messages that they were lucky to be alive, and should be grateful; complaints about anxiety, fear, and real and anticipated short-term and long-term effects of treatment fell mostly on deaf ears.[14] Over time, the length of survival became only 1 measure of success, and our focus began to include the quality of the lives saved.[14] Survivors increasingly reported that learning to live with posttreatment challenges is not good enough.[15] Nevertheless, essential cornerstones of survivorship,[16] namely knowledge, empowerment, control, and self-advocacy, are often at odds with the basic tenants of the paternalistic, physician-dominated US health care system, an ongoing source of challenges to advancing cancer survivorship.

In the United States, health remains a private matter, not a public responsibility. The United States stands alone as the only country in the Western world that does not guarantee each citizen a basic level of health insurance

and access to health care services. The United States lacks a national health policy and continues to focus on cure, rather than prevention and the preservation of health. For Americans, poverty, not race or ethnicity, is a major determinant of who lives and who dies.[17] Health care system-generated dilemmas are at play throughout the cancer trajectory, from cancer prevention, early detection, treatment, and survivorship, centering around access to providers with survivorship-related expertise and technology, costs, and questions of who pays for what.

A contentious debate in the American cancer care community involves the determination of which health care disciplines and even subspecialties within each discipline are now or should be prepared to accept roles in survivorship care planning and delivery (eg, oncology specialists or primary care physicians? Oncology nurse specialists or nurse case managers?).[18] Responsibility and accountability have yet to be designated.[18] Limited numbers of physicians, nurses, social workers, nutritionists, and financial counselors with expertise in issues of survivorship are available for the growing population of survivors; workforce issues are of major concern.[19] Private and public payer sources extend limited payment for cancer survivorship services provided by most disciplines, services that require expert knowledge and substantial commitments of time.

Getting to accessible and quality survivorship care in America mandates drastic and creative revisions to the status quo. Rose et al highlighted 6 objectives for a 21st century system: safe, effective, patient-centered, timely, efficient, and equitable.[20] To accomplish this, basic philosophical and cultural shifts must occur in the United States, and in the design and delivery of health care and cancer care. The Institute of Medicine report[19] on oncology workforce issues similarly highlighted the need for cultural changes in health care delivery systems. These changes must include[21]:

- Change the medical (illness) model to a transdisciplinary and holistic (healthiness) model;
- Adapt the definition of "survivor" to guide cancer care delivery to patients, survivors, family, and caregivers from the moment of diagnosis through the remainder of life;
- Reconsider the traditional role of physicians as gatekeepers to health care and survivor care services;
- Look outside the current and traditional roles of health care professions to allow all health care providers to practice at their highest levels of competency and scopes of practice;
- Adapt professional education for health care providers accordingly;
- Devise and define community-based, holistically designed service delivery models that include nontraditional providers; and
- Collaboration with nononcology providers to offer needed services.

Some of these elements are already in place within European models of health care, thereby giving international survivorship advocates, and survivors themselves, significant advantages. Crafting and implementing models that reflect these elements require tremendous political will, multidisciplinary collaboration and cooperation, the ongoing commitment of advocates and survivors, courage, and imagination.

The goal is simple. Survivorship care planning and delivery is an expected part of cancer care, regardless of a survivor's ability to pay, provider specialty, or practice setting. The challenge is getting there. It is time we learn from our European colleagues.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al; Profiles Registry Group. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer.* 2011;47:2188-2194.
2. Mols F, Thong MS, Vreugdenhil G, van de Poll-Franse LV. Long-term cancer survivors experience work changes after diagnosis: results of a population-based study. *Psychooncology.* 2009;18:1252-1260.
3. Mullan F. Seasons of survival: reflections of a physician with cancer. *N Engl J Med.* 1985;313:270-273.
4. National Coalition for Cancer Survivorship. National Coalition for Cancer Survivorship Charter. Silver Spring, MD: National Coalition for Cancer Survivorship; 1986
5. http://dccps.nci.nih.gov/ocs/definitions.html. About Cancer Survivorship Research: Survivorship Definitions, 2013.
6. Hewitt M, Greenfield S, Stovall E, eds; Institute of Medicine and National Research Council of the National Academies. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press; 2006.
7. De Tocqueville A. Democracy in America [reprint of original text, first published in 1835]. New York: Bantam Books; 2000.

8. Curtiss CP, Haylock PJ, Houldin A. State of the Science on Nursing Approaches to Managing Late and Long-Term Sequelae of Cancer and Cancer Treatment. Podium Abstract. Presented at Proceedings of the International Society of Nurses in Cancer Care; September 27-October 1, 2006; Toronto, Ontario, Canada.
9. Curtiss CP, Haylock PJ. Managing late and long-term sequelae of cancer and cancer treatment [abstract]. *Eur J Cancer*. 2007;5(suppl 4):413.
10. Mattioli V. Cancer Survivorship: An Emerging Problem in Italy. From the American Data to the Italian Project PIO 7 (review). 2008, Human Health Foundation Onlus, Spoleto, Italy. www.hhfonlus.org.
11. Kahn NF, Harrison S, Rose PW, Ward A, Evans J. Interpretation and acceptance of the term 'cancer survivor': a United Kingdom-based qualitative study. *Eur J Cancer Care (Engl).* 2012;21:177-186.
12. Herzlinger RE. Market-Driven Health Care: Who Wins, Who Loses in the Transformation of America's Largest Service Industry. New York: Perseus Books; 1997.
13. Porter-O'Grady T. Visions for the 21st century: new horizons, new health care. *Nurs Adm Q.* 2000;25:30-38.
14. Leigh S. From anecdote to evidence: the survivor's perspective. In: Lester JL, Schmitt P, eds. Cancer Rehabilitation and Survivorship: Transdisciplinary Approaches to Personalized Care. Pittsburgh, PA: The Oncology Nursing Society; 2011:Pages.
15. LIVESTRONG Report: "I Learned to Live With It" Is Not Good Enough: Challenges Reported by Post-Treatment Cancer Survivors in the LIVESTRONG Surveys. Austin, TX: LIVESTRONG Foundation; 2011. LIVESTRONG.org. Accessed April 30, 2012.
16. Clark EJ, Stovall EL. Advocacy: the cornerstone of cancer survivorship. *Cancer Pract.* 1996;4:239-244.
17. Freeman HP, Reuben SH. Voices of a Broken System: Real People, Real Problems. President's Cancer Panel, Report of the Chairman. Washington, DC: National Institutes of Health, National Cancer Institute; 2001.
18. Institute of Medicine. Implementing Cancer Survivorship Care Planning: Workshop Summary. Washington, DC: National Academies Press; 2007.
19. Institute of Medicine. Ensuring Quality Cancer Care Through the Oncology Workforce: Sustaining Research and Care in the 21st Century. Washington, DC: National Academies Press; 2009.
20. Rose C, Stovall E, Ganz PA, Desch C, Hewitt M. Cancer Quality Alliance: blueprint for a better cancer care system. *CA: A Cancer J Clin.* 2008;58:266-292.
21. Haylock PJ, Curtiss CP. The paradigm shift to survivorship care planning. In JL Lester, Schmitt P, eds. *Cancer Rehabilitation and Survivorship: Transdisciplinary Approaches to Personalized Care*. Pittsburgh, PA: The Oncology Nursing Society; 2011;15-23.

Original Article

Cancer Survivorship Research in Europe and the United States: Where Have We Been, Where Are We Going, and What Can We Learn From Each Other?

Julia H. Rowland, PhD[1]; Erin E. Kent, PhD[1,2]; Laura P. Forsythe, PhD, MPH[1,2]; Jon Håvard Loge, MD, PhD[3,4]; Lars Hjorth, MD, PHD[5]; Adam Glaser, DM[6,7]; Vittorio Mattioli, MD[8]; and Sophie D. Fosså, MD, PhD[3,4]

The growing number of cancer survivors worldwide has led to of the emergence of diverse survivorship movements in the United States and Europe. Understanding the evolution of cancer survivorship within the context of different political and health care systems is important for identifying the future steps that need to be taken and collaborations needed to promote research among and enhance the care of those living after cancer. The authors first review the history of survivorship internationally and important related events in both the United States and Europe. Lessons learned from survivorship research are then broadly discussed, followed by examination of the infrastructure needed to sustain and advance this work, including platforms for research, assessment tools, and vehicles for the dissemination of findings. Future perspectives concern the identification of collaborative opportunities for investigators in Europe and the United States to accelerate the pace of survivorship science going forward. ***Cancer* 2013;119(11 suppl):2094-108.** *© 2013 American Cancer Society.*

KEYWORDS: cancer; survivorship; research; Europe; United States.

INTRODUCTION

The dawning of the new millennium ushered in a new era for cancer control globally, one heralded by the rise of interest in the health, functioning, and psychosocial well-being of those living through and beyond a cancer diagnosis. The "cancer survivorship" movement started in the United States and is increasingly being championed in diverse countries across Europe. However, to date, survivorship research has occurred in a fragmented fashion with the need for international ventures only now being recognized. In this article, we: 1) review and compare the evolution of the field of cancer survivorship research in the United States and in Europe, with illustrative examples; 2) discuss the knowledge generated from this work and the new directions this science is taking; and 3) identify resources needed to advance this science. We also highlight areas where future international collaborations will serve to accelerate the pace of translation from research findings to improvements in care of the growing population of cancer survivors.

Corresponding author: Julia Rowland, PhD, Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, NIH/DHHS, 6116 Executive Boulevard, Suite 404, Bethesda, MD 20892-7397; Fax: (301) 594-5070; rowlandj@mail.nih.gov

Erin E. Kent's current affiliation: Outcomes Research Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, NIH/DHHS, Bethesda, Maryland.
Laura P. Forsythe's current affiliation: Patient Centered Outcomes Research Institute, Washington, DC.

[1]Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH)/Department of Health and Human Services (DHHS), Bethesda, Maryland; [2]Cancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute, NIH/DHHS, Bethesda, Maryland; [3]National Resource Center for Late Effects After Cancer Treatment, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [4]University of Oslo, Oslo, Norway; [5]Consultant Pediatric Oncology and Hematology, Department of Pediatrics, Skåne University Hospital, Clinical Sciences, Lund University, Lund, Sweden; [6]Paediatric and Adolescent Oncology Program, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; [7]National Cancer Survivor Initiative, Department of Health, London, United Kingdom; [8]Department of Critical Area and Surgery, National Cancer Research Centre, "Giovanni Paolo II" Cancer Institute, Bari, Italy.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28060, **Received:** July 27, 2012; **Revised:** January 16, 2013; **Accepted:** January 16, 2013, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

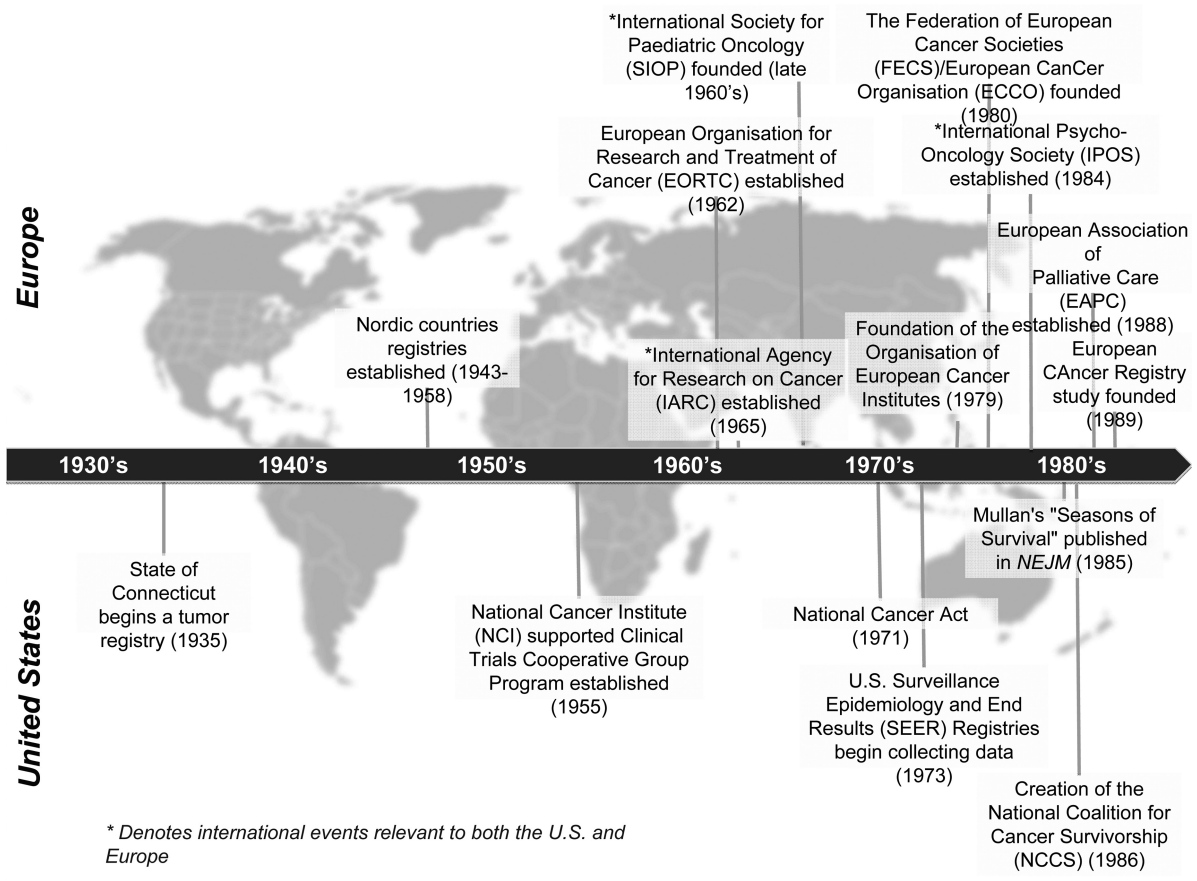

Figure 1. Timeline of important events in the evolution of the field of cancer survivorship.

Evolution of a Field

Forty years ago, the survival rates for all cancers combined were low.[1,2] Relatively few effective treatment options were available; of those that were, many had serious side effects. Because of advances in recent decades in early detection, effective therapies, and supportive care, 5-year survival rates have increased to 50% or more in adults with a history of cancer in the United States and in many European countries,[3] and there are growing numbers of people living with and beyond a diagnosis of cancer.[4,5] In the United States and Europe, the greatest improvements in survival were seen for childhood cancers and malignancies of young adults (eg, Hodgkin's lymphoma, testicular cancer).[6]

These advances have led us to begin to ask important questions: What are the persistent problems and late effects in individuals who have survived their cancer? Which survivors are at particular risk for developing late effects? What is the impact of a history of cancer on individuals' careers, families, and wider society? How can late and long-term effects be cost-effectively prevented, detected, and managed?

Evolution of Survivorship Science in the United States

Progress made in cancer prevention and control in the United States is often dated from the signing of the National Cancer Act on December 23, 1971 (Fig. 1). However, the launch of the survivorship movement in the United States is generally linked to 2 events: a 1985 publication in the *New England Journal of Medicine* by a young physician, Dr. Fitzhugh Mullan, describing his journey with cancer, which he labeled as the "Seasons of Survival,"[7] and the creation a year later of the National Coalition for Cancer Survivorship (NCCS). At the first meeting of the NCCS in October 1986 in Albuquerque, New Mexico, Mullan and the two dozen founding members proposed a new definition for "cancer survivor." Up to that time, the term "cancer survivor" was deemed by the medical community to refer to someone who had remained disease-free for a minimum of 5 years. NCCS members reasoned that cancer patients could not wait 5 years to make decisions about outcomes

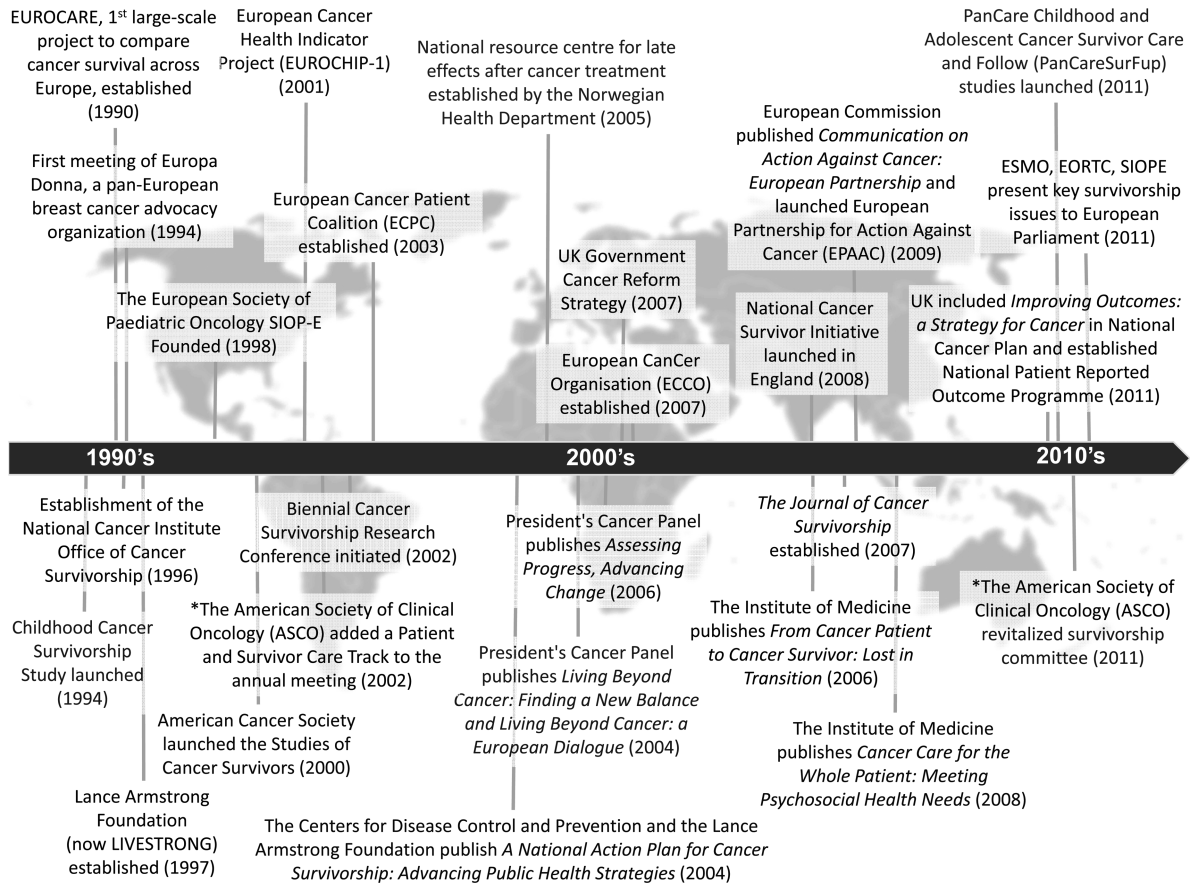

Figure 1. Continued.

that would be affected by specific treatment choices (eg, fertility preservation, receiving a drug that could alter lung capacity or risk for peripheral neuropathy). They proposed that a person should be considered a survivor from the time of diagnosis onward. The revised definition was designed to provide hope and, importantly, to change the medical dialogue such that cancer treatment decisions would be made predicated on a patient's preferences and desires regarding life after cancer. Although many treated for cancer do not refer to or think of themselves as survivors,[8] this language has taken hold broadly in the United States. It also launched a cascade of activities promoting attention to the unique needs of cancer survivors.

One of the most compelling rationales for cancer survivorship research, namely, the sheer growth in numbers of those living through and beyond cancer in the United States,[4] has been documented by the Surveillance, Epidemiology, and End Results (SEER) cancer registries (Fig. 2). The SEER registries, which were established by the National Cancer Act and currently cover approximately 28% of the US population (http://seer.cancer.gov/about/factsheets/SEER_brochure.pdf), provide a unique resource for quantifying the growing prevalent population of cancer survivors because they track survival through the balance of life for all cases reported. As of 2012, there were an estimated 13.7 million cancer survivors in the United States alone,[9] representing approximately 4% of the population.[10]

Several other key achievements in policy and research support have contributed to the growth of the field of cancer survivorship in the United States. The Office of Cancer Survivorship (OCS) at the National Cancer Institute (NCI) was established in 1996 to champion and direct research to identify and address the challenges faced by those living long-term after cancer. The American Cancer Society (ACS), established in 1913, funds research in cancer survivorship, and made a major commitment in 2000 to support survivorship science with the initiation of the Study of Cancer Survivors, a

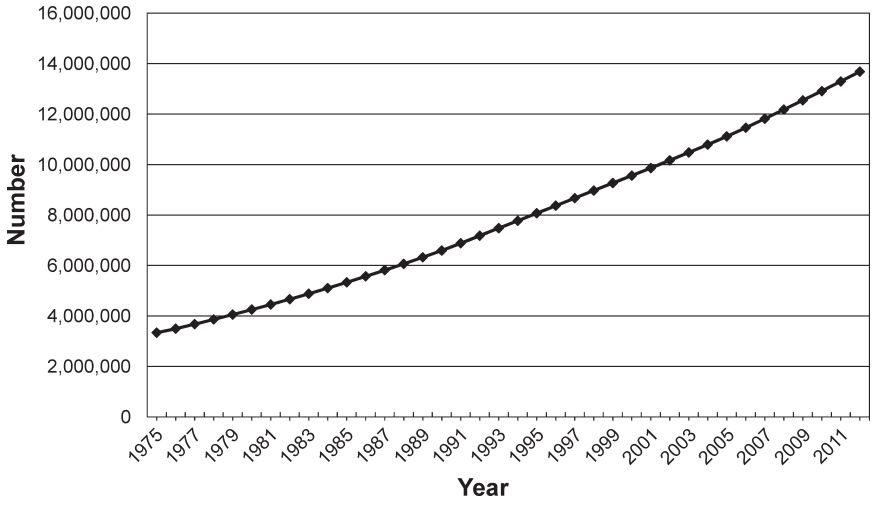

Figure 2. Estimated number of cancer survivors in the United States from 1975 to 2012. Estimations and modeling provided by Angela Mariotto, PhD, based on: Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst.* 2011 Jan 19;103(2):117–28. Epub 2011 Jan 12.

large population-based longitudinal study of quality of life.[11] Part of the mission statement of the ACS is to diminish suffering from cancer.

In addition, the President's Cancer Panel, also established by the National Cancer Act, was tasked with monitoring the progress of the National Cancer Plan. The steady increase in the number of survivors and the lack of information about their health status and needs became the topic of the annual report of the President's Cancer Panel in 2003 to 2004.[12] This report, and 4 additional national reports on the challenges to understanding and addressing the care of pediatric[13] and adult cancer survivors,[14-16] brought national visibility to cancer survivorship research. These reports state that cancer survivorship needs to be addressed as a unique place on the cancer control continuum.

Attention to cancer survivors' health and needs in the United States has further benefited from a rich history of patient advocacy and public visibility around cancer. The informed consent movement in the late 1960s promoted attention to the rights of patients regarding information about the nature of their illness, and also their role in treatment decision-making. To be truly "informed," a patient needs to understand the consequences of choices in care. Since the late 1970s, a number of high-profile figures have acknowledged their status as cancer survivors (eg, Betty Ford, wife of President Ford in 1976, and Lance Armstrong, whose visibility and foundation have had worldwide impact). These disclosures, along with a growing advocacy movement, helped lower cancer-related stigma in the United States and prompted a level of public dialogue about this disease. One measure of the impact these conversations have had is that when someone dies of cancer in the United States today, obituaries in major city newspapers now cite the cause of death as such, often indicating the specific type of cancer, instead of using the euphemism "died of a lingering illness." In the absence of these types of public disclosures and dialogues, cancer still continues to be stigmatized in other countries around the world.

The growing visibility of cancer survivors in the United States also led to the creation of a number of organizations championing the research and care of specific populations of cancer survivors, with breast cancer advocates leading the way in the early 1990s, but who were quickly followed by organizations for diversity of cancer sites such as leukemia, colorectal cancer, prostate cancer, bladder cancer, pancreatic cancer, and so forth. Consumer advocacy was a driver behind the creation of the OCS at the NCI; it has also, at least in the past, functioned to increase federal spending on cancer.[17]

There is wide variability in health care receipt and coverage by region, state, and health insurance type in the United States. Across the United States, cancer treatment and posttreatment follow-up care are poorly coordinated across multiple providers, settings, and payers. In particular, posttreatment cancer care lacks clear delineation of responsibility among providers, guidance for appropriate tests and treatments, and adequate reimbursement for all aspects of comprehensive care. This is true even for older adult survivors (aged 65 years and older) who are eligible for federally run Medicare health care coverage and programs. As a result, there was an initial dearth of attention

paid to the needs of posttreatment cancer survivors.[15] The well-documented limitations of the US health care system present challenges moving forward not only for understanding the multilevel problems experienced by those surviving cancer, but also for systematic implementation of clinical practice changes based on emerging research findings.

Another challenge to understanding and advancing health after cancer in the United States relates to limitations around cancer control plans. Individual state cancer plans, supported by the Centers for Disease Control and Prevention (CDC), have been in place since 1998.[18] However, the inclusion of goals addressing cancer survivorship issues only occurred in the past decade, and only about a third of state plans in 2009 included survivorship sections or chapters (Irene Prabhu Das, NCI, personal communication, April 30, 2012). Furthermore, recommendations in cancer control plans related to survivorship are often unfunded or underfunded mandates addressed only to the extent annual state level budgets permit. Thus, although the United States has in the past decade seen a rapid increase in the attention to cancer survivors and survivorship research and practice, the ability to act on this knowledge is at times stymied by the lack of a uniform delivery system within which to test and implement changes designed to enhance the quality of life and length of survival of all of those diagnosed with cancer.

Evolution of Survivorship Science in Europe

Europe is a complex grouping of 50 countries (including Kazakhstan, in addition to the 49 listed here: http://europa.eu/about-eu/countries/index_en.htm) with more than 700 million inhabitants; marked cultural, economic, and societal variations; and significant variation in the models and levels of health and social welfare provision. Not surprisingly, the field of cancer survivorship research has followed a somewhat different trajectory in Europe. In contrast to the United States, in Europe, the term "cancer survivor" is used less often by individuals with a cancer diagnosis.[19,20] In the European medical literature, this term is typically applied to cancer patients surviving tumor-free at least 5 years after their diagnosis, as described in the President's Cancer Panel Report *Living Beyond Cancer: a European Dialogue*.[19] This distinction is reflected in the focus on late and long-term effects in European survivorship studies.

National cancer registries have existed in the Nordic countries for 60 to 70 years (since 1943 in Denmark, since 1951 in Norway, since 1952 in Finland, since 1955 in Iceland, and since 1958 in Sweden) and the Netherlands for more than 20 years (Fig. 1). In other countries (for example, Germany and the United Kingdom) regional cancer registries provide epidemiological data on cancer incidence and mortality. The establishment of both the International Agency for Research on Cancer (IARC) in 1965 and of the EUROpean CAncer REgistry (EUROCARE) in 1989 represented 2 important steps to generate pan-European data on cancer incidence, mortality, and 5-year prevalence (ie, those surviving at least 5 years after cancer diagnosis). However, the level of national coverage by such regional registries varies widely.[21] In 2002, the prevalence of cancer survivors was estimated by a statistical model to be 2% of the total population in Europe,[22] which represents an increase from 1% in the figures published for 1990 by IARC.[23]

Although Europe lacks organizations specifically devoted to cancer survivorship comparable to those which have evolved in the United States, certain pan-European organizations representing different segments of cancer care have promoted the field of survivorship science; of note, many of these were established during the last decade (Fig. 1). Among these are the European Cancer Patient Coalition which represents the interests of all cancer patient groups, and the European Cancer League, an umbrella organization representing the majority of the national cancer organizations in Europe. A major policy achievement in Europe was the publication of "Communication on Action Against Cancer: European Partnership" in 2009, which highlighted several areas for improvement of cancer care in Europe, including a need for stronger collaboration within the European Union (EU) in cancer survivorship.[24] Specifically, the report emphasized the need for identification and dissemination of evidence based practices to reduce the inequalities across the continent. Provision of comparable data on incidence, mortality and prevalence was mentioned explicitly. The European Commission also launched in 2009 The European Partnership for Action Against Cancer (EPAAC) with the aim, under a common platform, to unify cancer burden indicators (incidence, mortality, survival, and prevalence) provided by existing European data collection activities. The Commission also urged all member states to publish a cancer care plan by the end of 2013. National cancer plans have subsequently been published by 24 of 27 EU member states at the time of this publication (www.epaac.eu/national-cancer-plans). Most of these care plans deal with prevention, diagnosis, and treatment of cancer. The topic of cancer survivorship appears in approximately half of these plans, under sections referring to survivorship, rehabilitation, supportive and palliative care (beyond end-of-life care), and after-care.

In most European countries, treatment for cancer is free of charge for the individual patient, but the availability of novel drugs and application of new technologic advances differs. There are also considerable variations among countries regarding the structure of follow-up care for cancer patients after they have discontinued their cancer treatment. Follow-up care generally falls under the responsibility of medical specialists or family physicians, who often have limited knowledge of long-term follow-up and late complications, which renders systematic medical surveillance of long-term effects difficult.

Looked upon broadly, the concept of cancer survivorship does not seem to have had either a broad or uniform impact on the philosophy or aims of various stakeholders in European contemporary oncology and policy. The one exception to this has been in England, which formally launched a National Cancer Survivorship Initiative in September 2008. This latter is currently poised not only to transform medical care for those after treatment for cancer, but also to test models for the most effective and cost-efficient way to provide this care.[25] Across other parts of Europe, some relevant efforts for survivorship research and care, such as providing reliable prevalence data or providing information of after-care such as rehabilitation, are noticeable nevertheless. During the last 5 years, both ESMO (European Society for Medical Oncology) and ESTRO (European Society for Therapeutic Radiology and Oncology) have included within their annual conferences organized sessions devoted to cancer survivorship. During the ECCO (European CanCer Organization)-ESMO conference in September 2011, medical specialists and representatives from European cancer advocacies, outlined cancer survivors' needs, including the need for attention to their continued participation in the work force. To the best of our knowledge, the first European conference solely addressing cancer survivorship (European Symposium on Late Complications after Childhood Cancer [ESLCCC]) was held in 2007 and now occurs in alternate years. These efforts notwithstanding, the large and increasing number of European cancer survivors and their expected national health burden in the years to come are not sufficiently reflected in the present aims of European efforts to improve cancer care.

Cancer survivorship research in Europe has so far largely been restricted to specified malignancies (childhood cancer, breast cancer, testicular cancer, Hodgkin's lymphoma) and conducted by a subset of medical specialists (mostly oncologists and pediatricians) and epidemiologists using existing databases and surveys.[26,27] Most of these efforts have depended on time-limited grants. With a few exceptions, research and activities within the field of cancer survivorship have been hampered by the limited involvement of politicians and health care administrators on the national and the European levels. In the last 2 years, ESMO, the EORTC (European Organization for Research and Treatment of Cancer), and SIOPE (European Society of Pediatric Oncology) presented key issues in cancer survivorship to the European Parliament with the aim to attract European politicians' attention. So far, it seems that research and care in cancer survivorship has not attracted the attention of European health care researchers and decision-makers.

A principal challenge to survivorship research in Europe is the limited access to funding, both in terms of financial support and time restrictions. Some improvement has been observed during recent years in some countries, including the establishment of academic positions within the fields of cancer survivorship (eg, in Denmark, Norway, the Netherlands, and the United Kingdom) and government financial support of voluntary organizations' survivorship projects. A 5-year EU grant, funded by the 7th Framework Program of the European Commission and awarded in 2010 to the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) project, indicates an awakening understanding of the importance of cancer survivorship research. A consortium of 16 institutions, PanCareSurFup will carry out research studies into the late effects of treatment for cancer, identify a virtual cohort of childhood cancer survivors for future studies, establish guidelines for follow-up, disseminate the results, and provide training and workshops for stakeholders. The overall goal of this project is to give health care providers the information they need to improve the long-term health of every European childhood cancer survivor.

In an effort to illustrate differences within Europe that affect cancer survivorship interest, we have summarized the nature of the cancer registry, care delivery, and in-country governmental activities for 3 countries familiar to the authors: Norway, the United Kingdom, and Italy (Table 1). Although all 3 of these nations have strong registry systems and national health programs, there is considerable variability in national attention to cancer survivorship. Whereas Norway has for a number of years drawn attention to the need for long-term follow-up for some cancer survivors (the current national guidelines for breast, prostate, and testicular cancer and Hodgkin's lymphoma contain recommendations for long-term follow-up), England's National Cancer Survivor Initiative is a relatively new but unique and comprehensive effort to advance survivorship research and care nationwide. Both

TABLE 1. Characteristics of the United Kingdom, Norway, and Italy

	Cancer Statistics	Health Care System	Key Achievements in Policy and Research Support
United Kingdom	• Population-based cancer statistics are available through 11 cancer registries, each covering populations of between approximately 1.65 million and 13.8 million people (http://www.ukacr.org/registration-organisation)	• Health care is largely provided free of charge by the welfare state, through the National Health Service (NHS), at the time and point of need • Cancer follow-up care occurs in hospital, community, or primary care settings. The duration and intensity of hospital follow-up has been inconsistent and variable and not always robustly evidence-based	• The Government's Cancer Reform Strategy identified key priorities, including the need for a greater focus on survivorship (2007) • The *National Cancer Survivor Initiative* (2010) was established to enhance cancer survivor care, and promote epidemiologic health services research in cancer survivorship • *Improving Outcomes: A Strategy for Cancer* (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_123394.pdf) highlighted the national commitment to enhancing care for survivors (2011) • The Department of Health committed significant recourses to cancer data collection through the *National Cancer Intelligence Network* (2011) and the *National Patient Reported Outcome Programme* (2012-2015)
Norway	• National registry with 100% coverage provides cancer incidence, mortality and prevalence in the population (5 million) • Survivors can be linked to other databases (eg, the National Birth registry) through a unique personal identification number	• Cancer treatment and follow-up are free after the patient has paid annual expenses comparable to $625 • Cancer follow-up is viewed as a shared responsibility between specialists and family doctors, with care shifting more to family doctors as years elapse since treatment	• The National Cancer Plan (NCP) identified palliation (1997) and awareness of late effects after and rehabilitation after cancer treatment (2004) • The National Resource for Studies after Treatment of Cancer established to promote research, training, and knowledge dissemination (2005) • The Directorate of Health expert group (2010) outlined physical and psychosocial needs of cancer survivors and proposed solutions to meet these needs
Italy	• 29 cancer registries (ICR) that cover <50% of Italy's population report incidence, mortality and survival • There are also 3 diagnosis-specific registries and 2 regional childhood registries	• Cancer treatment and follow-up is free and includes necessary long-term follow-up	• The Italian National Cancer Plan (2010-2013) aims to improve cancer follow-up and improve compliance with cancer registries • National Multisite Research Program on Cancer Survivors funded to investigate the physical, psychological, and social sequelae of adult long-term cancer survivors; to identify the potential actions to prevent cancer sequelae; and to develop a rehabilitation plan to meet Italian cancers survivors' needs

Norway (National Resource Center for Studies after Treatment of Cancer Center, established in 2005) and Italy (National Multisite Research Program on Cancer Survivors, launched in 2008)[28] invested in research infrastructures to study cancer survivors.

Comparison of the Evolution of Survivorship Research in the United States and Europe

The number of publications dealing with cancer survivorship research has grown dramatically in both the United States and Europe (Fig. 3). The emerging interest in long-term cancer survivors has paralleled their growing numbers on both sides of the Atlantic.[1,29] Survivorship science has become more sophisticated over time. Studies conducted in the 1970s and early 1980s focused on trends in overall survival and development of second malignancies. Subsequently, research into the broader aspects of cancer survivorship was greatly stimulated in both the United States and Europe by the dramatic progress in treating pediatric cancers and resulting concerns about the long-term consequences of cancer treatments (for example, Rowland et al[30]). Later studies in the 2000s focused on the incidence and prevalence of persistent and late-onset adverse effects, including psychosocial problems,[31,32] and interventions to treat these.[33] More recent studies published since 2010 examine the markers and mechanisms of risk for poor outcomes and the cost-effectiveness of current health care provision for reducing preventable morbidity and mortality among long-term survivors.[34-36] Challenges encountered on both sides of the Atlantic in providing quality health care to a growing population of cancer survivors in the context of shrinking resources are a driving force behind current and emerging research. Furthermore, the lack of attention to and funding for recommendations related to survivorship in cancer control plans in both the United States and Europe needs to be addressed. Failure to attend to the major recommendations made by entities in the United States and Europe will result in an inability to appropriately support and care for the growing population of survivors globally.

Whereas the volume and pace of cancer survivorship research has accelerated rapidly in the past several years,

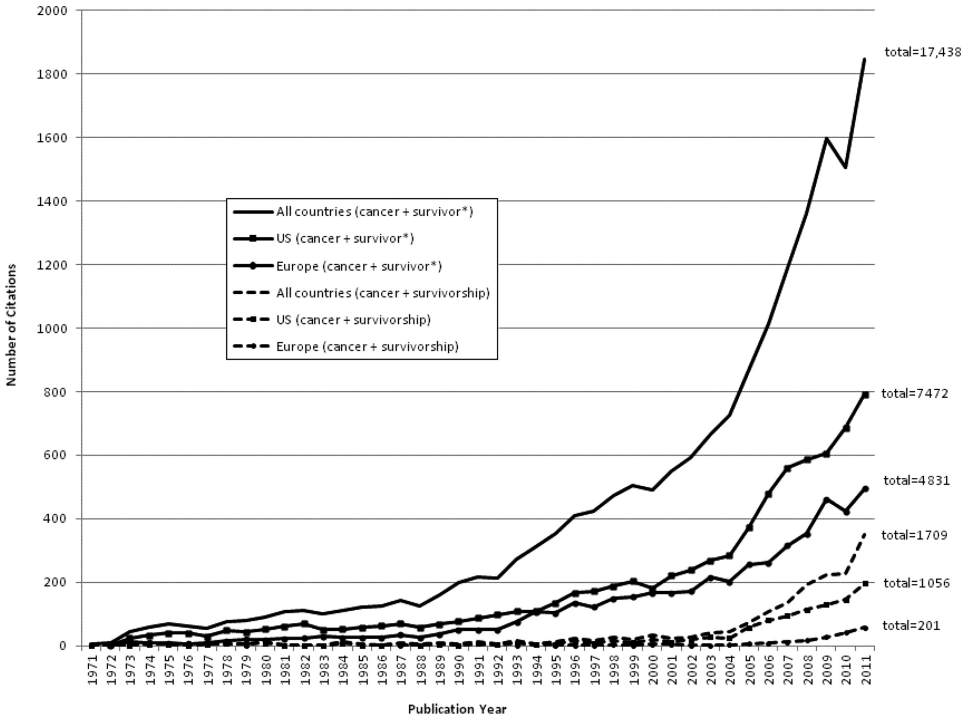

Figure 3. Citations related to cancer survivorship science are shown. The data are based on search in SciVerse Scopus database (www.scopus.com/home.url), the largest abstract and citation database, which covers 17,500 peer-reviewed journals (www.info.-sciverse.com/scopus). Citations include articles, review articles, conference papers, letters, notes, editorials, and short surveys from 1971 through 2011. The search for "cancer + survivor*" includes all citations with "cancer" and "survivor," "survivors," "survivor's," "survivors'," or "survivorship" in the title or abstract, whereas the search for "cancer + survivorship" includes only citations that specifically use the word "survivorship." Europe was defined by the 27 countries in the European Union.

this effect has been more pronounced in the United States than in Europe (Fig. 3). Three key reasons may account for this difference. First, the 5-year survival rates for several European nations are still < 50% (Fig. 4).[3] In these countries, focusing research on enhancing survival rather than on survivorship outcomes is a reasonable priority, while recognizing, nevertheless, that *quantity* of life and *quality* of life are both valued survivorship outcomes. Although the overall 5-year relative cancer survival is higher in the United States than in several European countries, the United States demonstrates poorer overall health than most European nations according to most World Health Organization (WHO) indicators.[37] Survivorship researchers and clinicians in Europe and the United States are keenly aware that increasing length of survival must be weighed thoughtfully against the human cost of such efforts.[38,39] Second, historically, most European nations have not provided sufficient funding resources for long-term survivorship research.[40] In contrast, the United States has benefited from strong congressional support for government-lead investment in cancer research, including survivorship science. The recent high profile of cancer survivorship in English national health policy and charity activities, with significant service improvement initiatives being centrally and locally commissioned, has not been mirrored by an equal investment in cancer survivorship research despite identification of the need for a systematic comprehensive research program.[41] Finally, due to the greater stigma of cancer in some European countries relative to the United States, there has been less public discourse around, and hence more limited political attention paid to, cancer survivor issues in some European nations.[19]

Lessons From Survivorship Research

A number of key lessons have been learned with considerable consistency on both sides of the Atlantic. First, most cancer survivors do well after treatment; they manifest remarkable resilience.[42] However, it is also clear that there are few cancer therapies without any adverse effects. A second important finding is that cancer has the potential to affect every aspect of an individual's life: physical, psychological, social, economic, and existential or spiritual.[43] Third, as survivors are followed for longer periods, the

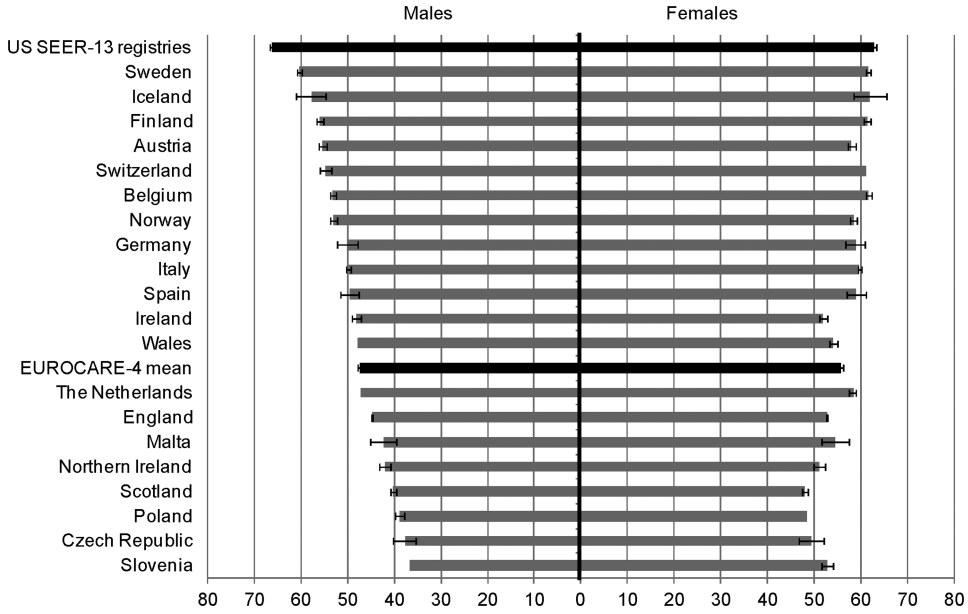

Figure 4. The 5-year relative survival of all malignancies diagnosed from 2000 to 2002, are shown stratified by sex. Data source: Verdecchia et al.[3] Relative survival was calculated as the ratio of absolute survival of patients with cancer to the expected survival of a group of people of the corresponding sex and age in the general population. Registry quality and coverage varied by country; see Verdecchia et al.[3] for data quality metrics.

emergence of late effects (eg, second cancers, cardiac failure), sometimes years after discontinuation of cancer treatment, is often unexpected and has major impact on survivors' lives.[44] Fourth, cancer survivors need risk-adapted follow-up care that reflects individual challenges, related to the type and treatment of their cancer and their specific other medical and psychosocial needs.[45,46]

Taken as a whole, the research conducted in Europe and the United States highlights a number of gap areas in our knowledge base. It is unclear who may be at risk for what types of chronic or late-occurring effects of cancer and its treatment. Although some survivors experience few problems, others with similar disease and treatment may have many. More basic research is required to understand the mechanisms behind and the etiology of the observed long-term effects. Furthermore, limited interventions exist to address many of these effects (eg, chronic fatigue, sexual dysfunction, memory problems). Teasing apart what health problems may be secondary to cancer, exacerbated by the diagnosis and treatment, the result of underlying genetic predisposition, a function of environment or lifestyle, and/or simply an effect of aging remains a challenge. Because most survivorship research has included tumor-free and/or still young individuals, future studies have to deal with the problems of those living with some form of chronic treatment (eg, hormonal treatment in breast or prostate cancer) and elderly long-term cancer survivors. Finally, greater appreciation is also needed regarding what medical care should be delivered, by whom, when, and to which survivors. Future research should provide the evidence base for models of care for treating the growing population of cancer survivors, given a shrinking oncology workforce[47] and including evidence for risk categorization. Furthermore, specific guidance is needed regarding surveillance for late and long-term effects and interventions to address future health status once cancer therapy ends.

Infrastructure for Survivorship Research

Platforms for Research

A vital barrier to studying survivors is access to this population as a whole and, importantly, detailed information on the treatments they may have received as part of their care. Some research documenting the long-term and late effects of cancer among survivors in both the United States and Europe is drawn from data from registries versus patient-contact studies; however, an increasing diversity of platforms (eg, surveys, epidemiological cohorts, and data linkages) is rapidly emerging within which to conduct survivorship research. Cancer registries are an important primary source for research on survival and persistent and long-term effects after cancer and were the basis

for the earliest studies on second malignancies (www.e-paac.eu/cancer-data-and-information). However, these registries historically do not contain reliable data on follow-up experiences. In particular, patient-reported outcomes (PROs), detailed treatment history (eg, specific chemotherapeutic agents and doses received), which can be important predictors of late effects, and comorbidities are not systematically collected in these registries. Registries can also be used as a sampling frame for recruitment to studies intended to contact survivors for further assessment, but registry-based recruitment presents challenges in terms of the delays for populating the registry with cancer cases, incomplete or inaccurate contact information for survivors, and nonresponse to recruitment and survey efforts.[48] Despite this, progress is being made, and some registries have shown that PROs can be successfully linked to population-based registries (www.profilesregistry.nl).[49] Moreover, whereas many registries have the capacity to capture second malignancies,[50] few are capable of tracking recurrent or progressive disease. In certain countries, such as in Nordic countries, some of these shortcomings are overcome by linkages to other population-based registries, such as national birth registries or registries on education, income, sick leave, disability pensions, hospitalizations, and use of medications. The Nordic countries and the United Kingdom, with national health care systems and registries that serve almost 100% of cancer patients, have a unique advantage in conducting population-based survivorship studies because the health and resource utilization of their populations can be tracked. The use of a unique identification number for every citizen in Nordic countries enables researchers to approach cancer survivors even decades after a diagnosis to assess self-reported persisting or late-occurring effects of cancer and its treatment. Surveys among these individuals, especially when coupled with the collection of biological material and physical examination of survivors, can provide the opportunity to examine etiological mechanisms underlying the incidence of late effects among well-documented groups of survivors.[27,34] There are 2 systems in the United Kingdom and the Netherlands in which patient-reported outcomes are integrated on a routine basis with cancer registry data: the ePOCS system[51] and the PROFILES registry.[52] The latter also disseminates cancer survivorship data free of charge for academic use (www.profilesregistry.nl). Across all registries, researchers must be aware of the variable quality of the data ascertained.

Access to these types of platforms is more limited in the United States where there are multiple health care delivery and payer systems and limited communication among these groups. The one exception is for survivors over the age of 65 years, the age at which US citizens can enter the government Medicare system. In recent years, linkages between the Medicare and the SEER cancer registry systems make it possible to examine health care utilization of the large population of older cancer survivors.[53] However, complete records of cancer treatments are not available from SEER, and as noted earlier, SEER covers only 28% of the US population. This is a significant limitation for investigators who wish to identify treatment exposures that may be associated with specific types and severity of cancer-related symptoms or conditions. In addition, because there is usually limited information on the health status and behaviors of survivors prior to diagnosis, ascertaining what may be cancer-related effects versus problems or conditions with another etiology is difficult to assess. In an effort to address this challenge and to better understand the relationship between patterns of care and survivorship outcomes, the NCI created the Health Maintenance Organization Cancer Research Network (http://crn.cancer.gov/about/CRN_fact_sheet.pdf). A consortium of 14 health care delivery systems, covering almost 11 million US individuals, the Cancer Research Network has the potential to examine such questions as what the impact of different types of service use may have on survivors' health outcomes, how cancer in one member may affect health care status and utilization by other family members, and whether patient navigator programs can reduce illness-associated morbidity; these are questions some of their European counterparts are already able to answer for their own populations.

Other complementary platforms for survivorship research used by US investigators include national health surveys[54] and data from large, prospective epidemiologic cohorts. Examples of these include the National Health Interview Survey (NHIS) an annual in-person, population-based survey of noninstitutionalized household members,[55] and the Nurses' Health Study, a large, longitudinal cohort study of the health and well-being of these professionals over their life course.[56,57] Although often lacking detailed cancer treatment information, these databases permit comparison of the health and functioning of survivors with that of their peers not affected by cancer.

An additional source of survivor populations used in both the United States and Europe include samples drawn from those entered into cancer clinical trials. In many cases, clinical trial cohorts have the unique advantage of permitting access to detailed treatment information, and data on therapies delivered under carefully controlled conditions. However, participation rates in clinical trials among adults

in Europe (approximately 5% of the adult cancer population; Jon Bean, EORTC personal communication, April 26, 2012) and the United States (approximately 2% to 3% of the adult cancer population,[58] although these numbers are much higher for pediatric cancer patients, most of whom are entered into one or more clinical trials) are low. It is important to note that for many of those diagnosed with cancer, there may be no available trial or they may be ineligible for study entry. The fact that the denominator commonly used to estimate trial participation includes all diagnosed individuals may account for the disturbingly low figures. Furthermore, due to stringent exclusion criteria, only the healthiest patients are entered into these studies, a practice that severely limits generalizability of findings to the broader population of survivors. Importantly, comorbid health conditions, more common among older survivors, often preclude trial inclusion, thus eliminating the opportunity to characterize those who may be most vulnerable to experiencing adverse survivorship outcomes. Finally, in addition to these challenges, one study details the barriers to recruiting cancer survivors retrospectively from clinical trials and reported a final participation rate of only 29%, due to difficulty locating patients, lack of institutional commitment, and lack of patient interest.[59] Maintaining low rates of those who drop out or are lost to follow-up is critical in efforts to reliably identify those at risk for adverse effects. A number of retention strategies may be needed to ensure long-term participation.

The development and support of cancer survivor-specific cohorts for the purpose of advancing survivorship studies remain limited. Despite this, a number of these have been enormously productive including, but not limited to, the longitudinal follow-up of the childhood cancer cohort in the United States (Childhood Cancer Survivor Study, CCSS),[60] the British Childhood Cancer Survivor Study (BCCSS),[26] the American Cancer Society's Studies of Cancer Survivors cohort study,[11] the Health, Eating, Activity and Lifestyle (HEAL) study of breast cancer survivors,[61] the repeated examination of breast cancer survivors as done by the Early Breast Cancer Clinical Trial Group organized from Oxford (United Kingdom), and the European-American studies on long-term effects after testicular cancer.[27,62]

Assessment Tools

A number of broadly used tools exist in Europe (eg, EORTC-QLQ-C30) and the United States (eg, FACT system) to evaluate the health-related quality of life of cancer survivors, in particular during active treatment.[63] Fewer measures, however, are designed to capture survivors' outcomes after treatment, with exceptions such as the Impact of Cancer (IOC) scale.[64] Two US efforts over the past several years show promise of helping to fill this gap, and potentially prove useful for international collaboration: the Patient-Reported Outcomes Measurement Information System (PROMIS)[65] and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).[66] Both of these NCI-sponsored data collection systems provide a data collection platform for measuring PROs with the purpose of investigating health outcomes. While PRO-CTCAE is currently being tested in the context of clinical trials, the measures are intended to be used for long-term follow-up to identify late-effects of therapy. The modular approach followed by both the EORTC Quality of Life group and the Functional Assessment of Cancer Therapy (FACT) system, in which patients complete a core health-related quality-of-life assessment tool in combination with disease-specific supplementary tools, may provide a useful basis for the development of survivorship-specific tools.[67] Studies suggest that survivors report poorer physical and mental health than individuals without a history of cancer.[68,69] A key lesson learned, as this science has evolved, is that a single summary score of quality of life may fail to reflect the diversity of chronic and late effects experienced by subsets of this population.[70] The capacity to describe and compare across diverse countries and cultures these different illness-related outcomes will be important to advancing our knowledge about and ability to effectively care for cancer survivors globally.

Dissemination Vehicles

Fortunately, as the field has grown, so too have outlets for dissemination of the findings of the emerging body of survivorship science. As noted earlier, a number of international groups now host survivorship content at their annual meetings. In 2002, the American Society of Clinical Oncology (ASCO) added a "Patient and Survivor" track to its annual proceedings. This track received increased visibility in 2005 under ASCO's then president, Dr. David Johnson, a cancer survivor himself. In collaboration with the ACS, and subsequently LIVESTRONG and the CDC, the NCI's OCS has hosted 6 Biennial Cancer Survivorship Research conferences.[42] In 2007, the *Journal of Cancer Survivorship* was launched.[71] A number of professional journals have issued special issues focused on cancer survivorship (eg, *Journal of Clinical Oncology*, *Journal of Pediatric Psychology*, *The Cancer Journal*) or contain separate sections on cancer survivorship in each volume (eg, *Pediatric Blood and Cancer*; *Cancer Epidemiology,*

Biomarkers, and Prevention). Two textbooks addressing cancer survivorship have also appeared.[72,73] Supporting the continued presentation and application of pertinent findings resulting from survivorship studies remains a pressing need. History has taught us that knowing about the problems survivors face is insufficient, but rather finding and disseminating evidence-based ways to address these must be an integral part of the science being conducted.[14]

Future Perspectives

Research for cancer survivors, while no longer in its infancy, is being challenged to keep pace with global changes in demography, the economy, and patterns of cancer-related and non-cancer-related morbidity and mortality. The evolution of novel cancer therapies and the means to deliver these are also putting pressure on the scientific community to understand the acute and long-term effects of these innovations on survivors' health and function. It is clear that to meet these demands for knowledge in a timely fashion, efforts to identify the unique strengths of specific countries to answer given questions, and to foster cross-continental collaboration whenever advantageous, will be at a premium. For example, international collaborative efforts would facilitate increased power to study less common cancers or cancer-related events, answering similar research questions in multiple populations (eg, by cancer site, health care systems, and the like), greater generalizability of research findings, and more efficient use of otherwise disjointed research funds allotted to similar causes.[74] The European Collaborative Group on Cancer Survivorship (ECGCS; www.ecgcs.eu), founded in April 2012 in Bari, Italy, hopes to do just this by bringing together European survivorship researchers and international advisors from the United States, Canada, and Australia in order to share knowledge more efficiently, reduce research fragmentation and overlap, and take advantage of larger, multinational cohorts.

Moving forward, models for research will benefit from using experiences in other related areas of health care. Although cancer may be episodic or cured for some, cancer has become or will be, for many, a chronic disease, making experiences from other fields within the health care system that deal with chronic disease increasingly relevant. In particular, the premium placed by these models on support of patient self-management of symptoms, on good patient-doctor communication, and long-term involvement in medical surveillance may be particularly helpful in structuring long-term survivorship care. Furthermore, systematic use of disability assessment may also be appropriate. For example, the International Classification of Functioning, Disability and Health (ICF) is WHO's framework for measuring health and disability at both individual and population levels.[75] The ICF is officially endorsed by all 191 WHO Member States.

A number of collaborative opportunities exist to move this science forward in an efficient and effective manner. Specific areas for future development include:

Research

- Promotion of international and collaborative research that examines mechanisms underlying development of late effects and their interindividual variability. This research should include genomic studies, which require large samples and warrant establishment of research collaboration, and should inform the development of targeted preventive and treatment programs.
- Performance of continuous surveillance to better understand the prevalence and trajectory of long-term and late effects, as well as yet-to-be-discovered late effects.
- Development of evidence-based models for risk-adapted long-term follow-up for different risk groups of survivors that consider survivor outcomes as well as cost-effectiveness and health care systems factors.
- Determining which countries have the best resources to answer specific research questions. For example, studies examining different models of care and associated outcomes/costs may be easier to conduct in Europe than in the United States, given varied health care systems across the European nations.

Infrastructure Development/Enhancement

- Establishment or expansion of national cancer registries with valid exposure data (disease variables and cancer treatment). This must include finding solutions to the challenges associated with harmonizing data across countries/registries due to differences in care delivery, differences in populations covered by health care systems, and different structures of the registries.
- Routine linkage and inclusion of patient-reported outcomes data into regional and national cancer registries.[49,52]
- Development of brief, standardized cancer-specific measures to assess patient-reported outcomes of health-related quality-of-life dimensions, symptoms, health behaviors, and comorbid conditions in cancer survivors.

- Coordination of efforts to stimulate the use of common data elements in clinical trials so that findings can be compared or combined.
- Establishment of international cohorts that can be followed and assessed at regular intervals during the patient's lifetime with the aim to examine the interaction between cancer survivorship, comorbidity, and aging.
- Application of new technologies to make convening key international players and development of new international collaborations more feasible.

Policy

- Fostering creation of unique international collaborations to share best practices in relation to policy development.
- Identification of effective communication strategies to make politicians and stake-holders aware of this rapidly growing area within health care, especially in Europe.
- Leveraging the voice of survivors/advocates to advance attention to and funding for research among and care of cancer survivors.

Conclusions

In this article, we review both the accomplishments and the lingering challenges in survivorship in the context of the growing number of cancer survivors worldwide. By providing details on the state of survivorship in both the United States and Europe, we highlight the need for and emergence of collaborative opportunities across borders. We further hope that this article will galvanize future research efforts, particularly in the realm of implementing interventions to improve the health and well-being of cancer survivors moving forward. Finally, we were tasked for this article with describing US/European activities around cancer survivorship research. A similar comparative exercise across additional regions, such as Asia, Australia, Africa, and Central and South America, may identify best practices and models to reduce cancer survivors' morbidity and mortality globally.

FUNDING SOURCES

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

REFERENCES

1. Engholm G, Ferlay J, Christensen N, et al. NORDCAN - a Nordic tool for cancer information, planning, quality control and research. *Acta Oncol*. 2010;49:725-736.
2. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. *CA Cancer J Clin*. 2012;62:10-29.
3. Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol*. 2007;8:784-796.
4. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1996-2005.
5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127:2893-2917.
6. Ries L, Smith MA, Gurney JG, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. NIH Publication 99-4649. Bethesda, MD: National Cancer Institute, SEER Program; 1999.
7. Mullan F. Seasons of survival: reflections of a physician with cancer. *N Engl J Med*. 1985;313:270-273.
8. Deimling GT, Bowman KF, Wagner LJ. Cancer survivorship and identity among long-term survivors. *Cancer Invest*. 2007;25:758-765.
9. American Cancer Society. Cancer Treatment and Survivorship Facts & Figures 2012-2013. Atlanta, GA: American Cancer Society; 2012.
10. Frieden TR, Jaffe HW, Stephens JW, Thacker SB, Zaza S; Centers for Disease Control and Prevention. Cancer Survivors - United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2011;60:269-272.
11. Smith T, Stein KD, Mehta CC, et al. The rationale, design, and implementation of the American Cancer Society's studies of cancer survivors. *Cancer*. 2007;109:1-12.
12. Hoey LM, Ieropoli SC, White VM, Jefford M. Systematic review of peer-support programs for people with cancer. *Patient Educ Counseling*. 2008;70:315-337.
13. National Research Council. Childhood Cancer Survivorship: Improving Care and Quality of Life. Washington, DC: National Academies Press; 2003.
14. Adler N, Page A. Cancer Care for the Whole Patient: Meeting Psychosocial Healthcare Needs. Washington, DC: Institute of Medicine (IOM); 2008.
15. Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press; 2006.
16. Centers for Disease Control and Prevention (CDC); the Lance Armstrong Foundation. A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies. Atlanta, GA: CDC; 2004.
17. Rich IM, Andejeski Y, Alciati MH, et al. Perspective from the Department of Defense Breast Cancer Research Program. *Breast Dis*. 1998;10:33-45.
18. Fairley TL, Pollack LA, Moore AR, Smith JL. Addressing cancer survivorship through public health: an update from the Centers for Disease Control and Prevention. *J Womens Health*. 2009;18:1525-1531.
19. Reuben SH; President's Cancer Panel. 2003-2004 Annual Report Supplement. *Living beyond cancer: A European dialogue*. NIH Publication P996. Bethesda, MD: National Institutes of Health, National Cancer Institute; 2004.
20. Khan NF, Harrison S, Rose PW, Ward A, Evans J. Interpretation and acceptance of the term 'cancer survivor': a United Kingdom-based qualitative study. *Eur J Cancer Care*. 2012;21:177-186.
21. De Angelis R, Francisci S, Baili P, et al. The EUROCARE-4 database on cancer survival in Europe: data standardisation, quality control and methods of statistical analysis. *Eur J Cancer*. 2009;45:909-930.
22. Capocaccia R, Colonna M, Corazziari I, et al. Measuring cancer prevalence in europe: the EUROPREVAL project. *Ann Oncol*. 2002;13:831-839.

23. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. *Int J Cancer*. 2002;97:72-81.
24. Commission of the European Communities. Communication from the Commission to the European Parliament, the Council, and the European Economic and Social Committee and the Committee of the Regions on Action Against Cancer: European Partnership. Publication COM(2009) 291/4. Brussels, Belgium: Commission of the European Communities; 2009.
25. Jefford M, Rowland J, Grunfeld E, Richards M, Maher J, Glaser A. Implementing improved post-treatment care for cancer survivors in England, with reflections from Australia, Canada and the USA. *Br J Cancer*. 2013;108:14-20.
26. Hawkins MM, Lancashire ER, Winter DL, et al. The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. *Pediatr Blood Cancer*. 2008;50:1018-1025.
27. Sprauten M, Darrah TH, Peterson DR, et al. Impact of long-term serum platinum concentrations on neuro- and ototoxicity in cisplatin-treated survivors of testicular cancer. *J Clin Oncol*. 2012;30:300-307.
28. Mattioli V, Montanaro R, Romito F. The Italian response to cancer survivorship research and practice: developing an evidence base for reform. *J Cancer Surviv*. 2010;4:284-289.
29. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1996-2005.
30. Rowland JH, Glidewell OJ, Sibley RF, et al. Effects of different forms of central nervous system prophylaxis on neuropsychologic function in childhood leukemia. *J Clin Oncol*. 1984;2:1327-1335.
31. Dahl AA, Haaland CF, Mykletun A, et al. Study of anxiety disorder and depression in long-term survivors of testicular cancer. *J Clin Oncol*. 2005;23:2389-2395.
32. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572-1582.
33. Pinto AC, de Azambuja E. Improving quality of life after breast cancer: dealing with symptoms. *Maturitas*. 2011;70:343-348.
34. Fossa SD, Cvancarova M, Chen L, et al. Adverse prognostic factors for testicular cancer-specific survival: a population-based study of 27,948 patients. *J Clin Oncol*. 2011;29:963-970.
35. Bhatia S. Role of genetic susceptibility in development of treatment-related adverse outcomes in cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2011;20:2048-2067.
36. Grunfeld E, Julian JA, Pond G, et al. Evaluating survivorship care plans: results of a randomized, clinical trial of patients with breast cancer. *J Clin Oncol*. 2011;29:4755-4762.
37. World Health Organization. World Health Statistics 2011. Geneva, Switzerland: WHO; 2011.
38. Niraula S, Seruga B, Ocana A, et al. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. *J Clin Oncol*. 2012;30:3012-3019.
39. D'Angio GJ. Cure is not enough. *J Pediatr Hematol Oncol*. 2005;27:508-509.
40. Eckhouse S, Castanas E, Chieco-Bianchi L, et al. European Cancer Research Funding Survey. London, UK: European Cancer Research Managers Forum; 2005.
41. National Cancer Survivorship Initiative. *Priorities for Research on Cancer Survivorship*: A Report From the National Cancer Survivorship Initiative Research Workstream. UK: Macmillan Cancer Support; 2010.
42. Rowland JH, Baker F. Introduction: resilience of cancer survivors across the lifespan. *Cancer*. 2005;104:2543-2548.
43. Alfano CM, Rowland JH. Recovery issues in cancer survivorship: a new challenge for supportive care. *Cancer J*. 2006;12:432-443.
44. van der Pal HJ, van Dalen EC, van Delden E, et al. High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol*. 2012;30:1429-1437.
45. Oeffinger KC, McCabe MS. Models for delivering survivorship care. *J Clin Oncol*. 2006;24:5117-5124.
46. Magee CE, Hillan JA, Badger SA, Kennedy RJ, Kirk SJ. Risk stratification as a means of reducing the burden of follow-up after completion of initial treatment for breast cancer. *Surgeon*. 2011;9:61-64.
47. Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract*. 2007;3:79-86.
48. Pakilit AT, Kahn BA, Petersen L, Abraham LS, Greendale GA, Ganz PA. Making effective use of tumor registries for cancer survivorship research. *Cancer*. 2001;92:1305-1314.
49. Den Oudsten BL, Traa MJ, Thong MS, et al. Higher prevalence of sexual dysfunction in colon and rectal cancer survivors compared with the normative population: a population-based study. *Eur J Cancer*. 2012;48:3161-3170.
50. Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: a growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev*. 2007;16:566-571.
51. Ashley L, Jones H, Thomas J, et al. Integrating cancer survivors' experiences into UK cancer registries: design and development of the ePOCS system (electronic Patient-reported Outcomes from Cancer Survivors). *Br J Cancer*. 2011;105(suppl 1):S74-S81.
52. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al; Profiles Registry Group. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer*. 2011;47:2188-2194.
53. Potosky AL, Warren JL, Riedel ER, Klabunde CN, Earle CC, Begg CB. Measuring complications of cancer treatment using the SEER-Medicare data. *Med Care*. 2002;40:IV-62 to IV-68.
54. Lerro CC, Stein KD, Smith T, Virgo KS. A systematic review of large-scale surveys of cancer survivors conducted in North America, 2000-2011. *J Cancer Surviv*. 2012;6:115-145.
55. Hewitt M, Breen N, Devesa S. Cancer prevalence and survivorship issues: analyses of the 1992 National Health Interview Survey. *J Natl Cancer Inst*. 1999;91:1480-1486.
56. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293:2479-2486.
57. Buettner C, Kroenke CH, Phillips RS, Davis RB, Eisenberg DM, Holmes MD. Correlates of use of different types of complementary and alternative medicine by breast cancer survivors in the nurses' health study. *Breast Cancer Res Treat*. 2006;100:219-227.
58. Institute of Medicine (IOM). A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington, DC: National Academies Press; 2010.
59. Ganz PA, Land SR, Antonio C, et al. Cancer survivorship research: the challenge of recruiting adult long term cancer survivors from a cooperative clinical trials group. *J Cancer Surviv*. 2009;3:137-147.
60. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol*. 2009;27:2308-2318.
61. Irwin ML, Crumley D, McTiernan A, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer*. 2003;97:1746-1757.
62. Fossa SD, Gilbert E, Dores GM, et al. Noncancer causes of death in survivors of testicular cancer. *J Natl Cancer Inst*. 2007;99:533-544.
63. Luckett T, King MT, Butow PN, et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. *Ann Oncol*. 2011;22:2179-2190.
64. Zebrack BJ, Ganz PA, Bernaards CA, Petersen L, Abraham L. Assessing the impact of cancer: development of a new instrument for long-term survivors. *Psychooncology*. 2006;15:407-421.
65. Khanna D, Krishnan E, Dewitt EM, Khanna PP, Spiegel B, Hays RD. The future of measuring patient reported outcomes in rheumatology: Patient-Reported Outcomes Measurement Information System (PROMIS). *Arthritis Care Res (Hoboken)*. 2011;63(suppl 11):S486-S490.
66. Badalucco S, Reed KK. Supporting quality and patient safety in cancer clinical trials. *Clin J Oncol Nurs*. 2011;15:263-265.

67. Arora NK, Hamilton AS, Potosky AL, et al. Population-based survivorship research using cancer registries: a study of non-Hodgkin's lymphoma survivors. *J Cancer Surviv*. 2007;1:49-63.
68. Weaver KE, Forsythe LP, Reeve BB, et al. Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev*. 2012;21:2108-2117.
69. Smith AW, Reeve BB, Bellizzi KM, et al. Cancer, comorbidities, and health-related quality of life of older adults. *Health Care Financ Rev*. 2008;29:41-56.
70. Reeve BB, Potosky AL, Smith AW, et al. Impact of cancer on health-related quality of life of older Americans. *J Natl Cancer Inst*. 2009;101:860-868.
71. Feuerstein M. Innovations in health care for cancer survivors: let's learn from the past. *J Cancer Surviv*. 2007;1:177-178.
72. Ganz PA. Cancer Survivorship: Today and Tomorrow. New York: Springer; 2007.
73. Feuerstein M. Handbook of Cancer Survivorship. New York, NY: Springer; 2007.
74. Elena JW, Travis LB, Simonds NI, et al. Leveraging epidemiology and clinical studies of cancer outcomes: recommendations and opportunities for translational research. *J Natl Cancer Inst*. 2013;105:85-94.
75. World Health Organization (WHO). World Health Organization: International Classification of Functioning, Disability and Health (ICF). Geneva, Switzerland: WHO; 2001.

Original Article

Population-Based Cancer Registries for Quality-of-Life Research

A Work-in-Progress Resource for Survivorship Studies?

Melissa S. Y. Thong, PhD[1,2]; Floortje Mols, PhD[1,2]; Kevin D. Stein, PhD[4,5]; Tenbroeck Smith, MA[4]; Jan-Willem W. Coebergh, MD, PhD[2,3]; and Lonneke V. van de Poll-Franse, PhD[1,2]

BACKGROUND: With the increasing number and diversity of cancer survivors, studies of survivors' physical, emotional, and social health and well being are of growing importance. Population-based cancer registries, which collect data on incident cases, can play an important role in quality-of-life (QoL) studies. In this review, the authors provide an overview of QoL studies that have used cancer registry data in this emerging area of research. **METHODS:** Publication databases were searched for relevant peer-reviewed original articles published between 2001 and mid-2011. Inclusion criteria were articles published in English that used cancer registries as the sampling frame and/or that used registry data in analyses with QoL data. All included articles were assessed on the quality of information provided, cancer registry procedures, and study design. **RESULTS:** In total, 173 articles from 13 countries were reviewed, and a large proportion were from the United States (n = 72) and Europe (n = 70). Fourteen different malignancies were studied, and the most frequent were breast cancer. Most studies focused on adult survivors, and only 4 focused on the elderly (aged >70 years). Of the reviewed articles, 110 (64%) provided a good amount of information on the cancer registry. Information less frequently reported included mainly follow-up of vital status and characteristics of respondents/nonrespondents. **CONCLUSIONS:** QoL studies increasingly use population-based registries, which provide important clinical variables and an excellent sampling frame for identifying subgroups. Until now, most studies have tended to focus on more prevalent cancers, and surprisingly few studies have focused on QoL of elderly survivors, who remain understudied in clinical trials. ***Cancer* 2013;119(11 suppl):2109-23.** © *2013 American Cancer Society.*

KEYWORDS: cancer survivors; cancer registry; health-related quality of life; population-based; symptoms.

INTRODUCTION

The number of cancer survivors worldwide is increasing because of a combination of rising cancer incidence rates and improving 5-year survival rates. Specifically, as the absolute size and proportion of the world population aged >65 years continues to grow, it is likely that the number of individuals being diagnosed with cancer also will continue to rise. In addition, advances in cancer screening, early detection, and treatment strategies have resulted in significant increases in the 5-year survival rate for all cancers combined in most industrialized countries.[1] However, despite these advances, cancer treatments often are quite debilitating and may put cancer survivors at risk for late/long-term effects, such as fatigue, cardiomyopathy, or second primary cancers.[2] Consequently, the long-term well being of cancer survivors has begun to demand increasing attention.[2,3] Clearly, more research is needed to address these issues. However, the identification and recruitment of post-treatment cancer survivors can be a challenge to conducting such studies.

One potential solution to the challenges of identification and recruitment of cancer survivors for research purposes is the use of national, state, and regional cancer registries. Cancer registries originally were developed to track incidence,

Corresponding author: Melissa S. Y. Thong, PhD, CoRPS, PO Box 90153, 5000 LE, Tilburg, The Netherlands; Fax: (011) 31 13 466 2067; m.thong@tilburguniversity.edu

[1]Center of Research on Psychology in Somatic Diseases (CoRPS) Tilburg University, Tilburg, the Netherlands; [2]Comprehensive Cancer Center South (CCCS), Eindhoven Cancer Registry, Eindhoven, the Netherlands; [3]Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands; [4]Behavioral Research Center, American Cancer Society, Atlanta, Georgia; [5]Rollins School of Public Health, Emory University, Atlanta, Georgia.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

The opinions or views expressed in this supplement are those of the authors and do not necessarily reflect the opinions or recommendations of the journal editors, the American Cancer Society, John Wiley & Sons, Inc., or the National Cancer Research Center Istituto Tumori "Giovanni Paolo II" Bari.

We thank the participants of the Eurocourse WP6 Quality of Life workgroup for their contribution: Volker Arndt, Annemarie Bouvier, Valerie Jooste, Linda Sharp, and Penny Wright.

DOI: 10.1002/cncr.28056, **Received:** August 29, 2012; **Revised:** January 22, 2013; **Accepted:** January 31, 2013, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

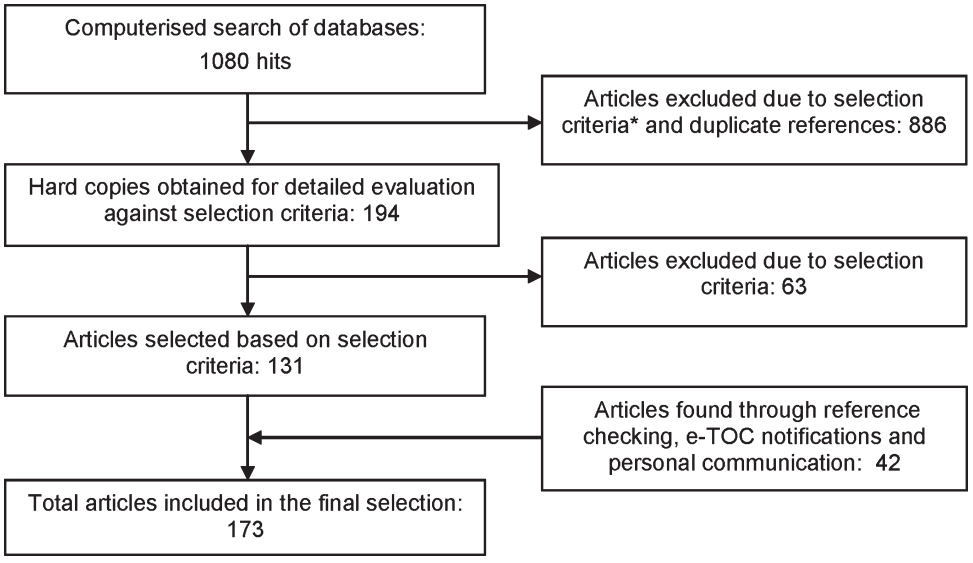

Figure 1. This is a flow diagram of articles that were accepted and rejected during the selection procedure. *The selection criteria were: studies in English, a population-based registry was used for sampling or data linkage, and the articles were published in peer-reviewed journals within the last 10 years from 2001 to mid-June 2011. e-TOC indicates electronic table of contents.

patterns of care, and cancer mortality in well defined populations.[4] Advantages of using national or regional registry data include their wide geographic reach, the inclusion of all patients/survivors regardless of treating facility, the large numbers of cancer patients/survivors they include, and the wealth of information on patients' sociodemographic and clinical characteristics available; thus, registries provide an excellent sampling frame from which to identify cases for survival studies. Because they are population-based, data from cancer registries can attain better external validity and are less likely to have problems with referral biases associated with institutional registries, especially those coming from traditional cancer centers.[5]

Quality of life (QoL) is an umbrella term that covers information on symptoms (eg pain and fatigue), functioning (eg physical functioning), health status, psychological well being, and overall QoL. Patient-reported outcomes (PROs) are the gold standard for QoL assessment and are defined as data provided by the patient without amendments or interpretation from clinicians or others.[6] QoL assessed using PROs is now recognized as an indicator of treatment efficacy, because many new treatments offer only marginal improvements in survival. The US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products have recently acknowledged the essential role of QoL and PROs in clinical trials.[7,8] The US National Cancer Institute is encouraging the use of QoL and PRO assessment as primary and secondary endpoints in clinical trials when appropriate.[9,10] PRO is also an important tool for measuring long-term outcomes among post-treatment survivors—especially QoL and symptoms—in a patient-centered way.[11]

The stated advantages of using cancer registry data in survival studies are also applicable to QoL studies.[12] These QoL studies can investigate the prevalence of late/long-term effects of cancer and its treatment, identify groups of survivors at increased risk for such effects, and identify the risk factors for developing such effects. By providing externally valid data that describe the prevalence of and risk factors for late/long-term effects, registry-based QoL studies can inform efforts to improve the quality of care of cancer survivors and to design interventions that improve their QoL.[2] Such information could be used to develop interventions to reduce inequities in cancer care and improve patients' well being after diagnosis and treatment.[13] The objectives of this review were to provide a broad overview of QoL studies among cancer survivors that use cancer registry data; to describe the issues, procedures, and regulations that are relevant to these studies in Europe and the United States; and to discuss approaches to optimizing the use of cancer registries in QoL cancer survivor studies.

MATERIALS AND METHODS

Search Strategy

We conducted a computerized literature search in July 2011 for articles published between 2001 and mid-June

TABLE 1. Checklist of Information Provided in Registry-Based, Quality of Life Articles (n = 173)

Criteria	No. of Articles That Met Criterion (%)
Description of cancer registry	
1. Geographic name and location of the registry are provided	158 (91)
2. Coverage of the cancer registry; "population-based" is stated in title, abstract, or text	150 (87)
3. Variables available from the cancer registry are described (eg patient demographics, stage, grade, primary treatment)	107 (62)
4. The registry performs active follow-up of patients' vital status	66 (38)
Study population	
5. Cancer registry used as a sampling frame or linkage of QoL data with clinical and/or demographic data from the cancer registry after sample inclusion	169 (98)
6. Description of the sampling process	165 (95)
7. Description of inclusion/exclusion criteria	170 (98)
8. Participation rates for patient groups are described and are >70%	73 (42)
9. Information on the characteristics of respondents vs nonrespondents	101 (58)
Study design	
10. The study size is at least 100 patients/survivors	165 (95)
11. Data registered by the cancer registry are used in the analyses (eg stage, grade, primary treatment)	105 (61)
12. Validated PRO assessments (health-related quality of life, health status, symptoms, functioning) are used	170 (98)

Abbreviations: PRO, patient-reported outcome; QoL, quality of life.

2011. We restricted our search to this time frame because most of the articles were published in the last decade. Searches on PubMed using the Medical Subject Heading (MeSH) terms ("neoplasms" [MeSH] AND "registries" [MeSH] AND "quality of life" [MeSH]; and ("neoplasms" [MeSH] AND "quality of life" [MeSH] AND "population-based") and searches of the PsycInfo and Medline databases using the combinations of "quality of life" and "cancer" with "registry" or "population-based" were carried out.

Selection Criteria

Only studies that used population-based cancer registries were included; most studies used the registry as a sampling frame and source of clinical data, whereas other "linkage" studies used the registry only as a source of data. Cancer registries could be regional or national or could be specialized registries, like those focused on childhood and hematologic malignancies or gastrointestinal cancer. Studies that used data from a single-site registry or clinical databases (for example, a hospital registry or database) were excluded. The search was limited to original articles in English that were published in peer-reviewed journals.

The search terms produced 1080 initial hits. Of these, a review of the titles or abstracts revealed that 886 articles were either duplicates or did not meet our inclusion criteria. The remaining 194 articles were downloaded for further evaluation. Of these, 131 met eligibility criteria for this study. Reasons for further excluding 63 articles included the use of registries that were not population-based, methodology articles, or qualitative reports. Another 42 articles were identified through reference checking, electronic table-of-contents notification, or personal communication. In total, 173 articles were selected for this review (Fig. 1).

For each of the 173 selected articles, we quantified the amount of information reported regarding the cancer registry, the study population, and the study design. Two authors (M.S.Y.T. and F.M.) conducted the assessment using a 12-point standardized checklist modified from established criteria for systematic reviews (Table 1).[14-16]

First, the articles were assessed independently; then, the results from reviewers were compared. The reviewers agreed on the ratings of most criteria. Four of the criteria (Table 1, criteria 3, 4, 6, and 10) generated disagreement between the 2 reviewers (M.S.Y.T. and F.M.), mainly because of differences in interpretation with criteria 3 and 4 relating to the data recorded by the cancer registry, its use in the analyses, and information on the sampling process. Differences in interpretation were resolved through consensus meetings.

A total score was generated for each article by awarding 1 point for each criterion met. If the information provided in the article did not meet the criterion, was insufficiently described, or was not provided, then that criterion was scored zero. Thus, an article could score a maximum of 12 points. Articles that scored $\geq$9 points on the description checklist were considered to have "good" descriptions. Articles that scored between 6 and 8 points were rated as "moderate," and those that scored $\leq$5 points provided "insufficient" descriptions.

RESULTS

Characteristics of the reviewed articles, including references, are outlined in Table 2. Of the 173 reviewed articles, 39% reported on independent samples. The remaining 61% involved 2 to 8 articles per sample, and most came

TABLE 2. Characteristics of Included Studies (n = 173)

Characteristic	No. of Articles	Reference(s)
Sample		
Independent	65	44-108
Repeat	108	109-216
Design		
Longitudinal	55	28, 34, 51, 62, 72-74, 80, 82-128
Cross-sectional	118	44-54, 56-60, 62-77, 79-88, 90-98, 102-106, 108, 109, 118-124, 128-131, 137-139, 145, 146, 148, 150, 153, 155-157, 160, 161, 163, 169-182, 187, 188, 190-194, 198, 200, 201, 203-206, 209-215
Country of article(s)		
North America		
USA	72	18-20, 22, 25, 26, 29-33, 37-39, 41-44, 54, 56-58, 62, 67, 68, 73-75, 79, 80, 82, 83, 90-92, 103, 105, 106, 110, 115-123, 125-148
Canada	10	48, 62, 78, 90, 92, 98, 108, 123, 200, 201
Europe		
Netherlands	23	80, 104, 109, 153, 163, 173-182, 203-206, 209-212
Germany	19	96, 97, 105, 112-117, 140-144, 154, 158, 159, 169, 170, 217
Sweden	13	51, 54, 74-76, 82, 139, 191-194, 213, 214
Norway	7	63, 72, 129-131, 160, 161
France	4	55, 77, 79, 86
Finland	1	88
Denmark	1	91
Italy	1	44
France and Italy	1	67
Australasia		
Australia	13	50, 61, 87, 93, 99, 136-138, 149, 166, 167, 190, 199
China	7	103, 132-135, 164, 165
Japan	1	73
Survivorship		
Short (<5 y)	78	47, 48, 50, 55, 56, 64-66, 69, 76, 81, 83-85, 87, 89, 93, 94, 96, 98-108, 111-116, 118-122, 125, 128, 132, 133, 136-139, 141, 142, 147-149, 155-157, 160, 161, 164-168, 183, 185, 186, 189-192, 196, 197, 199, 213-216
Long (≥5 y)	51	44, 45, 49, 51, 54, 57, 58, 60, 63, 67, 71, 73, 75, 77, 79, 86, 88, 91, 92, 97, 109, 117, 126, 127, 140, 143-145, 151, 152, 162, 163, 173-176, 178-182, 184, 195, 203, 204, 207-212
Short and long	44	46, 52, 53, 59, 61, 62, 68, 70, 72, 74, 78, 80, 82, 90, 95, 110, 123, 124, 129-131, 134, 135, 146, 150, 153, 154, 158, 159, 169-172, 177, 187, 188, 193, 194, 198, 200-202, 205, 206
Special patient samples		
Children and adolescents	1	211
Adult survivors of childhood or adolescent cancer	5	44, 75, 88, 92, 97
Elderly (aged >70 y)	4	55, 151, 162, 175
Rural population	4	29, 74, 187, 188
Types of cancer		
Breast	56	46, 53, 57-59, 64, 66, 74, 76, 79, 83, 87, 91, 95, 104-106, 108, 110, 111, 113, 115-117, 119-121, 125-128, 132-138, 140, 143, 144, 149, 155-157, 159, 164, 165, 168-170, 181, 190, 197, 210, 216
Colorectal	24	55, 67, 72, 73, 90, 100, 107, 112, 114, 129-131, 142, 154, 158, 166, 167, 187, 188, 195, 199, 205, 206, 208
Prostate	20	94, 99, 101, 109, 147, 151, 152, 160, 161, 174, 178, 180, 183-186, 193, 194, 204, 207
Bladder	3	45, 78, 86
Testis	2	63, 77
Thyroid	1	82
Retinoblastoma	2	211, 212
Melanoma	3	96, 153, 177
Laryngeal	1	81
Central nervous system	2	54, 75
Extracranial malignancies	1	88
Gynecologic cancers		
Cervical	6	47, 49, 51, 68, 71, 80
Ovarian	3	93, 200, 201
Endometrial	2	62, 209
All 3 gynecologic cancers	1	50
Upper gastrointestinal		
Esophagus	5	139, 191, 192, 213, 214
Gastric	1	103
Lymphoma		
Non-Hodgkin	3	65, 124, 173
Hodgkin	1	182
Various cancers (≥2 types of cancers)	36	44, 48, 52, 56, 60, 61, 69, 70, 84, 85, 89, 92, 97, 98, 102, 118, 122, 123, 141, 145, 146, 148, 150, 162, 163, 171, 172, 175, 176, 179, 189, 196, 198, 202, 203, 215

TABLE 3. Summary of Current Methods for Sampling Quality-of-Life Studies Using Cancer Registry Data

Sampling Method	Example	Positive	Negative	Considerations
Identify survivors through cancer registry before sending PRO	ACS-SCS, PROFILES	• Population-based • Compare the clinical and demographic characteristics of respondents with nonrespondents • Create samples with specific medical characteristics (eg cancer or treatment type) • Create samples of patients with rare cancers	Bias (survival, response)	• Patient contact procedures (informed consent from patients and physicians) • Coverage of cancer registry; length of time between diagnosis and registration • Amount and quality of collected clinical and demographic data • Follow-up of vital status by cancer registry—allow for tracking of patients
PRO collected before linkage with cancer registry	IWHS; MHOS; ePOC	• Identify incident cancer patients at diagnosis • (Possible) availability of PRO before cancer diagnosis	Bias (survival, response)	• Population-based

Abbreviations: ACS-SCS: American Cancer Society's Studies of Cancer Survivorship[12]; ePOCS, electronic Patient-Reported Outcomes From Cancer Survivors[28,29]; IWHS, Iowa Women's Health Study (available at: http://www.cancer.umn.edu/research/programs/peiowa.html, last accessed 15 March 2013); MHOS, Medicare Health Outcomes Survey (available at: http://outcomes.cancer.gov/surveys/seer-mhos, last accessed 15 March 2013); PRO, patient-reported outcome; PROFILES, Patient-Reported Outcomes Following Initial Treatment and Long-Term Evaluation of Survivorship.[18]

from the Prostate Cancer Outcomes Study. Most studies were either cross-sectional in design, whereas 55 articles reported on longitudinal data.

Countries of Articles

Certain countries were more prolific in QoL research using cancer registries. Of the included articles, 72 were from the United States. A significant number of articles also came from Canada (n = 10). Many articles (n = 70) came from Europe, including 23 from the Netherlands, 19 from Germany, and 13 from Sweden. Seven Norwegian articles and 4 French articles were identified, whereas 1 publication each came from Finland, Denmark, and Italy. One publication reported on results using data from 2 European registries in France and Italy. From the Australasia region, there were 13 Australian publications. Few articles came from Asia, 7 came from China, and 1 came from Japan. We identified no articles from Africa or South America.

Sample Characteristics

Most articles (n = 78) focused on patients who were <5 years from diagnosis ("short-term survivors"). Fifty-one articles focused on long-term survivors (≥5 years since diagnosis), whereas 44 articles included both short-term and long-term survivors.

In general, all articles sampled adult survivors of cancer, except for 1 article on pediatric survivors and 5 articles on adult survivors of childhood or adolescent cancers. Only 4 articles reported on the outcomes of elderly cancer survivors based on the European Society for Medical Oncology definition of elderly oncology patients (aged >70 years at diagnosis).[17] Only a few articles used registry data to report on underserved populations, like those living in rural areas.

Types of Cancer

Studies on breast cancer survivors dominated with 56 articles, and studies of prostate cancers were the next most common (n = 20). Other specific cancers studied included bladder (n = 3), testis (n = 2), thyroid (n = 1), retinoblastoma (n = 2), melanoma (n = 3), laryngeal (n = 1), central nervous system (n = 2), and extracranial malignancies (n = 1). Of the 12 articles on gynecologic cancers, there were 6 on cervical cancer, 3 on ovarian cancer, 2 on endometrial cancer, and 1 on all 3 gynecologic cancers. For upper gastrointestinal cancers, there were 5 articles on esophageal cancer and 1 on gastric cancer. Four articles focused on patients with lymphomas, including 3 articles on non-Hodgkin lymphoma and 1 article on Hodgkin lymphoma. The remaining 36 articles included 2 or more cancer types, which were often combinations of high-prevalence cancers of the colon or rectum, breast, prostate, or the lymphomas.

Assessment of Information Provided

Assessment of the amount of information provided on the cancer registry, study population, and design yielded the following results: the summary score, which was a summation of the number of criteria each article met, ranged from 5 to 12. According to this rating system, 110 articles provided a good amount of information (9-12 points), 59 articles provided a moderate amount of information (6-8

points), and 4 articles provided an insufficient amount of information (≤5 points). The most common insufficiencies were a lack of information on the follow-up of vital status (Table 1, criterion 4), a lack of information on the characteristics of respondents and nonrespondents (criterion 9), and a response rate that was either unreported or <70% (criterion 8). These shortcomings also occurred among highly rated articles (Table 1).

Cancer Registry Information

Information on the cancer registry provided in the Methods section of each reviewed article varied in detail and length. Some reports described the mandate, coverage, and tracking system of the cancer registry, whereas others provided only the name of the cancer registry.

Description of cancer registry

Most articles provided the name of the cancer registry from which its sample was selected, thus giving an indication of the geographic coverage of the registry (Table 1, criterion 1). The articles that did not name the registry (9%) often indicated that the data source was a state-wide cancer registry or a group of several registries. Similarly, most authors (87%) explicitly stated that their sample was selected from a population-based registry (Table 1, criterion 2). Otherwise, authors either provided the name of a cancer registry known to be population-based or indicated that the cancer registry used was part of the Surveillance, Epidemiology, and End Results (SEER) registry system in the United States, which is population-based. Over one-third (38%) of the articles did not provide a description of the clinical variables available from the registry (such as stage, grade, or primary treatment) (Table 1, criterion 3). Follow-up of patients' vital status by the registry, which refers to whether the registry actively tracks the vital status (alive or not) of the patients in the registry, either was not reported or was not clearly stated in 38% of the articles (Table 1, criterion 4).

Data used from registry

In 98% of articles, registries were used as a sampling frame or for data linkage (Table 1, criterion 5). Of the 2% of articles that did not meet criterion 5, all reported on follow-up assessments. Although registries were most often used as a sampling frame, there were exceptions. For example, if legislation did not allow registries to be used for sampling or if rapid patient identification for study eligibility was necessary, then clinical data from the participating patients were abstracted from the relevant registry after informed consent and were then merged with PRO data.

In addition to sampling, clinical data from the registry, such as date of diagnosis and cancer stage, were commonly accessed for use in the analyses (Table 1, criterion 11). Although most articles included clinical data in the analyses, only 61% clearly described which variables came from the registry.

Sampling Process

Most articles (95%) described the sampling process (criterion 6). Similarly, nearly all articles (98%) provided inclusion/exclusion criteria used in the study (criterion 7). Those articles that did not provide information regarding these 2 criteria referred to previous publications.

Response Rates and Characteristics of Respondents and Nonrespondents

Only 42% of the articles (n = 71) reported a response rate >70% (criterion 8). Over half of the articles (n = 101) described the sample selected and compared the clinical/demographic characteristics of respondents and nonrespondents (Table 1, criterion 9). The vast majority of articles (95%) had sample sizes greater than 100 survivors (Table 1, criterion 10).

Use of Validated Patient-Reported Outcome Instruments

Almost all articles used validated PRO instruments to assess QoL (Table 1, criterion 12). Only 3 articles did not get a score on this criterion. One article reported that a 21-item questionnaire was used to assess QoL, whereas another used a computer-assisted telephone interview to assess the presence of symptoms that interfered with daily mood or function, and a third reported data collected from a questionnaire that was also used in a normative population.

Given the wide range of instruments used in assessing QoL, only a few of the most commonly used are mentioned here. For the assessment of general QoL, the most commonly used instrument was the Medical Outcome Study 36-item short-form health survey (SF-36). For disease-specific QoL, the European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy (FACT) were the most commonly used questionnaires.

DISCUSSION

In overview, we identified 173 articles published between January 2001 and June 2011 that assessed the QoL of

cancer survivors with the assistance of a cancer registry. Most articles scored high on the amount of information provided on the cancer registry, study population, and study design. However, data on the follow-up of vital status provided by the cancer registry was the least often reported element of our assessment in these reports. Response rates for the included articles varied from 91% to 24%, and the majority fell below 70%.

Sampling-Related Issues

Tumor registries vary in their procedures for identifying and following cancer patients,[19] which was also exhibited in this review. A significant proportion of cancer registries do not routinely update contact information (eg address, telephone number) after the patient is entered into registry records. Consequently, locating cancer survivors may be difficult at times, particularly for those who are further out from diagnosis or those who have moved from the original address at which they resided at the time of diagnosis. This is reflected by the reality that longer term survivors are less likely to respond to questionnaires than shorter term survivors.[12] This may explain in part why only 73 studies (42%) reported a response rate >70%. Efforts to update both vital status and contact information should be important considerations in QoL research that uses cancer registry records. Indeed, conducting research using those registries that routinely update contact information and vital status of patients in their databases may offer significant advantages.

Lack of vital status follow-up information in these studies raises the question of how representative the sample was and also the differences in characteristics of respondents, nonrespondents, and those who have died. Vital status follow-up is essential for studies in which death is a primary outcome. For example, loss of patients to death can introduce major bias in case-control studies when a dose-response relation causes patients with greater exposure to die sooner. Although vital status information and loss of patients to death are less important in QoL studies with primary outcomes like as symptoms, functioning, and overall QoL, the provision of vital status information (if routinely collected by the cancer registry) is good practice, because it indicates the representativeness of the sample.

A large proportion of the articles covered common malignancies, such as breast, colorectal, or prostate cancers. It is worth noting that we identified no articles on less common malignancies, such as hepatobiliary or pancreatic cancers; the high mortality rate of these cancers may make it difficult to accrue samples. Also, there are relatively few articles specifically focusing on the QoL of the elderly, although they are more likely to be diagnosed with cancer than younger individuals. Because cancer is more likely to occur among older individuals, study samples are likely to contain significant numbers of elderly survivors; however, articles rarely focused on this group. The use of cancer registry data to study the QoL of elderly survivors will be important, because they often are understudied or are not included in clinical studies. Since the review selection for the current study was completed (July 2011), several articles on the physical and emotional functioning of elderly cancer survivors have been published using data from the American Cancer Society's Studies of Cancer Survivorship (ACS-SCS) project.[20,21]

Only 62% of the articles provided information on the clinical data routinely collected by cancer registries, such as stage and grade of cancer at diagnosis or primary treatment. Although most articles did include clinical data in their analyses, a substantial minority did not specify whether these were registry data. Similar to survival studies, high-quality clinical data from registries also are important for QoL studies, but the quality of data may vary within and across registries. Consistent with the goal of tracking cancer incidence, the quality of registry data on diagnosis is generally excellent. In contrast, the quality of data on stage or receipt of adjuvant treatments may be lower and may be related to patient or cancer center characteristics.[22-25] Researchers should take into account the strengths and weaknesses of the data at the specific registry they are using when designing studies, conducting analyses, or interpreting results.

Although the majority of studies used validated scales to assess QoL, the wide range of measures used makes it difficult to compare results between studies or to encourage collaboration between different research organizations. Incidence and survival data traditionally collected by cancer registries are readily merged across registries or research organizations, because they have broadly accepted, uniform definitions. This facilitates the study of trends in cancer incidence, survival, and treatment effectiveness at national and international levels. However, QoL comparisons among samples from different registries are more challenging not only because of variations of care but also because of differences in the QoL instruments used. With QoL increasingly becoming accepted as a routine endpoint in assessing treatment efficacy, some have suggested that a core set of QoL data should be part of the regular data collected for effectiveness and should be recorded by cancer registries. Naturally, this idea raises questions. What constitutes core

QoL data? How should the cancer registry collect such information? Along these lines, in the United States, the National Institutes of Health have developed a publicly available set of QoL assessment tools referred to as the Patient-Reported Outcome Measurement Information System (PROMIS). Built on the World Health Organization framework, PROMIS includes a core set of items that assess several QoL domains, such as pain, fatigue, depression, and physical function.[26] Among the goals of PROMIS is to increase standardization and data harmonization in QoL assessments. Another initiative is the Grid Enabled Measures (GEM) database by the US National Cancer Institute (www.gem-beta.org). GEM is a dynamic, web-based database that was designed to organize PRO measures by theoretical constructs and to facilitate the exchange of harmonized data.

Models of Registry-Based Quality-of-Life Studies

The vast majority of articles used 1 of the 2 models of registry-based studies (for a summary, see Table 3). Most of the articles reported using a cancer registry as a sampling frame. Those studies used the registry to identify and sample cancer survivors before sending a questionnaire to collect QoL data. Examples of studies using this model are reports from the ACS-SCS project[12] and publications from the PROFILES registry in the Netherlands.[18] The other commonly used model collects sample participants before linking with the registry. The Iowa Women's Health Study (IWHS) is an example of this second common model. In that sample, women ages 55 to 69 years from the Iowa drivers' license register were randomly sampled to complete a self-reported questionnaire on QoL and other factors (http://www.cancer.umn.edu/research/programs/peiowa.html). This cohort is then linked with the SEER cancer registry annually to identify incident cancer cases. Regardless of the strengths of these methods, both methods will have to contend with issues of survival and response bias.

The first model, which uses registry data as a sampling frame, has several advantages. Because these registries are population-based, the studies using this model have the potential to achieve excellent external validity. Because the registry provides a limited set of medical and demographic variables on everyone who was sampled, it enables the investigator to assess bias by comparing respondents with nonrespondents.[19] However, only 58% of the articles in our review provided such information. Given the large number of cancer survivors contained in registries, investigators can assemble samples with specific demographic, disease, and/or treatment characteristics. This is important, because the issues faced by cancer survivors vary widely, depending on these characteristics. Registries also can enable investigators to assemble samples of less common or even rare cancers, which would be difficult at individual hospitals.

An advantage of using the second model, which samples participants before linkage with a cancer registry, is the possibility of including participants and the collection of QoL data *before* the cancer diagnosis. The availability of QoL data before the participant is diagnosed with cancer allows the assessment of changes in QoL as a result of the disease and/or treatment.

Although both models have to contend with issues of survival and response bias, another consideration for the second model is the degree to which the sample collected is sufficiently population-based. Other considerations salient to both models include the geographic coverage of the cancer registry, the amount and quality of data registered by the cancer registry, and whether the registry conducts regular vital status follow-up and updates contact information of the registered patients.

Using Cancer Registries in Quality-of-Life Research

Currently, there is much discussion regarding whether cancer registries should be involved in approaching survivors for collecting QoL data. Unfortunately, such a proposal may not be feasible for most countries in the European Union, because direct contact with cancer survivors for QoL studies is not allowed without first obtaining consent from or providing notification to the attending (and reporting) physician. In the United States, each state has its own regulations for registry operations such as physician and patient contact procedures. For example, some states require physician consent before recruitment of their current or former patient. Investigators conducting the ACS-SCS used data from their study to demonstrate that obtaining written physician consent reduced response rates sufficiently to convince registry staff in 3 states to abandon the requirement of physician consent and to use physician notification instead.[12] Furthermore, research suggests that most patients (87%) do not want physicians to decide whether they will be approached for a study.[27] Researchers may consider suggesting changes to registry policies, especially when they have data to support their request. Because of the (sometimes great) variability in registry laws and regulations, the adoption of national standards around collecting QoL data represents a significant challenge. This barrier likely

could be overcome by pilot projects demonstrating the safety and utility of collecting QoL data.

Common barriers to using cancer registries to conduct QoL research include issues with patient sampling and recruitment that have adequate response rates. In the United States, concerns around privacy and the use of publicly reportable data for patient follow-back studies are sometimes cited as barriers to registry-based QoL research. Although cancer registries often have a mandate to collect clinical data, such as date of diagnosis or cancer characteristics from pathology reports and medical records, this mandate frequently does not extend to initiating the contact with patients necessary for QoL studies. Including the attending physicians with interests in QoL into the study can circumvent the problem and facilitate access to patients. However, this may also vary in relation to the regional organization of the participating physician and may be reflected in the response rate to studies. Another consideration is that physicians may not always be an adequate source of information of survivors' current eligibility or ability to complete a survey. This pertains especially to situations in which data on survivors are sampled years after diagnosis and the registry no longer maintains follow-up with their initial treating physician. Regardless of the methods used, the collection of QoL data are outside the current scope of registry operations, and additional funding would be required for registries to engage in this activity.

Another consideration is the amount and quality of data registered by the cancer registry. In Europe, both the European Network of Cancer Registries (ENCR), now with a common data portal for quality control, and the EUROCARE (EUROpean CAncer REgistry-based study on survival and care of cancer patients) project focus on the standardized reporting of population-based survival data. EUROCARE, which started in 1989 with 13 population-based cancer registries in the European Union, has now expanded to almost 100 registries that, all together, cover 13 million patients with newly diagnosed cancers (www.eurocare.it), whereas ENCR comprises almost 200 registries. Nevertheless, data incompleteness remains an issue, and ENCR has guidelines to ensure completeness of data reporting by the participating registries (www.encr.com.fr). The US equivalents would be the National Program of Cancer Registries (NPCR) and the SEER registry. The NPCR, which is administered by the Centers for Disease Control and Prevention, supports state cancer registries and represents data from 96% of the US population (http://www.cdc.gov/cancer/npcr/). The SEER registry was started in 1973 to collect complete and accurate data on cancer cases and currently covers approximately 28% of the US population (http://seer.cancer.gov/).

The registry-based collection of QoL data also requires specifying the time point after diagnosis or treatment at which to recruit survivors and, for longitudinal studies, the frequency of follow-up. After all, cancer survivors experience changes in QoL over time, depending on where they are on the survivorship trajectory. Another challenge of using cancer registries in QoL studies is the lack of information on patients' status before cancer. However, this problem can be overcome with a design like that of the IWHS, which links data collected through a large population-based cohort with data from of a cancer registry.

Despite these barriers, growing interest in cancer survivorship within the European Union and the United States is pushing the cancer registries in the direction of addressing QoL. In the European Union, the "EUROpe Against Cancer: Optimization of the Use of Registries for Scientific Excellence in research" (EUROCOURSE) project (www.eurocourse.org) was started to optimize the use of cancer registries in outcome research. Under the auspices of EUROCOURSE, European cancer registries discussed the feasibility of collecting QoL data within cancer registries. In September 2011, EUROCOURSE organized a 2-day workshop that was attended by investigators from France, Germany, Ireland, the Netherlands, and the United Kingdom who were active in the field of QoL research using cancer registry data. In the United States, SEER and NPCR registries have begun to explore different mechanisms to integrate registry-based data with QoL data. Specifically, efforts have been made to link SEER registry data with several publicly available data sets to allow for the examination of QoL in the context of cancer cases that are identified through cancer registry databases. For example, SEER data have been linked with Medicare data, providing mechanisms for epidemiologic and health services research with cancer patients and survivors aged >65 years who are enrolled in Medicare (http://healthservices.cancer.gov/seermedicare). In addition, SEER data have been linked with the Medicare Health Outcomes Survey (MHOS), allowing for the investigation of QoL data from cancer patients and survivors who are enrolled in the Medicare Advantage health plans (http://outcomes.cancer.gov/surveys/seer-mhos). These 2 initiatives mark an increasing recognition in the United States of the importance of PROs and the value that cancer registry data can bring to QoL research studies.

Patient-Reported Outcomes Registries

In addition to the possibility of cancer registries collecting patient-reported data, such as QoL, current developments include the setting up of separate psychosocial registries that collect QoL data from cancer survivors. Examples of such registries in Europe include the PROFILES registry from the Netherlands[18] and the electronic Patient-Reported Outcomes from Cancer Survivors (ePOCS) registry from North and West Yorkshire in the United Kingdom.[28,29] These 2 registries collect QoL data, which then are merged with cancer registry data to provide a more in-depth commentary on patients' survivorship trajectory. The sampling process of both registries differs; PROFILES uses the cancer registry as a sampling frame to approach cancer survivors and, thereafter, to link the collected QoL with cancer registry data. For ePOCS, a hospital-based and clinician-led approach is used for patient recruitment, after which, the collected QoL data are linked with clinical data from the cancer registry. The number of QoL publications (n = 13) from the PROFILES registry since mid-2011 attest to the value of linking QoL data with data from a cancer registry.[30-42] Further details of the PROFILES registry and the open-access policy to its data can be obtained at www.profilesregistry.nl. Several such registries also have been developed in the United States. The Psychosocial Data Registry from the Ireland Cancer Center in Cleveland, Ohio has the goal of collecting QoL data from new patients and family caregivers at diagnosis and following them through the entire cancer experience.[43] Another example is the Breast Cancer Mind Affects the Physical (M.A.P.) Project conducted by the Cancer Support Community (http://www.breastcancerregistry.org). To date, over 3500 women with a history of breast cancer from across the United States and over 30 countries have voluntarily enrolled in the registry and have completed self-report surveys on their physical and psychosocial health.

In this overview, we provide important information regarding the use of cancer registries in QoL research. However, there are some limitations that should be addressed. Although main search engines were used to find relevant articles in a systematic manner, this search may not have been exhaustive. Using the PubMed MeSH term "quality of life" may have excluded studies that did not use this term as a keyword. Nevertheless, the proportion of duplicate references eliminated from the initial searches (82%) suggests that the included articles are representative of the publications on this topic. Furthermore, the large number of articles included in this overview limited detailed descriptions of methodology and the scope of topics covered, which should be done in relation to the content of individual articles.

Conclusions

Population-based cancer registries are used in QoL studies covering a range of cancers. Nevertheless, there is room for improvement. Cancer registries are an underused resource for cancer survivorship studies, especially with regard to patients who have rare cancers, patients who have specific disease and treatment profiles, or the elderly, who are understudied in clinical trials. Furthermore, registry-based QoL studies have the advantage of drawing population-based samples with the potential for providing the best possible external validity. Because the majority of the articles identified in our search were conducted in Europe and the United States, future directions might include an international meeting to discuss relevant results, common concerns, and best practices for registry-based QoL research.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

The current research was supported in part by intramural funding from the American Cancer Society as well a Social Psychology Fellowship from the Dutch Cancer Society to Dr. Thong (UVT2011-4960), a Veni grant (451-10-041) from the Netherlands Organization for Scientific Research (The Hague, the Netherlands) awarded to Dr. Mols, a EUROCOURSE Health-F2-2008-219453 grant awarded to Comprehensive Cancer Center South, and a Cancer Research Award from the Dutch Cancer Society (UVT-2009-4349) to Dr. van de Poll-Franse. The funding sources were not involved in the collection, interpretation, or analysis of the data or in the decision to write or submit this report for publication.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. American Cancer Society. Global Cancer Facts & Figures. 2nd ed. Atlanta, GA: American Cancer Society; 2011.
2. Ganz PA. Why and how to study the fate of cancer survivors: observations from the clinic and the research laboratory. *Eur J Cancer*. 2003;39:2136-2141.
3. Oberguggenberger A, Hubalek M, Sztankay M, et al. Is the toxicity of adjuvant aromatase inhibitor therapy underestimated? Complementary information from patient-reported outcomes (PROs). *Breast Cancer Res Treat*. 2011;128:553-561.

4. Armstrong BK. The role of the cancer registry in cancer control. *Cancer Causes Control*. 1992;3:569-579.
5. Su D, Jang TL. Using large institutional or national databases to evaluate prostate cancer outcomes and patterns of care: possibilities and limitations. *ScientificWorldJournal*. 2011;11:147-160.
6. US Department of Health and Human Services. Food and Drug Guidance for Industry. Patient-reported outcome measures. Use in medical product development to support labeling claims. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed August 4, 2011.
7. Gondek K, Sagnier P-P, Gilchrist K, et al. Current status of patient-reported outcomes in industry-sponsored oncology clinical trials and product labels. *J Clin Oncol*. 2007;25:5087-5093.
8. Rock EP, Kennedy DL, Furness MH, et al. Patient-reported outcomes supporting anticancer product approvals. *J Clin Oncol*. 2007;25:5094-5099.
9. Clauser SB, Ganz PA, Lipscomb J, et al. Patient-reported outcomes assessment in cancer trials: evaluating and enhancing the payoff to decision making. *J Clin Oncol*. 2007;25:5049-5050.
10. Lipscomb J, Reeve BB, Clauser SB, et al. Patient-reported outcomes assessment in cancer trials: taking stock, moving forward. *J Clin Oncol*. 2007;25:5133-5140.
11. Ayanian JZ, Jacobsen PB. Enhancing research on cancer survivors. *J Clin Oncol*. 2006;24:5149-5153.
12. Smith T, Stein KD, Mehta CC, et al. The rationale, design, and implementation of the American Cancer Society's Studies of Cancer Survivors. *Cancer*. 2007;109:1-12.
13. Sanson-Fisher R, Carey M, Mackenzie L, et al. Reducing inequities in cancer care: the role of cancer registries. *Cancer*. 2009;115:3597-3605.
14. Borghouts JAJ, Koes BW, Bouter LM. The clinical course and prognostic factors of nonspecific neck pain: a systematic review. *Pain*. 1998;77:1-13.
15. Kuijpers T, van der Windt DA, van der Heijden GJ, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. *Pain*. 2004;109:420-431.
16. Scholten-Peeters GGM, Verhagen AP, Bekkering GE, et al. Prognostic factors of whiplash-associated disorders: a systematic review of prospective cohort studies. *Pain*. 2003;104:303-322.
17. Kristjansson SR, Wyller TB. Introduction. In: Schrijvers D, Aapro M, Zakotnik B, et al, eds. ESMO Handbook of Cancer in the Senior Patient. London, United Kingdom: Informa Healthcare; 2010:1-5.
18. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer*. 2011;47:2188-2194.
19. Pakilit AT, Kahn BA, Petersen L, et al. Making effective use of tumor registries for cancer survivorship research. *Cancer*. 2001;92:1305-1314.
20. Bellury L, Pett MA, Ellington L, et al. The effect of aging and cancer on the symptom experience and physical function of elderly breast cancer survivors. *Cancer*. 2012;118:6171-6178.
21. Bellury LM, Ellington L, Beck S, et al. Older breast cancer survivors: can interactive analyses identify vulnerable subgroups? A report from the American Cancer Society's Studies of Cancer Survivors. *Oncol Nurs Forum*. In press.
22. Cress RD, Zaslavsky AM, West DW, et al. Completeness of information on adjuvant therapies for colorectal cancer in population-based cancer registries. *Med Care*. 2003;41:1006-1012.
23. Du XL, Key CR, Dickie L, et al. Information on chemotherapy and hormone therapy from tumor registry had moderate agreement with chart reviews. *J Clin Epidemiol*. 2006;59:53-60.
24. Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from 1 county in Denmark. *Eur J Cancer Prev*. 2002;11:359-364.
25. Malin JL, Kahn KL, Adams J, et al. Validity of cancer registry data for measuring the quality of breast cancer care. *J Natl Cancer Inst*. 2002;94:835-844.
26. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first 2 years. *Med Care*. 2007;45:S3-S11.
27. Beskow LM, Sandler RS, Millikan RC, et al. Patient perspectives on research recruitment through cancer registries. *Cancer Causes Control*. 2005;16:1171-1175.
28. Ashley L, Jones H, Forman D, et al. Feasibility test of a UK-scalable electronic system for regular collection of patient-reported outcome measures and linkage with clinical cancer registry data: the electronic Patient-Reported Outcomes from Cancer Survivors (ePOCS) system [serial online]. *BMC Med Inform Decis Mak*. 2011;11:66.
29. Ashley L, Jones H, Thomas J, et al. Integrating cancer survivors' experiences into UK cancer registries: design and development of the ePOCS system (electronic Patient-reported Outcomes from Cancer Survivors). *Br J Cancer*. 2011;105(suppl 1):S74-S81.
30. Buffart LM, Thong MS, Schep G, et al. Self-reported physical activity: its correlates and relationship with health-related quality of life in a large cohort of colorectal cancer survivors [serial online]. *PloS One*. 2012;7:e36164.
31. Den Oudsten BL, Traa MJ, Thong MS, et al. Higher prevalence of sexual dysfunction in colon and rectal cancer survivors compared with the normative population: a population-based study. *Eur J Cancer*. 2012;48:3161-3170.
32. Husson O, Thong MS, Mols F, Oerlemans S, Kaptein AA, van de Poll-Franse LV. Illness perceptions in cancer survivors: what is the role of information provision [published online ahead of print February 6, 2012]? *Psychooncology*. 2012.
33. Mols F, Denollet J, Kaptein AA, et al. The association between type D personality and illness perceptions in colorectal cancer survivors: a study from the population-based PROFILES registry. *J Psychosom Res*. 2012;73:232-239.
34. Mols F, Oerlemans S, Denollet J, et al. Type D personality is associated with increased comorbidity burden and health care utilization among 3080 cancer survivors. *Gen Hosp Psychiatry*. 2012;34:352-359.
35. Mols F, Oerlemans S, Vos AH, et al. Health related quality of life and disease-specific complaints among multiple myeloma patients up to 10 years after diagnosis: results from a population-based study using the PROFILES registry. *Eur J Haematol*. 2012;89:311-319.
36. Mols F, Thong MS, van de Poll-Franse LV, et al. Type D (distressed) personality is associated with poor quality of life and mental health among 3080 cancer survivors. *J Affect Disord*. 2012;136:26-34.
37. Mols F, Thong MS, Vissers P, et al. Socio-economic implications of cancer survivorship: results from the PROFILES registry. *Eur J Cancer*. 2012;48:2037-2042.
38. Nicolaije KA, Husson O, Ezendam NP, et al. Endometrial cancer survivors are unsatisfied with received information about diagnosis, treatment and follow-up: a study from the population-based PROFILES registry. *Patient Educ Couns*. 2012;88:427-435.
39. Oerlemans S, Husson O, Mols F, et al. Perceived information provision and satisfaction among lymphoma and multiple myeloma survivors-results from a Dutch population-based study. *Ann Hematol*. 2012;91:1587-1595.
40. Oerlemans S, Mols F, Issa DE, et al. A high level of fatigue among (long-term) non-Hodgkin lymphoma survivors: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. *Haematologica*. 2013;98:479-496.
41. Soerjomataram I, Thong MS, Ezzati M, et al. Most colorectal cancer survivors live a large proportion of their remaining life in good health. *Cancer Causes Control*. 2012;23:1421-1428.
42. Soerjomataram I, Thong MS, Korfage IJ, et al. Excess weight among colorectal cancer survivors: target for intervention. *J Gastroenterol*. 2012;47:999-1005.
43. Daly BJ, Douglas SL, Foley H, et al. Psychosocial registry for persons with cancer: a method of facilitating quality of life and symptom research. *Psychooncology*. 2007;16:358-364.
44. Alessi D, Dama E, Barr R, et al. Health-related quality of life of long-term childhood cancer survivors: a population-based study from the Childhood Cancer Registry of Piedmont, *Italy Eur J Cancer*. 2007;43:2545-2552.

45. Allareddy V, Kennedy J, West MM, et al. Quality of life in long-term survivors of bladder cancer. *Cancer*. 2006;106:2355-2362.
46. Andersen MR, Bowen DJ, Morea J, et al. Involvement in decision-making and breast cancer survivor quality of life. *Health Psychol*. 2009;28:29-37.
47. Ashing-Giwa KT, Tejero JS, Kim J, et al. Cervical cancer survivorship in a population based sample. *Gynecol Oncol*. 2009;112:358-364.
48. Barbera L, Seow H, Howell D, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. *Cancer*. 2010;116:5767-5776.
49. Bartoces MG, Severson RK, Rusin BA, et al. Quality of life and self-esteem of long-term survivors of invasive and noninvasive cervical cancer. *J Womens Health (Larchmt)*. 2009;18:655-661.
50. Beesley V, Janda M, Eakin E, et al. Lymphedema after gynecological cancer treatment: prevalence, correlates, and supportive care needs. *Cancer*. 2007;109:2607-2614.
51. Bergmark K, Avall-Lundqvist E, Dickman PW, et al. Synergy between sexual abuse and cervical cancer in causing sexual dysfunction. *J Sex Marital Ther*. 2005;31:361-383.
52. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. *J Clin Oncol*. 2008;26:2198-2204.
53. Boehmer U, Glickman M, Milton J, et al. Health-related quality of life in breast cancer survivors of different sexual orientations. *Qual Life Res*. 2012;21:225-236.
54. Boman KK, Hoven E, Anclair M, et al. Health and persistent functional late effects in adult survivors of childhood CNS tumours: a population-based cohort study. *Eur J Cancer*. 2009;45:2552-2561.
55. Bouvier AM, Jooste V, Bonnetain F, et al. Adjuvant treatments do not alter the quality of life in elderly patients with colorectal cancer: a population-based study. *Cancer*. 2008;113:879-886.
56. Burris JL, Andrykowski M. Disparities in mental health between rural and nonrural cancer survivors: a preliminary study. *Psychooncology*. 2010;19:637-645.
57. Carpenter CL, Ganz PA, Bernstein L. Complementary and alternative therapies among very long-term breast cancer survivors. *Breast Cancer Res Treat*. 2009;116:387-396.
58. Cimprich B, Ronis DL, Martinez-Ramos G. Age at diagnosis and quality of life in breast cancer survivors. *Cancer Pract*. 2002;10:85-93.
59. Claus EB, Petruzella S, Carter D, et al. Quality of life for women diagnosed with breast carcinoma in situ. *J Clin Oncol*. 2006;24:4875-4881.
60. Clauser SB, Arora NK, Bellizzi KM, et al. Disparities in HRQOL of cancer survivors and noncancer managed care enrollees. *Health Care Financ Rev*. 2008;29:23-40.
61. Correa-Velez I, Clavarino A, Barnett AG, et al. Use of complementary and alternative medicine and quality of life: changes at the end of life. *Palliat Med*. 2003;17:695-703.
62. Courneya KS, Karvinen KH, Campbell KL, et al. Associations among exercise, body weight, and quality of life in a population-based sample of endometrial cancer survivors. *Gynecol Oncol*. 2005;97:422-430.
63. Dahl CF, Haugnes HS, Bremnes R, et al. A controlled study of risk factors for disease and current problems in long-term testicular cancer survivors. *J Cancer Surviv*. 2010;4:256-265.
64. Deshpande AD, Sefko JA, Jeffe DB, et al. The association between chronic disease burden and quality of life among breast cancer survivors in Missouri. *Breast Cancer Res Treat*. 2011;129:877-886.
65. Diamond C, Taylor TH, Anton-Culver H. Quality of life, characteristics and survival of patients with HIV and lymphoma. *Qual Life Res*. 2010;19:149-155.
66. Fobair P, Stewart SL, Chang S, et al. Body image and sexual problems in young women with breast cancer. *Psychooncology*. 2006;15:579-594.
67. Gatta G, Ciccolallo L, Faivre J, et al. Late outcomes of colorectal cancer treatment: a FECS-EUROCARE study. *J Cancer Surviv*. 2007;1:247-254.
68. Gotay CC, Farley JH, Kawamoto CT, et al. Adaptation and quality of life among long-term cervical cancer survivors in the military health care system. *Mil Med*. 2008;173:1035-1041.
69. Gotay CC, Holup JL, Pagano I. Ethnic differences in quality of life among early breast and prostate cancer survivors. *Psychooncology*. 2002;11:103-113.
70. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer*. 2011;117:1994-2003.
71. Greenwald HP, McCorkle R. Sexuality and sexual function in long-term survivors of cervical cancer. *J Womens Health (Larchmt)*. 2008;17:955-963.
72. Guren MG, Eriksen MT, Wiig JN, et al. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. *Eur J Surg Oncol*. 2005;31:735-742.
73. Hamashima C. Long-term quality of life of postoperative rectal cancer patients. *J Gastroenterol Hepatol*. 2002;17:571-576.
74. Helgesson O, Lissner L, Mansson J, et al. Quality of life in cancer survivors as observed in a population study of Swedish women. *Scand J Prim Health Care*. 2007;25:220-225.
75. Hoven E, Lannering B, Gustafsson G, et al. The met and unmet health care needs of adult survivors of childhood central nervous system tumors: a double-informant, population-based study. *Cancer*. 2011;117:4294-4303.
76. Hoyer M, Johansson B, Nordin K, et al. Health-related quality of life among women with breast cancer—a population-based study. *Acta Oncol*. 2011;50:1015-1026.
77. Joly F, Heron JF, Kalusinski L, et al. Quality of life in long-term survivors of testicular cancer: a population-based case-control study. *J Clin Oncol*. 2002;20:73-80.
78. Karvinen KH, Courneya KS, North S, et al. Associations between exercise and quality of life in bladder cancer survivors: a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2007;16:984-990.
79. Klein D, Mercier M, Abeilard E, et al. Long-term quality of life after breast cancer: a French registry-based controlled study. *Breast Cancer Res Treat*. 2011;129:125-134.
80. Korfage IJ, Essink-Bot ML, Mols F, et al. Health-related quality of life in cervical cancer survivors: a population-based survey. *Int J Radiat Oncol Biol Phys*. 2009;73:1501-1509.
81. Major MS, Bumpous JM, Flynn MB, et al. Quality of life after treatment for advanced laryngeal and hypopharyngeal cancer. *Laryngoscope*. 2001;111:1379-1382.
82. Malterling RR, Andersson RE, Falkmer S, et al. Differentiated thyroid cancer in a Swedish county—long-term results and quality of life. *Acta Oncol*. 2010;49:454-459.
83. Maly RC, Stein JA, Umezawa Y, et al. Racial/ethnic differences in breast cancer outcomes among older patients: effects of physician communication and patient empowerment. *Health Psychol*. 2008;27:728-736.
84. Mao JJ, Cronholm PF, Stein E, et al. Positive changes, increased spiritual importance, and complementary and alternative medicine (CAM) use among cancer survivors. *Integr Cancer Ther*. 2010;9:339-347.
85. Maskarinec G, Shumay DM, Kakai H, et al. Ethnic differences in complementary and alternative medicine use among cancer patients. *J Altern Complement Med*. 2000;6:531-538.
86. Matsuda T, Aptel I, Exbrayat C, et al. Determinants of quality of life of bladder cancer survivors 5 years after treatment in France. *Int J Urol*. 2003;10:423-429.
87. Milne HM, Gordon S, Guilfoyle A, et al. Association between physical activity and quality of life among Western Australian breast cancer survivors. *Psychooncology*. 2007;16:1059-1068.
88. Mort S, Salantera S, Matomaki J, et al. Cancer related factors do not explain the quality of life scores for childhood cancer survivors analysed with 2 different generic HRQL instruments. *Cancer Epidemiol*. 2011;35:202-210.
89. Park CL, Chmielewski J, Blank TO. Post-traumatic growth: finding positive meaning in cancer survivorship moderates the impact of intrusive thoughts on adjustment in younger adults. *Psychooncology*. 2010;19:1139-1147.

90. Peddle CJ, Au HJ, Courneya KS. Associations between exercise, quality of life, and fatigue in colorectal cancer survivors. *Dis Colon Rectum*. 2008;51:1242-1248.
91. Peuckmann V, Ekholm O, Rasmussen NK, et al. Health-related quality of life in long-term breast cancer survivors: nationwide survey in Denmark. *Breast Cancer Res Treat*. 2007;104:39-46.
92. Pogany L, Barr RD, Shaw A, et al. Health status in survivors of cancer in childhood and adolescence. *Qual Life Res*. 2006;15:143-157.
93. Price MA, Zachariae R, Butow PN, et al. Prevalence and predictors of insomnia in women with invasive ovarian cancer: anxiety a major factor. *Eur J Cancer*. 2009;45:3262-3270.
94. Rondorf-Klym LM, Colling J. Quality of life after radical prostatectomy. *Oncol Nurs Forum*. 2003;30:E24-E32.
95. Sammarco A. Quality of life of breast cancer survivors: a comparative study of age cohorts. *Cancer Nurs*. 2009;32:347-356.
96. Schlesinger-Raab A, Schubert-Fritschle G, Hein R, et al. Quality of life in localised malignant melanoma. *Ann Oncol*. 2010;21:2428-2435.
97. Seitz DC, Hagmann D, Besier T, et al. Life satisfaction in adult survivors of cancer during adolescence: what contributes to the latter satisfaction with life? *Qual Life Res*. 2011;20:225-236.
98. Sisler JJ, Brown JB, Stewart M. Family physicians' roles in cancer care. Survey of patients on a provincial cancer registry. *Can Fam Physician*. 2004;50:889-896.
99. Smith DP, King MT, Egger S, et al. Quality of life 3 years after diagnosis of localised prostate cancer: population based cohort study (serial online). *BMJ*. 2009;339:b4817.
100. Smith-Gagen J, Cress RD, Drake CM, et al. Quality-of-life and surgical treatments for rectal cancer—a longitudinal analysis using the California Cancer Registry. *Psychooncology*. 2010;19:870-878.
101. Steenland K, Goodman M, Liff J, et al. Quality of life among men with prostate cancer in rural Georgia. *Urology*. 2011;77:927-933.
102. Steiner JF, Cavender TA, Nowels CT, et al. The impact of physical and psychosocial factors on work characteristics after cancer. *Psychooncology*. 2008;17:138-147.
103. Tian J, Chen JS. Nutritional status and quality of life of the gastric cancer patients in Changle County of China. *World J Gastroenterol*. 2005;11:1582-1586.
104. van Gestel YR, Voogd AC, Vingerhoets AJ, et al. A comparison of quality of life, disease impact and risk perception in women with invasive breast cancer and ductal carcinoma in situ. *Eur J Cancer*. 2007;43:549-556.
105. Waldmann A, Pritzkuleit R, Raspe H, et al. The OVIS study: health related quality of life measured by the EORTC QLQ-C30 and -BR23 in German female patients with breast cancer from Schleswig-Holstein. *Qual Life Res*. 2007;16:767-776.
106. Yoon J, Malin JL, Tao ML, et al. Symptoms after breast cancer treatment: are they influenced by patient characteristics? *Breast Cancer Res Treat*. 2008;108:153-165.
107. Yost KJ, Hahn EA, Zaslavsky AM, et al. Predictors of health-related quality of life in patients with colorectal cancer [serial online]. *Health Qual Life Outcomes*. 2008;6:66.
108. Zick SM, Sen A, Feng Y, et al. Trial of Essiac to ascertain its effect in women with breast cancer (TEA-BC). *J Altern Complement Med*. 2006;12:971-980.
109. Aarts MJ, Mols F, Thong MS, et al. Long-term prostate cancer survivors with low socioeconomic status reported worse mental health-related quality of life in a population-based study. *Urology*. 2010;76:1224-1230.
110. Ahmed RL, Prizment A, Lazovich D, et al. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. *J Clin Oncol*. 2008;26:5689-5696.
111. Alfano CM, Smith AW, Irwin ML, et al. Physical activity, long-term symptoms, and physical health-related quality of life among breast cancer survivors: a prospective analysis. *J Cancer Surviv*. 2007;1:116-128.
112. Arndt V, Merx H, Stegmaier C, et al. Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. *J Clin Oncol*. 2004;22:4829-4836.
113. Arndt V, Merx H, Stegmaier C, et al. Persistence of restrictions in quality of life from the first to the third year after diagnosis in women with breast cancer. *J Clin Oncol*. 2005;23:4945-4953.
114. Arndt V, Merx H, Stegmaier C, et al. Restrictions in quality of life in colorectal cancer patients over 3 years after diagnosis: a population based study. *Eur J Cancer*. 2006;42:1848-1857.
115. Arndt V, Merx H, Sturmer T, et al. Age-specific detriments to quality of life among breast cancer patients 1 year after diagnosis. *Eur J Cancer*. 2004;40:673-680.
116. Arndt V, Stegmaier C, Ziegler H, et al. A population-based study of the impact of specific symptoms on quality of life in women with breast cancer 1 year after diagnosis. *Cancer*. 2006;107:2496-2503.
117. Arndt V, Stegmaier C, Ziegler H, et al. Quality of life over 5 years in women with breast cancer after breast-conserving therapy versus mastectomy: a population-based study. *J Cancer Res Clin Oncol*. 2008;134:1311-1318.
118. Arora NK, Weaver KE, Clayman ML, et al. Physicians' decision-making style and psychosocial outcomes among cancer survivors. *Patient Educ Couns*. 2009;77:404-412.
119. Ashing-Giwa KT, Lim JW. Examining the impact of socioeconomic status and socioecologic stress on physical and mental health quality of life among breast cancer survivors. *Oncol Nurs Forum*. 2009;36:79-88.
120. Ashing-Giwa KT, Lim JW. Exploring the association between functional strain and emotional well-being among a population-based sample of breast cancer survivors. *Psychooncology*. 2010;19:150-159.
121. Ashing-Giwa KT, Tejero JS, Kim J, et al. Examining predictive models of HRQOL in a population-based, multiethnic sample of women with breast carcinoma. *Qual Life Res*. 2007;16:413-428.
122. Beckjord EB, Arora NK, McLaughlin W, et al. Health-related information needs in a large and diverse sample of adult cancer survivors: implications for cancer care. *J Cancer Surviv*. 2008;2:179-189.
123. Belanger LJ, Plotnikoff RC, Clark A, et al. Physical activity and health-related quality of life in young adult cancer survivors: a Canadian provincial survey. *J Cancer Surviv*. 2011;5:44-53.
124. Bellizzi KM, Rowland JH, Arora NK, et al. Physical activity and quality of life in adult survivors of non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:960-966.
125. Bellizzi KM, Smith AW, Reeve BB, et al. Posttraumatic growth and health-related quality of life in a racially diverse cohort of breast cancer survivors. *J Health Psychol*. 2009;15:615-626.
126. Bloom JR, Stewart SL, Chang S, et al. Then and now: quality of life of young breast cancer survivors. *Psychooncology*. 2004;13:147-160.
127. Bloom JR, Stewart SL, Oakley-Girvan I, et al. Quality of life of younger breast cancer survivors: persistence of problems and sense of well-being. *Psychooncology*. 2012;21:655-665.
128. Bowen DJ, Alfano CM, McGregor BA, et al. Possible socioeconomic and ethnic disparities in quality of life in a cohort of breast cancer survivors. *Breast Cancer Res Treat*. 2007;106:85-95.
129. Bruheim K, Guren MG, Dahl AA, et al. Sexual function in males after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2010;76:1012-1017.
130. Bruheim K, Guren MG, Skovlund E, et al. Late side effects and quality of life after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2010;76:1005-1011.
131. Bruheim K, Tveit KM, Skovlund E, et al. Sexual function in females after radiotherapy for rectal cancer. *Acta Oncol*. 2010;49:826-832.
132. Chen X, Lu W, Zheng Y, et al. Exercise, tea consumption, and depression among breast cancer survivors. *J Clin Oncol*. 2010;28:991-998.
133. Chen X, Zheng Y, Zheng W, et al. The effect of regular exercise on quality of life among breast cancer survivors. *Am J Epidemiol*. 2009;170:854-862.
134. Cui Y, Shu XO, Gao Y, et al. The long-term impact of medical and socio-demographic factors on the quality of life of breast cancer survivors among Chinese women. *Breast Cancer Res Treat*. 2004;87:135-147.

135. Cui Y, Shu XO, Gao YT, et al. Association of ginseng use with survival and quality of life among breast cancer patients. *Am J Epidemiol*. 2006;163:645-653.
136. DiSipio T, Hayes S, Newman B, et al. Health-related quality of life 18 months after breast cancer: comparison with the general population of Queensland, *Australia Support Care Cancer*. 2008;16:1141-1150.
137. DiSipio T, Hayes S, Newman B, et al. What determines the health-related quality of life among regional and rural breast cancer survivors? *Aust N Z J Public Health*. 2009;33:534-539.
138. DiSipio T, Hayes SC, Newman B, et al. Does quality of life among breast cancer survivors 1 year after diagnosis differ depending on urban and nonurban residence? A comparative study [serial online]. *Health Qual Life Outcomes*. 2010;8:3.
139. Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. *J Clin Oncol*. 2009;27:1963-1968.
140. Engel J, Kerr J, Schlesinger-Raab A, et al. Predictors of quality of life of breast cancer patients. *Acta Oncol*. 2003;42:710-718.
141. Engel J, Kerr J, Schlesinger-Raab A, et al. Comparison of breast and rectal cancer patients' quality of life: results of a 4 year prospective field study. *Eur J Cancer Care (Engl)*. 2003;12:215-223.
142. Engel J, Kerr J, Schlesinger-Raab A, et al. Quality of life in rectal cancer patients: a 4-year prospective study. *Ann Surg*. 2003;238:203-213.
143. Engel J, Kerr J, Schlesinger-Raab A, et al. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. *Breast Cancer Res Treat*. 2003;79:47-57.
144. Engel J, Kerr J, Schlesinger-Raab A, et al. Quality of life following breast-conserving therapy or mastectomy: results of a 5-year prospective study. *Breast J*. 2004;10:223-231.
145. Gotay CC, Isaacs P, Pagano I. Quality of life in patients who survive a dire prognosis compared to control cancer survivors. *Psychooncology*. 2004;13:882-892.
146. Gotay CC, Ransom S, Pagano IS. Quality of life in survivors of multiple primary cancers compared with cancer survivor controls. *Cancer*. 2007;110:2101-2109.
147. Hamilton AS, Stanford JL, Gilliland FD, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. *J Clin Oncol*. 2001;19:2517-2526.
148. Hao Y, Landrine H, Smith T, et al. Residential segregation and disparities in health-related quality of life among Black and White cancer survivors. *Health Psychol*. 2011;30:137-144.
149. Harrison SA, Hayes SC, Newman B. Age-related differences in exercise and quality of life among breast cancer survivors. *Med Sci Sports Exerc*. 2010;42:67-74.
150. Hays RD, Smith AW, Reeve BB, et al. Cigarette smoking and health-related quality of life in Medicare beneficiaries. *Health Care Financ Rev*. 2008;29:57-67.
151. Hoffman RM, Barry MJ, Stanford JL, et al. Health outcomes in older men with localized prostate cancer: results from the Prostate Cancer Outcomes Study. *Am J Med*. 2006;119:418-425.
152. Hoffman RM, Gilliland FD, Penson DF, et al. Cross-sectional and longitudinal comparisons of health-related quality of life between patients with prostate carcinoma and matched controls. *Cancer*. 2004;101:2011-2019.
153. Holterhues C, Cornish D, van de Poll-Franse LV, et al. Impact of melanoma on patients' lives among 562 survivors: a Dutch population-based study. *Arch Dermatol*. 2011;147:177-185.
154. Jansen L, Herrmann A, Stegmaier C, et al. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study. *J Clin Oncol*. 2011;20:3263-3269.
155. Janz NK, Mujahid M, Chung LK, et al. Symptom experience and quality of life of women following breast cancer treatment. *J Womens Health (Larchmt)*. 2007;16:1348-1361.
156. Janz NK, Mujahid M, Lantz PM, et al. Population-based study of the relationship of treatment and sociodemographics on quality of life for early stage breast cancer. *Qual Life Res*. 2005;14:1467-1479.
157. Janz NK, Mujahid MS, Hawley ST, et al. Racial/ethnic differences in quality of life after diagnosis of breast cancer. *J Cancer Surviv*. 2009;3:212-222.
158. Kerr J, Engel J, Schlesinger-Raab A, et al. Doctor-patient communication: results of a 4-year prospective study in rectal cancer patients. *Dis Colon Rectum*. 2003;46:1038-1046.
159. Kerr J, Engel J, Schlesinger-Raab A, et al. Communication, quality of life and age: results of a 5-year prospective study in breast cancer patients. *Ann Oncol*. 2003;14:421-427.
160. Kyrdalen AE, Dahl AA, Hernes E, et al. Fatigue in hormone-naive prostate cancer patients treated with radical prostatectomy or definitive radiotherapy. *Prostate Cancer Prostatic Dis*. 2010;13:144-150.
161. Kyrdalen AE, Dahl AA, Hernes E, et al. Fatigue in prostate cancer survivors treated with definitive radiotherapy and LHRH analogs. *Prostate*. 2010;70:1480-1489.
162. Lazovich D, Robien K, Cutler G, et al. Quality of life in a prospective cohort of elderly women with and without cancer. *Cancer*. 2009;115:4283-4297.
163. Lehmann V, Oerlemans S, van de Poll-Franse LV, et al. Suffering in long-term cancer survivors: an evaluation of the PRISM-R2 in a population-based cohort. *Qual Life Res*. 2011;20:1645-1654.
164. Lu W, Cui Y, Chen X, et al. Changes in quality of life among breast cancer patients 3 years post-diagnosis. *Breast Cancer Res Treat*. 2009;114:357-369.
165. Lu W, Cui Y, Zheng Y, et al. Impact of newly diagnosed breast cancer on quality of life among Chinese women. *Breast Cancer Res Treat*. 2007;102:201-210.
166. Lynch BM, Cerin E, Owen N, et al. Associations of leisure-time physical activity with quality of life in a large, population-based sample of colorectal cancer survivors. *Cancer Causes Control*. 2007;18:735-742.
167. Lynch BM, Cerin E, Owen N, et al. Television viewing time of colorectal cancer survivors is associated prospectively with quality of life. *Cancer Causes Control*. 2011;22:1111-1120.
168. Meeske K, Smith AW, Alfano CM, et al. Fatigue in breast cancer survivors 2 to 5 years post diagnosis: a HEAL Study report. *Qual Life Res*. 2007;16:947-960.
169. Mehnert A, Berg P, Henrich G, et al. Fear of cancer progression and cancer-related intrusive cognitions in breast cancer survivors. *Psychooncology*. 2009;18:1273-1280.
170. Mehnert A, Koch U. Psychological comorbidity and health-related quality of life and its association with awareness, utilization, and need for psychosocial support in a cancer register-based sample of long-term breast cancer survivors. *J Psychosom Res*. 2008;64:383-391.
171. Mellon S, Northouse LL. Family survivorship and quality of life following a cancer diagnosis. *Res Nurs Health*. 2001;24:446-459.
172. Mellon S, Northouse LL, Weiss LK. A population-based study of the quality of life of cancer survivors and their family caregivers. *Cancer Nurs*. 2006;29:120-131.
173. Mols F, Aaronson NK, Vingerhoets AJ, et al. Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. *Cancer*. 2007;109:1659-1667.
174. Mols F, Aquarius AE, Essink-Bot ML, et al. Does diabetes mellitus as a comorbid condition affect the health-related quality of life in prostate cancer survivors? Results of a population-based observational study. *BJU Int*. 2008;102:1594-1600.
175. Mols F, Coebergh JW, van de Poll-Franse LV. Health-related quality of life and health care utilisation among older long-term cancer survivors: a population-based study. *Eur J Cancer*. 2007;43:2211-2221.
176. Mols F, Helfenrath KA, Vingerhoets AJ, et al. Increased health care utilization among long-term cancer survivors compared to the average Dutch population: a population-based study. *Int J Cancer*. 2007;121:871-877.
177. Mols F, Holterhues C, Nijsten T, et al. Personality is associated with health status and impact of cancer among melanoma survivors. *Eur J Cancer*. 2010;46:573-580.
178. Mols F, Korfage IJ, Vingerhoets AJ, et al. Bowel, urinary, and sexual problems among long-term prostate cancer survivors: a population-based study. *Int J Radiat Oncol Biol Phys*. 2009;73:30-38.

179. Mols F, Thong MS, Vreugdenhil G, et al. Long-term cancer survivors experience work changes after diagnosis: results of a population-based study. *Psychooncology*. 2009;18:1252-1260.
180. Mols F, van de Poll-Franse LV, Vingerhoets AJ, et al. Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study. *Cancer*. 2006;107:2186-2196.
181. Mols F, Vingerhoets AJ, Coebergh JW, et al. Well-being, posttraumatic growth and benefit finding in long-term breast cancer survivors. *Psychol Health*. 2009;24:583-595.
182. Mols F, Vingerhoets AJ, Coebergh JW, et al. Better quality of life among 10-15 year survivors of Hodgkin's lymphoma compared to 5-9 year survivors: a population-based study. *Eur J Cancer*. 2006;42:2794-2801.
183. Penson DF, Feng Z, Kuniyuki A, et al. General quality of life 2 years following treatment for prostate cancer: what influences outcomes? Results from the Prostate Cancer Outcomes Study. *J Clin Oncol*. 2003;21:1147-1154.
184. Penson DF, McLerran D, Feng Z, et al. Five-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study. *J Urol*. 2005;173:1701-1705.
185. Potosky AL, Legler J, Albertsen PC, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. *J Natl Cancer Inst*. 2000;92:1582-1592.
186. Potosky AL, Reeve BB, Clegg LX, et al. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. *J Natl Cancer Inst*. 2002;94:430-437.
187. Ramsey SD, Andersen MR, Etzioni R, et al. Quality of life in survivors of colorectal carcinoma. *Cancer*. 2000;88:1294-1303.
188. Ramsey SD, Berry K, Moinpour C, et al. Quality of life in long term survivors of colorectal cancer. *Am J Gastroenterol*. 2002;97:1228-1234.
189. Reeve BB, Potosky AL, Smith AW, et al. Impact of cancer on health-related quality of life of older Americans. *J Natl Cancer Inst*. 2009;101:860-868.
190. Round T, Hayes SC, Newman B. How do recovery advice and behavioural characteristics influence upper-body function and quality of life among women 6 months after breast cancer diagnosis? *Support Care Cancer*. 2006;14:22-29.
191. Rutegard M, Lagergren J, Rouvelas I, et al. Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. *Br J Surg*. 2008;95:592-601.
192. Rutegard M, Lagergren P. No influence of surgical volume on patients' health-related quality of life after esophageal cancer resection. *Ann Surg Oncol*. 2008;15:2380-2387.
193. Sandblom G, Carlsson P, Sennfalt K, et al. A population-based study of pain and quality of life during the year before death in men with prostate cancer. *Br J Cancer*. 2004;90:1163-1168.
194. Sandblom G, Carlsson P, Sigsjo P, et al. Pain and health-related quality of life in a geographically defined population of men with prostate cancer. *Br J Cancer*. 2001;85:497-503.
195. Sapp AL, Trentham-Dietz A, Newcomb PA, et al. Social networks and quality of life among female long-term colorectal cancer survivors. *Cancer*. 2003;98:1749-1758.
196. Shi Q, Smith TG, Michonski JD, et al. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. *Cancer*. 2011;117:2779-2790.
197. Smith AW, Alfano CM, Reeve BB, et al. Race, ethnicity, physical activity, and quality of life in breast cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2009;18:656-663.
198. Smith AW, Reeve BB, Bellizzi KM, et al. Cancer, comorbidities, and health-related quality of life of older adults. *Health Care Financ Rev*. 2008;29:41-56.
199. Steginga SK, Lynch BM, Hawkes A, et al. Antecedents of domain-specific quality of life after colorectal cancer. *Psychooncology*. 2009;18:216-220.
200. Stevinson C, Faught W, Steed H, et al. Associations between physical activity and quality of life in ovarian cancer survivors. *Gynecol Oncol*. 2007;106:244-250.
201. Stevinson C, Steed H, Faught W, et al. Physical activity in ovarian cancer survivors: associations with fatigue, sleep, and psychosocial functioning. *Int J Gynecol Cancer*. 2009;19:73-78.
202. Sweeney C, Schmitz KH, Lazovich D, et al. Functional limitations in elderly female cancer survivors. *J Natl Cancer Inst*. 2006;98:521-529.
203. Thong MS, Mols F, Coebergh JW, et al. The impact of disease progression on perceived health status and quality of life of long-term cancer survivors. *J Cancer Surviv*. 2009;3:164-173.
204. Thong MS, Mols F, Kil PJ, et al. Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden. *BJU Int*. 2010;105:652-658.
205. Thong MS, Mols F, Lemmens VE, et al. Impact of chemotherapy on health status and symptom burden of colon cancer survivors: a population-based study. *Eur J Cancer*. 2011;47:1798-1807.
206. Thong MS, Mols F, Lemmens VE, et al. Impact of preoperative radiotherapy on general and disease-specific health status of rectal cancer survivors: a population-based study[serial online]. *Int J Radiat Oncol Biol Phys*. 2011;81:e49-e58.
207. Thong MS, Van De Poll-Franse L, Hoffman RM, et al. Diabetes mellitus and health-related quality of life in prostate cancer: 5-year results from the Prostate Cancer Outcomes Study. *BJU Int*. 2011;107:1223-1231.
208. Trentham-Dietz A, Remington PL, Moinpour CM, et al. Health-related quality of life in female long-term colorectal cancer survivors. *Oncologist*. 2003;8:342-349.
209. van de Poll-Franse LV, Mols F, Essink-Bot ML, et al. Impact of external beam adjuvant radiotherapy on health-related quality of life for long-term survivors of endometrial adenocarcinoma: a population-based study. *Int J Radiat Oncol Biol Phys*. 2007;69:125-132.
210. van de Poll-Franse LV, Mols F, Vingerhoets AJ, et al. Increased health care utilisation among 10-year breast cancer survivors. *Support Care Cancer*. 2006;14:436-443.
211. van Dijk J, Huisman J, Moll AC, et al. Health-related quality of life of child and adolescent retinoblastoma survivors in the Netherlands [serial online]. *Health Qual Life Outcomes*. 2007;5:65.
212. van Dijk J, Imhof SM, Moll AC, et al. Quality of life of adult retinoblastoma survivors in the Netherlands [serial online]. *Health Qual Life Outcomes*. 2007;5:30.
213. Viklund P, Lindblad M, Lagergren J. Influence of surgery-related factors on quality of life after esophageal or cardia cancer resection. *World J Surg*. 2005;29:841-848.
214. Viklund P, Wengstrom Y, Rouvelas I, et al. Quality of life and persisting symptoms after oesophageal cancer surgery. *Eur J Cancer*. 2006;42:1407-1414.
215. Waters EA, Arora NK, Klein WM, et al. Perceived risk, trust and health-related quality of life among cancer survivors. *Ann Behav Med*. 2010;39:91-97.
216. Wayne SJ, Baumgartner K, Baumgartner RN, et al. Diet quality is directly associated with quality of life in breast cancer survivors. *Breast Cancer Res Treat*. 2006;96:227-232.
217. Yost KJ, Cella D, Chawla A, et al. Minimally important differences were estimated for the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument using a combination of distribution- and anchor-based approaches. *J Clin Epidemiol*. 2005;58:1241-1251.

Original Article

Cancer-Related Fatigue and Its Impact on Functioning

Ollie Minton, PhD[1]; Ann Berger, PhD, APRN, AOCNS[2]; Andrea Barsevick, PhD, RN, AOCN, FAAN[3]; Fiona Cramp, PhD[4]; Martine Goedendorp, PhD[5]; Sandra A. Mitchell, PhD, CRNP, AOCN[6]; and Patrick C. Stone, MA, MD, FRCP[7]

This article presents the contrasting European and American perspectives on cancer-related fatigue (CRF) and its impact on functioning in cancer survivors. The content is presented in 3 sections: state of the art, intervention studies, and future areas of research, followed by a discussion. Gaps identified include a lack of understanding of the etiology, definition, and measurement of CRF. Models to guide the study of CRF, selection of biomarkers, and design of interventions are needed. There is overlap between Europe and the United States concerning the future directions for research and collaboration related to CRF. The authors suggest the need for international consensus regarding the defining features of CRF in cancer survivors to identify phenotypes, a harmonized measurement of CRF outcomes using instruments that have demonstrated measurement equivalence across languages and cultures, and interventions (including exercise, rehabilitation, and psychoeducational) that have been manualized to permit intervention fidelity across diverse contexts. Coordinated intercontinental efforts would increase understanding of the biological, psychological, and social mechanisms underlying CRF and assist in the design of future intervention studies as well as revisions to clinical guidelines. ***Cancer* 2013;119(11 suppl):2124-30.** © *2013 American Cancer Society.*

KEYWORDS: cancer-related fatigue; neoplasms; survivors; interventions.

INTRODUCTION

Cancer-related fatigue (CRF) is the most common persistent and distressing symptom reported by cancer survivors in the months and years after the successful treatment of cancer. Fatigue presents as a sensation ranging from tiredness to exhaustion that affects the survivor's physical, emotional, and/or cognitive functioning. The majority of reports estimate that approximately one-third of survivors experience fatigue. The growing number of survivors makes this an important area of scientific development. Fatigue is often unrecognized and undertreated by health care professionals, in part because of a lack of knowledge of mechanism-targeted interventions.

State of the Art: Europe

In Europe, cancer patients are warned and indeed expected to become fatigued during treatment. However, the majority of patients do not expect long-term fatigue after treatment and are not routinely warned of the possibility of such problems occurring.[1] Although CRF may occur only in approximately one-third of survivors, the figures may vary with individual studies.[2,3] The absolute number of cancer survivors is increasing all the time.[4] The majority of studies regarding CRF have

Corresponding author: Ollie Minton, PhD, FRCP, Division of Population Health Sciences and Education, 6th Fl Hunter Wing, St. George's University of London, Cranmer Terrace, London SW17 ORE; ominton@sgul.ac.uk (for Europe); Ann M. Berger, PhD, APRN, AOCNS, FAAN, University of Nebraska College of Nursing, 985330 Nebraska Medical Center, Omaha, NE 68198-5330; Fax: (402) 559-8188; aberger@unmc.edu (for the United States)

[1]Division of Population Health Sciences and Education, St. George's University of London, London, United Kingdom; [2]University of Nebraska College of Nursing, Omaha, Nebraska; [3]Fox Chase Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania; [4]Musculoskeletal Health, Faculty of Health and Life Sciences, University of the West of England, Bristol, United Kingdom; [5]Expert Centre for Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; [6]Outcomes Research Branch, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland; [7]Palliative Medicine, Division of Population Health Sciences and Education, St. George's University of London, London, United Kingdom.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors&apos issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

The opinions or views expressed in this supplement are those of the authors and do not necessarily reflect the opinions or recommendations of the journal editors, the American Cancer Society, John Wiley & Sons Inc, or the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari.

The first 2 authors are the joint lead coauthors for this article.

DOI: 10.1002/cncr.28058, **Received:** July 27, 2012; **Revised:** December 19, 2012; **Accepted:** December 20, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

been conducted in women with breast cancer,[2] with a small number taking place in patients with lymphoma.[3] To the best of our knowledge, outside of these 2 diagnostic groups, there have been comparatively fewer studies conducted.[5]

The European Association for Palliative Care (EAPC) has produced a working definition of CRF, describing it as "a subjective feeling of tiredness, weakness or lack of energy."[6] A lack of consensus concerning the definition among researchers has led to the development of a myriad of tools to assess CRF,[7] and has meant there is no universally agreed upon definition. In Europe, data from patients experiencing fatigue during treatment have come from the 3 fatigue subscale items regarding tiredness, weakness, and lack of energy from the 30 items on the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life (QOL) (EORTC QLQ 30) questionnaire.[8] In addition, in survivors of a working age, an important area to assess is the impact of fatigue on vocational functioning.[9]

There are no European guidelines for monitoring CRF in survivors of cancer. Because many countries in Europe have their own language(s), it is difficult for researchers to achieve pan-European consensus regarding definitions and questionnaires. This is complicated further by health policies that are different for each country. However, CRF is recognized as a long-term sequel of treatment in survivorship strategies identified by the United Kingdom National Health Service and by the EORTC.[10]

A barrier to developing a coherent strategy for the treatment of CRF in patients with cancer is the lack of understanding of the multiple factors causing CRF in this group. There is evidence to suggest that CRF is associated with increased levels of inflammatory cytokines and that individuals are more susceptible to CRF because of genetic polymorphisms.[11] However, these studies have been conducted mainly in women with breast cancer and the results will need to be replicated in other tumor groups. Cytokine levels must be measured longitudinally and examined for associations with the subjective measurement of CRF. Cytokine changes may be secondary to disturbances in the hypothalamic-adrenal-pituitary axis (HPA). Results provide preliminary evidence of alterations in HPA axis regulation of cortisol among survivors of breast cancer.[12] However, HPA axis dysregulation has been observed less consistently than have alterations in the immunologic milieu.[1] There also may be changes in muscle metabolism and structure underpinning CRF. Any such changes are likely to be more pronounced in patients with advanced cancer,[1] but a similar process driven by autoimmune or generalized proinflammatory processes may be underway in survivors. One caveat is that muscle wasting is also a part of the natural aging process.[13]

There may be an overlap between CRF and the chronic fatigue syndrome and research conducted in this group of patients may provide insight and direction for future studies.[14,15] In both groups, the fatigue is chronic in duration (ie, with a duration of >1 month and temporarily separate from the initial "insult." In the case of chronic fatigue syndrome, there is a set of diagnostic criteria[16] that have been widely recognized and adopted by the clinical and research community. A similar set of diagnostic criteria for CRF syndrome has been developed in the United States by Cella et al.[17] These criteria have not been widely adopted in Europe. It may be possible to screen for this syndrome using questionnaire cutoff scores.[18]

State of the Art: United States

In the United States, CRF has been well documented in association with cancer diagnosis and treatment. Steadily increasing trends toward the use of multimodal cancer treatments have prompted an even greater interest in CRF and other symptom research in cancer.[19]

Over the last 35 years, oncology researchers in the United States have developed screening, assessment, treatment, and evaluation methods for CRF in patients with cancer. As cancer has evolved into a chronic disease, the focus has been extended to improving functional status and QOL for survivors. There are many challenges to providing state-of-the-art supportive care for CRF to survivors of cancer in the United States.

Although to the best of our knowledge there is no a good consensus regarding the definition of CRF, the most widely used is the National Comprehensive Cancer Network (NCCN)'s[20] definition that CRF is "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." Functioning has been defined by the World Health Organization to refer to all body functions, activities, and participation in various roles.[21] There has been a call to link the definition to the measurement of CRF and to reconcile differences across self-reported measures.[7,22] Most instruments used by researchers rely on perception alone; a few add items that reflect the consequences of fatigue for physical, role, social, and vocational functioning to the perceptions or, less commonly, use a case definition (International Classification of Diseases, 10th revision) approach. To facilitate

larger and more diverse studies, there is a need to achieve consensus on domains of measurement and to harmonize measures. The Patient-Reported Outcomes Measurement Information System (PROMIS) Network funded by the National Institutes of Health has developed a set of standardized self-report measures of symptoms for CRF and other health domains, including physical functioning, to meet this need.[23]

Although a majority of survivors speak English as their primary language, communication can be a significant barrier and limit access to care for approximately 20% of the population who speak a language other than English at home.[24] In addition, according to the National Assessment of Adult Literacy, only 12% of those living in the United States have proficient health literacy and 14% of the US population has below basic health literacy.[25] Low literacy in the United States is different from that in Europe because it impacts employment and the ability to obtain health insurance coverage. Communication barriers amplify the challenges of screening and managing CRF in survivors. To optimize the screening and management of CRF in the United States, measures are needed that are sensitive to low health literacy and translated with demonstrated measurement invariance across language and culture.

Another challenge to providing quality supportive care services for CRF to cancer survivors in the United States is the health care reimbursement system. Private medical insurance is usually obtained through employment and the management of CRF may only be partially reimbursed. The American Society of Clinical Oncology developed a policy statement[26] to integrate the elimination of cancer health disparities into the society's mission and activities. This effort falls short of ensuring that CRF will be screened and managed in patients with cancer. If patients undergoing multimodal cancer treatment are unable to function at the level needed to maintain employment and/or lack medical insurance, they may experience barriers in accessing supportive care or rehabilitation services that require self-payment.

National and private organizations in the United States have developed symptom management guidelines for oncology clinicians to use to educate and manage cancer patients and their families.[20,27] These evidenced-based practice guidelines are updated regularly to reflect current information on methods with which to screen, assess, and select interventions for CRF. The majority of study participants have been receiving active treatment for cancer[20,27] and evidence is lacking regarding the effectiveness of many CRF interventions in survivors of many types of cancer. Translational research is needed to test research techniques designed to improve the capacity of clinicians to screen, assess, and deliver effective interventions to lower CRF and improve function in survivors.

Intervention Studies: Europe

There have been 3 complementary Cochrane systematic reviews conducted by European research groups focusing on the treatment of CRF at all stages of cancer. These reviews have examined the role of pharmacologic agents,[28] exercise,[29] and psychological interventions[30] in modifying CRF, but rarely included functional outcomes. Although not limited to European trials, these reviews only examined randomized controlled trials; the vast majority of the trials were conducted during treatment. Specific implications of the findings for cancer survivors will now be discussed.

Psychostimulant drugs such as methylphenidate have been shown to be effective in patients undergoing chemotherapy, but concerns exist about their side effect profile and possible addiction in survivors.[31] Overall, there is insufficient evidence to recommend their adoption in routine use in European practice in cancer survivors. They are used very infrequently in clinical practice.

Exercise studies[29] have involved a mixture of resistance and cardiovascular training. The trials differed extensively in terms of frequency, intensity, and duration of the interventions. The majority of studies were conducted in women with breast cancer. A meta-analysis of all fatigue data was conducted,[29] the findings of which were that exercise was statistically more effective on a range of fatigue questionnaire scores than the control intervention at the end of the intervention period. This conclusion suggests that the mode of exercise is important, but there remain problems with the quality of studies and the outcome measures used.

A recent meta-analysis examining the role of exercise in cancer survivors was published in the *British Medical Journal*.[32] The results demonstrated an improvement in fatigue and physical functions; the reduction in fatigue was significant but small. Overall, the effect size of exercise was small and was less than that of the meta-analysis effect size noted in the psychostimulant drug studies.[33] This is perhaps one of the reasons limiting the universal recommendation of exercise for CRF in cancer survivors.

Although an intervention that can be delivered and promoted by classes and subsidized gym memberships might appear to be the most appropriate for the survivor, it is unclear what the optimum dose, type, or frequency of exercise needs to be. This may explain why there is an

overall suggestion for the use of exercise in national strategies, but these suggestions lack the details required for adoption into European practice.

Psychosocial interventions[30] include psychological, educational, and support group studies. There is a wide variation in study size, design, and quality. These studies were a heterogeneous category that included cognitive behavioral therapy, supportive therapies, and psychoeducation. Only 5 intervention studies included in the review[30] specifically examined the effect on CRF. In general, during these interventions patients were educated about fatigue and taught self-care or coping techniques, energy conservation, and activity management. This may be an effective treatment approach but is clearly resource-intensive and needs to be directed at those individuals who are most fatigued. Interventions aimed at severely fatigued survivors can realize large effects.[29]

The vast majority of psychoeducational interventions aimed at improving psychological distress, mood, and other symptoms such as sleep disturbances failed to improve CRF as a secondary outcome.[30] This suggests that any psychologically based intervention to treat CRF in survivors must focus on fatigue and not treat it as a secondary outcome. These interventions have time and resource implications in terms of training and standardization of delivery of the intervention. The lack of specifically identifiable components has meant that this is not offered routinely in European practices.

The overall aim of these reviews was to provide implications for future research and practice. These conclusions (limited by the absolute numbers and quality of studies) have not been widely adopted by European clinicians. In practice, this means these interventions are being undertaken in an inconsistent, non-evidence-based manner or they are not being attempted at all.

Intervention Studies: United States

Although there have been more than 170 empiric studies of pharmacologic and nonpharmacologic interventions to reduce or manage CRF, and several meta-analyses or systematic reviews,[27-30,34-36] many of the interventions in fatigue have not been tested in cancer survivors who have concluded active treatment. To the best of our knowledge, few of the studies have included functioning as a primary or secondary outcome. Similarly, although guidelines for the management of cancer-related fatigue have been disseminated by the NCCN[20] and the Oncology Nursing Society,[27] they are not tailored to the posttreatment phase.

Randomized trails support the benefits of several different exercise modalities in the management of fatigue after cancer treatment in patients with breast cancer or solid tumors, or those undergoing hematopoietic stem cell transplantation, although effect sizes are generally small.[37] Exercise may also produce favorable effects on sleep, mood, muscle strength, cardiorespiratory fitness, body composition, and the neuroendocrine milieu. These effects also may contribute to the observed improvement in fatigue outcomes noted in survivors. Studies are needed to define the type, intensity, and duration of physical exercise that is most beneficial in reducing fatigue after treatment and will set the stage to provide the rationale for exercise prescriptions to cancer survivors. A recent systematic review[38] concluded that structured rehabilitation results in statistically significant and sustained improvements in fatigue, particularly in patients who have completed treatment and are in the survivorship phase. Despite these promising results, rehabilitation services are not systematically offered to cancer survivors in the United States after the completion of cancer treatment due to lack of specialized programs for cancer survivors and reimbursement of fees.[39]

There is also preliminary evidence from open-label and/or uncontrolled studies to support the efficacy of integrative medicine approaches to the treatment of fatigue, including yoga, relaxation, mindfulness-based stress reduction, acupuncture, medical Qigong, massage, healing touch, Reiki, and combined modality interventions that include aromatherapy, lavender foot soaks, and reflexology.[34,40] However, the studies examining these interventions have tended to have small and/or heterogeneous samples, making it difficult to draw firm conclusions regarding the efficacy of these interventions in survivor populations.

Our bibliometric analysis of the literature comparing the fatigue trials published by European researchers with those conducted by investigators in the United States and Canada revealed that our current knowledge about the effectiveness of CRF interventions is supported by a generally balanced representation of studies conducted in Europe compared with the United States and Canada. However, some trends were noted. For example, a majority of the randomized trials of exercise, sleep, energy conservation, activity management, psychostimulant drugs, and antidepressants to treat CRF have been conducted by US investigators. Most of the randomized trials of structured rehabilitation interventions have been tested by European researchers. One reason may be the more prohibitive drug trial regulations in Europe than in the United States.

Psychoeducational and psychosocial support interventions, acupuncture, and levocarnitine

supplementation have been tested by both US and European researchers, although predominantly in patients receiving active anticancer treatment or those at the end of life. A majority of the systematic reviews have been conducted by European researchers, whereas the 2 guidelines for the management of CRF were developed by US-based investigator teams.

In summary, a wide range of pharmacologic and nonpharmacologic interventions for fatigue have been studied, although many potentially promising interventions have been tested in only uncontrolled or pilot studies. With the exception of exercise and rehabilitation, to our knowledge relatively few studies have been conducted in samples comprised exclusively of cancer survivors who are posttreatment.

Future Directions: European Perspective

There is overlap between Europe and the United States with regard to future areas of focus related to CRF. An overall aim will be to design international and transcontinental studies. European researchers and clinicians need to reach consensus on the clinical phenotype(s) of CRF in survivors, accommodating the variability in their presenting features. We also need to link the symptom of fatigue to its impact on functioning. It is not possible to intervene for all patients and the evidence[1,5] suggests those with the most severe fatigue are the ones most likely to respond to an intervention. This should be linked to the further intervention of biological markers.

European researchers now need to develop trials specifically for examining interventions in fatigued survivors. These may be exercise-based with a brief cognitive intervention, but also may be directed toward the modulation of the prolonged inflammatory response observed in this group.[11] Whatever intervention is used, the inclusion of biomarkers as surrogate endpoints, together with the measurement of CRF and physical functioning as primary and secondary endpoints, will contribute to our knowledge of the etiology of CRF and the mechanism of action underlying effective interventions.

Future Directions: United States Perspective

Variations in the conceptual definitions of CRF give rise to different requirements for adequate measurement. The European and US conceptual definitions differ; the European definition includes sensation only whereas the US definition includes both sensation and functional impact. These differences result in a lack of comparability of CRF measures and limit the ability to collaborate and replicate research findings and extend the theory base. However, studies examining the experience of CRF using qualitative methods conducted in Europe, the United States, and other countries reveal fairly consistent observations cross culturally. CRF is highly prevalent, experienced as distressing and unpredictable, amplifies symptoms and mood disturbances, and is problematic for patients to self-manage. There is a need for expert consensus on the key construct that should be measured in different types of CRF research including domains of self-reported CRF, use of case definition, and other behavioral or biological constructs. Such consensus on measurement will support investigators in leveraging data resources such as cancer registries and nationally representative panels and facilitate larger, more diverse samples for observational studies.[41] Despite a robust scientific literature of behavioral correlates for CRF, there is limited understanding of its biology. Research is needed to extend our understanding of biological mechanisms underlying CRF in survivors to include the role of proinflammatory cytokines and HPA axis dysfunction,[11,42] as well as other theoretically plausible mechanisms such as disrupted circadian rhythms, disturbed sleep, and dysregulated monoamine pathways that control dopamine, serotonin, and norepinephrine. Ultimately, an integrated understanding of these pathways is essential to complete our understanding of CRF.

Another important trend in symptom research is the examination of profiles of gene polymorphisms, which are mutations and/or common variations associated with gene function; gene expression, the evidence of activation and de activation of genes; and protein concentration, such as cytokines, to better understand the genetic basis of CRF.[43,44] A clearer understanding of the biology and genetics of CRF will enable the identification of new pharmacologic targets for CRF intervention.

Rigorously designed and adequately powered randomized controlled trails are urgently needed to test therapies for fatigue that have demonstrated therapeutic effects in preliminary studies in cancer survivors. Harmonized definitions of fatigue and the use of instruments with demonstrated measurement invariance across languages and cultures will permit pooling of data, including from those from non-cancer comparison groups. Additional research in large, heterogeneous samples is needed to isolate the components of an intervention, such as exercise, that account for observed improvements in fatigue outcomes.[45] Comparative effectiveness studies are also needed to determine how transferable findings will be across languages, clinical settings, and cultures.

Given the lack of international investigator teams and consortia, we identified a current opportunity to

strengthen collaboration between fatigue researchers in the United States and Europe in testing interventions for fatigued cancer survivors. Several substantive and methodological challenges will need to be addressed to set the stage for such collaborations, including international consensus on the defining features of fatigue in cancer survivors; harmonized measurement of fatigue outcomes using instruments that have demonstrated measurement equivalence across languages and cultures; and interventions, such as including exercise, rehabilitation, and psychoeducational interventions that have been manualized to permit intervention fidelity across diverse contexts. Study designs and sampling frames will need to be controlled for the possible effects of regional, cultural, and economically related differences in cancer treatment approaches and care delivery patterns and variability in selection biases for study participation and follow-up.[46]

DISCUSSION

As science advances in its attempt to identify and reduce the gaps in our understanding and management of CRF, we identified several priority areas in which to coordinate efforts. The first is the lack or underdevelopment of unifying model(s) of CRF mechanisms or CRF itself. A recently proposed framework provides a reference point for future testing and revision.[47]

We also agree that European and US investigators can benefit from the development of a core set of domains and correlates that should be measured to ensure complete reporting of CRF outcomes. Agreement on a core set of outcome domains also can facilitate comparison and pooling of data across investigations, ultimately maximizing the cost-benefit, power, and scientific yield of CRF research in survivors. Domains may include biological attributes as well as case definition, self-reported symptoms, and key aspects of functioning. Work by previous ad hoc groups to develop consensus statements on the measurement of symptoms such as pain, fatigue, and insomnia could serve as a model for the proposed efforts.[22,48,49]

Given that CRF is rooted in biology as well as behavior, we agree that it is unlikely that there is a simple biological or psychosocial explanation for this symptom. Studies are needed to explore whether there is a single phenotype of fatigue in cancer survivors or perhaps several distinct phenotypes, with those phenotypes united by self-report of fatigue, tiredness, or lack of energy. We identified the need to determine to what extent fatigue occurring in different groups of cancer survivors (groups based on gender, age, disease type, and treatment type) has different features (eg, a syndrome of asthenia, sarcopenia, diminished endurance, and perception of fatigue) versus a syndrome of perception of fatigue (eg, sleep disturbance, mood changes, and daytime dysfunction). Coordinated transcontinental efforts will increase our understanding of the biological, psychological, and social features of CRF and will contribute to the design of future studies.

In the United States, the development of clinical practice guidelines for the management of CRF has been a strong focus of professional organizations including the NCCN and the Oncology Nursing Society.[20,27] We agree that an important step forward will be to involve European experts in guideline revisions to ensure that the guidelines reflect European care standards and facilitate the uptake and adoption of the guidelines on both continents.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

Dr. Minton was supported by a Cancer Research UK psychooncology fellowship at the time of writing this article.

REFERENCES

1. Stone PC, Minton O. Cancer-related fatigue. *Eur J Cancer*. 2008;44:1097-1104.
2. Minton O, Stone P. How common is fatigue in disease-free breast cancer survivors? A systematic review of the literature. *Breast Cancer Res Treat*. 2008;112:5-13.
3. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol*. 1999;17:253-261.
4. Cancer Research UK. Breast Cancer Survival Statistics. info.cancerresearchuk.org/cancerstats/types/breast/survival/. Accessed December 7, 2011.
5. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: a critical appraisal. *Eur J Cancer*. 2006;42:846-863.
6. Radbruch L, Strasser F, Elsner F, et al; Research Steering Committee of the European Association for Palliative Care (EAPC). Fatigue in palliative care patients-an EAPC approach. *Palliat Med*. 2008;22:13-32.
7. Minton O, Stone P. A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). *Ann Oncol*. 2009;20:17-25.
8. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
9. Munir F, Yarker J, McDermott H. Employment and the common cancers: correlates of work ability during or following cancer treatment. *Occup Med (Lond)*. 2009;59:381-389.

10. Department of Health. Cancer Survivorship Initiative. dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_088879. Accessed January 12, 2012.
11. Minton O, Stone PC. Review: the use of proteomics as a research methodology for studying cancer-related fatigue: a review. *Palliat Med*. 2010;24:310-316.
12. Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. *Brain Behav Immun*. 2007;21:251-258.
13. Minton O, Stone P. Cancer related fatigue: mechanisms, assessment and treatment in older people. *Rev Clin Gerontol*. 2011;21:255-266.
14. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. *Support Care Cancer*. 2001;9:11-17.
15. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev*. 2003;24:236-252.
16. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. 1994;121:953-959.
17. Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W. Progress toward guidelines for the management of fatigue. *Oncology (Williston Park)*. 1998;12:369-377.
18. Alexander S, Minton O, Stone PC. Evaluation of screening instruments for cancer-related fatigue syndrome in breast cancer survivors. *J Clin Oncol*. 2009;27:1197-1201.
19. Piper B. Fatigue: current bases for practice. In: Funk SG, Tornquist EM, Champagne MT, Copp L, Wiese R, eds. Key Aspects of Comfort: Management of Pain, Fatigue and Nausea. New York: Springer; 1989:187-207.
20. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed March 14, 2013.
21. World Health Organization. International Classification of Functioning, Disability and Health. who.int/classifications/icf/en/. Accessed October 2, 2012.
22. Barsevick AM, Cleeland CS, Manning DC, et al; ASCPRO (Assessing Symptoms of Cancer Using Patient-Reported Outcomes). ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *J Pain Symptom Manage*. 2010;39:1086-1099.
23. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol*. 2007;25:5106-5112.
24. Shin HB, Kominski RA. Language Use in the United States: 2007-2010. American Community Survey Reports Vol 12. Washington, DC: US Census Bureau; 2010.
25. US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. US Department of Health and Human Services: Quick Guide to Health Literacy. health.gov/communication/literacy/quickguide/. Accessed March 14, 2013.
26. Goss E, Lopez AM, Brown CL, Wollins DS, Brawley OW, Raghavan D. American Society of Clinical Oncology policy statement: disparities in cancer care. *J Clin Oncol*. 2009;27:2881-2885.
27. Mitchell SA, Beck SL, Hood LE, Moore K, Tanner ER. Putting evidence into practice: evidence-based interventions for fatigue during and following cancer and its treatment. *Clin J Oncol Nurs*. 2007;11:99-113.
28. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev*. 2010;(7):CD006704.
29. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2008;(2):CD006145.
30. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev*. 2009;(1):CD006953.
31. Godfrey J. Safety of therapeutic methylphenidate in adults: a systematic review of the evidence. *J Psychopharmacol*. 2009;23:194-205.
32. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ*. 2012;344:e70.
33. Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. *J Pain Symptom Manage*. 2011;41:761-767.
34. Mitchell SA. Cancer-related fatigue: state of the science. *PMR*. 2010;2:364-383.
35. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull*. 2008;134:700-741.
36. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychol*. 2007;26:660-667.
37. Irwin ML. Physical activity interventions for cancer survivors. *Br J Sports Med*. 2009;43:32-38.
38. van Weert E, May AM, Korstjens I, et al. Cancer-related fatigue and rehabilitation: a randomized controlled multicenter trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention. *Phys Ther*. 2010;90:1413-1425.
39. Alfano CM, Ganz PA, Rowland JH, Hahn EE. Cancer survivorship and cancer rehabilitation: revitalizing the link. *J Clin Oncol*. 2012;30:904-906.
40. Kwekkeboom KL, Cherwin CH, Lee JW, Wanta B. Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. *J Pain Symptom Manage*. 2010;39:126-138.
41. Ashley L, Jones H, Thomas J, et al. Integrating cancer survivors' experiences into UK cancer registries: design and development of the ePOCS system (electronic Patient-reported Outcomes from Cancer Survivors). *Br J Cancer*. 2011;105(suppl 1):S74-S81.
42. Lyon DE, McCain NL, Pickler RH, Munro C, Elswick RK Jr. Advancing the biobehavioral research of fatigue with genetics and genomics. *J Nurs Scholarsh*. 2011;43:274-281.
43. Aouizerat BE, Dodd M, Lee K, et al. Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biol Res Nurs*. 2009;11:27-41.
44. Gilbertson-White S, Aouizerat BE, Miaskowski C. Methodologic issues in the measurement of cytokines to elucidate the biological basis for cancer symptoms. *Biol Res Nurs*. 2011;13:15-24.
45. Lakoski SG, Eves ND, Douglas PS, Jones LW. Exercise rehabilitation in patients with cancer. *Nat Rev Clin Oncol*. 2012;9:288-296.
46. Syse A, Geller B. A cross-cultural perspective on challenges facing comparative cancer survivorship research. *J Cancer Epidemiol*. 2011;2011:689025.
47. Berger A, Mitchell S. Cancer-related fatigue and sleep-wake disturbances. In: Lester J, Schmitt P, eds. Cancer Rehabilitation and Survivorship: Transdisciplinary Approaches to Personalized Care. Pittsburgh, PA: Pittsburgh Oncology Nursing Society; 2011:101-112.
48. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106:337-345.
49. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. *Sleep*. 2006;29:1155-1173.

Original Article

Cardiac Toxicity in Cancer Survivors

Daniel J. Lenihan, MD[1]; Stefano Oliva, MD[2]; Eric J. Chow, MD, MPH[3]; and Daniela Cardinale, MD, PhD[4]

Cardiac disease is a major concern for cancer survivors, and this can be manifested as cardiac dysfunction from myocardial damage, valvular disease, atherosclerosis, and/or pericardial disease. In this "dialogue" between select European and American investigators, present current perspectives (both similarities and differences) are presented regarding the diagnosis and management of cardiac disease among cancer survivors, with a focus on left ventricular (LV) systolic dysfunction and heart failure. The authors conclude that comprehensive cardiac risk assessment is necessary to optimally manage all cancer survivors, and the integration of common definitions is necessary. Ongoing and future research will need to incorporate cardiovascular management principles in the long-term assessment of cancer survivors. Cardiac biomarkers, troponin, and the natriuretic peptides are becoming essential in the management of cardiac disease in cancer survivors coupled with periodic use of sophisticated imaging tools. Recognition of specific cancer therapy and the increased cardiovascular risk is an ongoing task that will remain of paramount importance for optimal outcomes among cancer survivors. ***Cancer*** **2013;119(11 suppl):2131-42.** *© 2013 American Cancer Society.*

KEYWORDS: cardiotoxicity; heart failure; survivorship; cardioprotection.

INTRODUCTION

Over the past 10 to 15 years, cardiac complications resulting from cancer therapy have been recognized increasingly as major contributors to morbidity and, ultimately, mortality in cancer survivors.[1-6] However, despite this increased recognition, there are major limitations in our collective understanding of the proper tools necessary for the identification, treatment, or prevention of these complications. Although many systematic reviews have been conducted with regard to various topics related to cardiac disease in this population (and are referenced in the current article), this "dialogue" between European and American investigators will provide insight to some of the current perspectives in Europe and the United States on viewing and managing this burgeoning issue. Because of the success of cancer therapy and the complexity of the treatment regimens that are being increasingly used to control cancer, there are myriads of cardiac conditions that must be considered in cancer survivors. Although the term "cardiotoxicity" generally refers to heart damage as a result of treatment, specifically, this has been used most commonly to describe left ventricular (LV) systolic dysfunction and heart failure (HF) related to certain types of chemotherapy.[7-9] Although LV systolic dysfunction and HF are the focus of this report, it is important to recognize that other components of the cardiovascular system (eg valves, vasculature, pericardium) also may be affected by both chemotherapy and radiotherapy, with subsequent effects on heart function.[5,6,10-12] Featuring select European and American perspectives, 5 topics are discussed below: 1) definitions of "cardiotoxicity" and current limitations, 2)

Corresponding author: Daniel J. Lenihan, MD, Vanderbilt University Medical Center, Vanderbilt Heart and Vascular Institute, 1215 21st Avenue South, MCE 5209, Nashville, TN 37232-8802; Fax: (615) 875-3171; daniel.lenihan@vanderbilt.edu

[1]Divison of Cardiovascular Medicine, Vanderbilt University, Nashville, Tennessee; [2]Cardiology Unit, National Cancer Research Center, Istituto Tumori "Giovanni Paolo II,", Bari, Italy; [3]Public Health and Clinical Research Divisions, Fred Hutchinson Cancer Center, Seattle, Washington; [4]Cardioncology Unit, European Institute of Oncology, Milan, Italy.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

The opinions or views expressed in this supplement are those of the authors and do not necessarily reflect the opinions or recommendations of the journal editors, the American Cancer Society, John Wiley & Sons, Inc., or the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari.

All 4 authors contributed equally in this work.

We greatly appreciate the expert article preparation by Lauren Morrow.

DOI: 10.1002/cncr.28061, **Received:** July 27, 2012; **Revised:** January 22, 2013; **Accepted:** January 31, 2013, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

epidemiology and risk factors, 3) early detection, 4) treatment, and 5) possible prevention strategies. Finally, in conclusion, suggested areas for research and improved clinical practice are outlined for development internationally.

Definitions of "Cardiotoxicity" and Current Limitations

American perspective

Historically, HF resulting from cancer treatment was considered a synonym for "cardiotoxicity" largely based on the description of adverse cardiac events that resulted from anthracycline administration. The Common Terminology Criteria for Adverse Events (CTCAE) formulated by the US National Cancer Institute for clinical research reporting has defined "cardiotoxicity" solely as symptomatic LV systolic dysfunction (an LV ejection fraction [LVEF] of <50%) or congestive HF.[13] This method of reporting is a very insensitive assessment of HF as a clinical condition that results from chemotherapy, especially because nearly half of patients admitted in the United States for HF actually have a normal or nearly normal LVEF.[14,15] In addition, HF was not a codeable diagnosis in the first 3 versions of the CTCAE. Furthermore, in any trial that was not a phase 1 or 2 study, only grade 3 toxicity was reportable (symptomatic severe reduction of systolic dysfunction with an LVEF <20%) and, thus, milder cases of LV systolic dysfunction were not ascertained. Finally, rates of HF and LV systolic dysfunction generally are described best in the minority of patients who participate in clinical trials. Patients who are cancer survivors uniformly would be excluded from cardiology research trials, and cancer survivors who dropped out of an oncology trial because of toxicity generally would not have any systematic follow-up. Even for patients on clinical trials, ascertainment of late cardiotoxicity may be limited by the sometimes long interval between potential cardiotoxic exposure and the development of clinical or even subclinical findings.

Because of these reporting limitations, outside of some special populations, it has been extremely difficult to know the incidence and prevalence of LV systolic dysfunction or HF that results from chemotherapy, even anthracycline-based therapy, which is the most commonly recognized. Although not without limitations, Surveillance, Epidemiology, an End Results-Medicare linkages provide some population-based insight into the epidemiology among older cancer patients,[16,17] and large cohort studies like the Childhood Survivor Study provide important data on childhood cancer survivors.[18] The current CTCAE (version 4) is more detailed than previous versions in its reporting of LV dysfunction (reduced LVEF <50%) and HF. However, a more careful description of cardiac toxicity is represented in data from Italy that examines cardiac toxicity in terms of HF, asymptomatic LV dysfunction, arrhythmia requiring treatment, and sudden cardiac death.[19] These data form a broader and more complete description of cardiac toxicity that should serve as a model for future research efforts.[7]

European perspective

Given the potentially long interval (up to 2 or 3 decades in some instances) between cancer therapy exposure (both chemotherapy and radiotherapy) and subsequent adverse, measurable effects on cardiac health, such adverse effects can have an important, albeit delayed effect on the prognosis of long-term survivors.[2,4,9,19,20] It has been difficult even to develop a consensus for a more specific outcome, such as LV dysfunction, including identifying the most sensitive markers and the most appropriate threshold for action. LV dysfunction may result from many anticancer drugs through different mechanisms and may manifest as declined LVEF as a final common pathway.[21] However, although LVEF remains one of the most commonly used indexes of LV systolic myocardial performance, a reduction in LVEF is considered a very late finding.[22] Currently, cardiotoxicity is commonly defined either as an LVEF reduction of greater than 10 percentage points with a final LVEF <50% or as an LVEF reduction greater than 15 percentage points with a final LVEF >50%.[23] It is unclear whether a minimal reduction of 5 percentage points with accompanying HF symptoms is enough for a diagnosis of cardiotoxicity.[24] Nevertheless, currently, a change in LVEF remains the basis for all definitions of cardiotoxicity issued by scientific societies in both Europe and the United States.[10,25,26] Table 1 provides examples of different definitions of cardiotoxicity used by selected studies,[34] and one of the most commonly used severity grading systems of chemotherapy-related LV dysfunction is detailed Table 2.[13,32,35-38]

Epidemiology and Risk Factors

The dose relation between anthracyclines, radiation, and subsequent cardiotoxicity has been extensively reviewed by others.[20,39-41] The exact mechanism by which anthracyclines cause cardiac injury still is not well understood but likely involves the production of free radicals, which accentuate mitochondrial and cardiomyocyte damage.[41] Separate effects mediated by cardiomyocyte topoisomerase also may be important.[42] The relation between anthracycline exposure and cardiac injury was appreciated early on[43]; and, as dosing practices have evolved, acute toxicity

TABLE 1. Previous Definitions of Cardiotoxicity Used by Selected Clinical Trials[a]

Reference	Definition of Cardiotoxicity	Drug	Results and Cardiotoxicity
Tan-Chiu 2005[27]	Decline LVEF by 10% to <55%	Trastuzumab	Cardiac events at 3 y: 4.1% (AC-TH) vs 0.8% (AC-T)
Perez 2004[28]	LVEF decline ≥15% compared with baseline to below the LLN (toxicity grade 2)	Doxorubicin and cyclophosphamide	Grade 2 toxicity, 6.6%
Suter 2004[29]	Decline of LVEF ≥15 points to <50%	Trastuzumab	Received trastuzumab, 6.5%; did not receive trastuzumab, 0.7% (preliminary data from 6 trials)
O'Brien 2004[30]	Decline in LVEF of 20 points to >50% or at least 10 points to <50% or clinical CHF	Doxorubicin	Decline of LVEF, 18.8% (of which 21% had clinical CHF); clinical CHF without LVEF decline, 0.8%
Smith 2007[31]	Decline in LVEF of ≥10 points from baseline to <50%	Trastuzumab after adjuvant or neoadjuvant chemotherapy	Unadjusted HR for the risk of an event with trastuzumab compared with observation alone: 0.64 (95% CI, 0.54-0.76; $P < .0001$)
Romond 2005[32]	Decline of LVEF ≥16 points or <LLN	Doxorubicin and cyclophosphamide followed by trastuzumab	Discontinued trastuzumab because of toxicity: 31.4%
Ryberg 2008[33]	Decline of LVEF <45% or 15 points from baseline	Epirubicin	Developed cardiotoxicity: 11.4%

Abbreviations: AC-T, doxorubicin and cyclophosphamide followed by docetaxel; AC-TH, doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; LLN, lower limit of normal; LVEF, left ventricular ejection fraction.
[a] Adapted from Sawaya 2011.[34]

TABLE 2. Severity Grades of Chemotherapy-Related Left Ventricular Systolic Dysfunction

Grade I	Asymptomatic decline in LVEF of >10% from baseline evaluation
Grade II	Asymptomatic decrease in LVEF of <50% or ≥20% compared with baseline value
Grade III	Heart failure responsive to treatment
Grade IV	Severe or refractory heart failure or requiring intensive medical therapy and/or intubation
Grade V	Death related to cardiac toxicity

Abbreviations: LVEF, left ventricular ejection fraction.
[a]Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events,[13] Martin 2009,[24] Eschenhagen 2011,[25] Bovelli 2010,[26] Swaya 2011,[34] and Tarantini 2012.[35]

has become rare, but anthracycline-treated patients continue to experience an increased risk of chronic, typically dilated cardiomyopathy that may not be detected until years or even decades after exposure, especially with doses greater than 250 or 300 mg/m^2.[16,18,39]

In a European prospective, longitudinal study of childhood cancer survivors, the most important predictor of worsening cardiac performance was total anthracycline dose.[44] Similarly, a large, retrospective Swedish experience in young patients, including children, who received chemotherapy and radiotherapy for Hodgkin lymphoma indicated that age at diagnosis (<40 years) and family history of HF predicted the development of HF and stroke at follow-up after 20 years.[45] If young age is a risk for childhood patients, then, similarly, older age is a notable risk for older women with breast cancer who are currently receiving trastuzumab in an adjuvant setting[35] and for all patients who have received anthracyclines.[46,47] In addition to age, it also has been demonstrated that female childhood cancer survivors are at increased risk of cardiomyopathy in some studies, but that finding had borderline significance[44,48] or was not supported in other studies.[9]

Similarly, radiotherapy-related late effects usually take years to manifest in the form of accelerated (compared with expected population rates) coronary artery and other vascular diseases, valvular dysfunction, pericardial disease, and sometimes LV dysfunction and restrictive cardiomyopathy.[5,18,40,49] Although there also exists a clear dose-response relation, especially in patients with left-sided breast cancer, some reports suggest that the risk may be increased even with doses <5 Gy.[20]

Although cardiac complications associated with anthracyclines and radiotherapy are the best studied to date, other agents also have been associated with cardiotoxicity. Anthracycline-related derivatives, such as mitoxantrone, may be less likely to cause cardiomyopathy, but they are not risk-free either.[50] There are different anthracycline derivates that may reduce cardiotoxicity in cancer patients.[50] Other chemotherapy, such as high-dose alkylator therapy given as part of hematopoietic cell transplantation conditioning regimens, also have been linked to an increased risk of HF.[51] Finally, newer agents, such as trastuzumab, a monoclonal antibody to the human epidermal growth factor receptor-2 (HER2) (also called ErbB2), have been associated with LV dysfunction, including an

increased risk of clinical HF, when received by patients who previously received or are currently receiving anthracycline-based regimens.[52] The mechanism of this toxicity may be related to additive stress on repair mechanisms after anthracycline administration, like a response to the negative stress of chemotherapy.[53] Increased rates of myocardial ischemia and LV dysfunction also have been observed after treatments with tyrosine kinase inhibitors, such as sorafenib[54] and sunitinib,[55] respectively.

Finally, although cancer therapy-related cardiotoxic exposures are important, many studies have indicated that conventional risk factors, such as smoking,[38] hypertension, and diabetes,[26,42-44] remain important independent risk factors. Variation in individual risk may also be explained by underlying genetic variation. Recent studies have reported several candidate single nucleotide polymorphisms in drug metabolism pathway genes that may be associated with anthracycline-related cardiomyopathy among childhood cancer survivors,[48,56] supplementing previous work done using in vitro assays.[57,58] Investigators also have begun to examine the role of genetic polymorphisms in the inflammatory pathway genes in relation to heart disease after radiotherapy.[59] Because heterogeneity in phenotype has been a major barrier to replication in genetic epidemiology research,[60] a consistent, internationally accepted definition of key cardiotoxic outcomes will be important in facilitating future work in this area, including the validation of these preliminary findings.

Early Detection of Cardiac Toxicity

Given the significant impact of cardiotoxicity on prognosis for patients with cancer, earlier detection has become a primary goal for both cardiologists and oncologists. Many providers do not recognize that anthracycline-based chemotherapy is such a powerful risk factor for the development of LV dysfunction, although it is identified as a high-risk clinical indicator for the development of HF in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the detection and treatment of HF.[61] Currently, the most frequently used modality for detecting cardiotoxicity is the periodic measurement of LV systolic function (typically the ejection fraction and sometimes fractional shortening) by either 2-dimensional echocardiography (2D ECHO) or multigated acquisition scanning (MUGA).[62] To date, however, there are no evidence-based adult guidelines for cardiotoxicity monitoring during and after anticancer therapies (Table 3).[25,61] Evidence-based and consensus-based guidelines in pediatric oncology have been published by different national groups, although they differ in their recommendations.[64-66]

TABLE 3. Summary of Guidelines With Recommended Approaches for Cardiotoxicity Monitoring

Professional Organization	Reference	Recommendations[a]
ACC/AHA	Hunt 2009[61]	1, 2, 5
HFSA	Lindenfeld 2010[63]	1, 2, 5, 6
ASCO	Carver 2007[10]	2, 5, 6
ESC	Eschenhagen 2011[25]	2, 5, 6
ESMO	Curigliano 2012[21]	1, 2, 3, 4, 5, 6
COG	Landier 2004[64]	1, 2, 6
CCSG	Skinner 2006[65]	1, 2, 6
DCOG	Sieswerda 2012[66]	1, 2, 3, 6

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCO, American Society of Clinical Oncology; CCSG, Children's Cancer Study Group (United Kingdom); COG, Children's Oncology Group (primarily United States); DCOG, Dutch Children's Oncology Group; ESC, European Society of Cardiology; ESMO, European Society of Medical Oncology; HFSA, Heart Failure Society of America.

[a] The numbered guidelines with recommended approaches for cardiotoxicity monitoring are as follows: 1) All patients who receive cardiotoxic therapy are considered to be at high risk for the development of heart failure; 2) left ventricular systolic function assessment should be performed at baseline and at some subsequent interval (no specific time point); 3) angiotensin-converting enzyme inhibitors and beta blockers are recommended for treatment; 4) angiotensin-converting enzyme inhibitors are recommended for prevention; 5) adult survivors; and 6) pediatric cancer survivors.

European perspective

Recently published European Society of Medical Oncology clinical practice guidelines specify more details, although these are not necessarily based on high levels of evidence.[21] For example, these guidelines recommend assessing cardiac function 4 years and 10 years after anthracycline therapy in patients who were treated at age <15 years (evidence level, III [with level I considered the most rigorous]; recommendation grade, B [with A considered superior]), or even at age >15 years but with a cumulative dose of doxorubicin >240 mg/m^2 or epirubicin >360 mg/m^2 (evidence level III B). If LV dysfunction is detected by imaging or cardiac biomarkers (evidence level III C), then the receipt of angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), or perhaps beta-blockers may limit progression to symptomatic HF. In fact, in the European guidelines, the aggressive medical treatment of those patients, even if they are asymptomatic, who demonstrate LV dysfunction after anthracycline therapy "is mandatory," especially if long-term survival is expected.

Recommendations also exist for trastuzumab-treated patients to receive serial evaluation of LVEF every 3 months.[24,67] However, not all patients who receive trastuzumab have LVEF monitoring as frequently as

suggested by the guidelines; conversely, a considerable percentage of patients do not have favorable outcomes even with close cardiac monitoring.[68,69] This reflects the reality that LVEF measurement is a relatively insensitive tool for detecting cardiotoxicity at an early stage, largely because no considerable change in LVEF occurs until a critical amount of myocardial damage has taken place, and it only comes to the forefront after compensatory mechanisms are exhausted. Serial measurements of troponin I can provide complimentary information in this setting but are not routinely done or recommended.[22,70] Therefore, evidence of a decrease in LVEF precludes any chance of preventing the development of cardiotoxicity.[71] Conversely, a normal LVEF does not exclude the possibility of later cardiac deterioration. In addition, the measurement of LVEF presents several challenges related to image quality, assumption of LV geometry, load dependency, and expertise. Novel echo imaging techniques, like contrast echocardiography and real-time, 3-dimensional echocardiography, have emerged that allow for an improvement in the accuracy of calculating LVEF.[72] Small studies examining tissue Doppler and strain rate imaging appear promising for detecting early subclinical changes in cardiac performance that anticipate a decrease in conventional LVEF, even if long-term data on large populations confirming the clinical relevance of such changes are not yet available.[73,74] The advantages are that these techniques do not require a separate examination and that the technology is available on most current machines. The disadvantage is that data analysis is currently off-line, very time-consuming, and still depends on the quality of the acoustic windows. Currently, although they are promising, these new echo imaging techniques cannot yet be recommended as part of routine assessment of cardiac function among cancer survivors.[75] Alternative imaging modalities and serum-based biomarkers are discussed further below.

American perspective

Currently, the measurement of cardiac biomarkers (troponin I and troponin T, B-type natriuretic peptide [BNP], and N-terminal pro-BNP) are becoming more widely used to detect cardiac toxicity among patients actively receiving cancer therapy as well as short-term survivors.[77-79] However, there is not a clear, consistent recommendation, because there are many variations in the techniques to measure each assay, and the optimal timing of measurement and interpretation in relation to chemotherapy have not been established. Furthermore, less established data exist to guide choices on how to respond to an abnormal value when a patient is receiving anthracyclines[79] and perhaps trastuzumab. Data for other drug regimens are even less well studied. Notwithstanding these limitations, the early detection of cardiac toxicity is possible and can facilitate earlier intervention, which may attenuate cardiac injury even if it is associated with anthracyclines.[22] Again, this is a critical difference from the long-held belief that the trajectory of anthracycline-related cardiac injury is not modifiable.

Cardiac imaging with 2D ECHO, MUGA, or magnetic resonance imaging (MRI) has been used for many years to detect cardiac toxicity. There is considerable evidence suggesting that 2D ECHO or MUGA are adequate screening tests for clinically detectable LV dysfunction, but they are not very sensitive for detecting earlier subclinical injury.[22] There have been no recent developments regarding MUGA and the utility of MUGA-based results for early detection. MRI has gained importance recently, primarily because of the accuracy of its LV measurements and its ability to characterize the myocardium as either normal, recently injured, or permanently damaged, which is superior using MRI compared with 2D ECHO.[80] Compared with 2D ECHO, MRI has disadvantages in terms of more limited availability and radiologic expertise as well as a potential for its accompanying contrast to worsen any renal insufficiency. MRI also is contraindicated in patients who have implanted mechanical devices. Finally, young children undergoing MRI often require anesthesia. However, these issues aside, MRI likely will be a valuable resource for monitoring and detecting cardiac damage for years to come.

Which ever imaging technique is used, it is best to repeat serial measurements with the same tool to minimize intermeasurement variability, although interobserver variability remains a potential issue. However, currently, there is no international consensus on recommendations regarding the expected or required interval for testing, although efforts are being made to harmonize recommendations for pediatric survivors,[64-66] and some consensus guidelines have been issued for hematopoietic cell transplantation survivors.[81] This has great importance, because these all of imaging studies are expensive, much more so than troponins and/or BNPs, and cannot be routinely repeated without clear benefit and necessity. One recommendation by the US Food and Drug Administration is to follow patients who are receiving long-term trastuzumab with imaging studies every 3 months, although this is not necessarily practical or economically feasible.[82] Issues related to an optimal screening schedule and relative cost-utility remain an understudied area but may very well differ in different health care delivery systems.

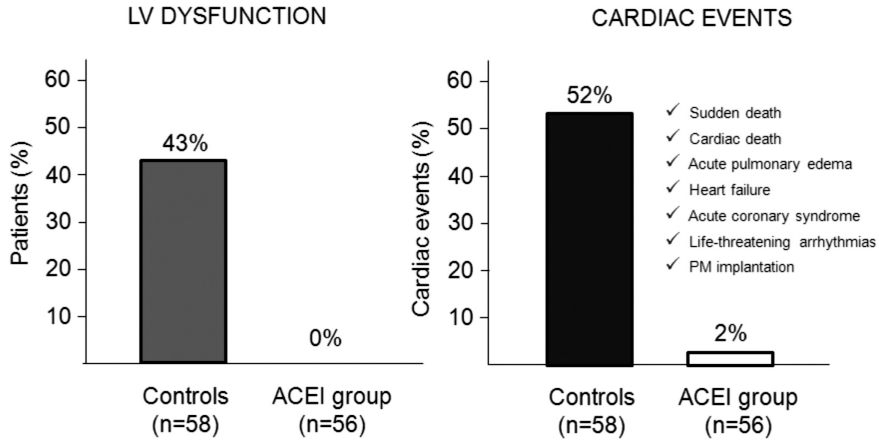

Figure 1. These charts illustrate the protective effect of angiotensin-converting enzyme inhibitors (ACE-I) on cardiac outcomes in patients undergoing chemotherapy (predominately anthracycline-based) who were randomized to receive ACE-I after an early increase in troponin I levels (ACE-I group, n = 56; controls, n = 58). LV dysfunction indicates left ventricular dysfunction (defined as a left ventricular ejection fraction <50% plus a decrease >10% from the starting value). Cardiac events include sudden death, any cardiac death, symptomatic heart failure, LV dysfunction, and serious rhythm disturbance requiring treatment. PM indicates pacemaker. (Adapted from Cardinale D, Colombo A, Sandri MT et al Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114:2474-2481.[85]).

Today, strong data indicate that troponin detects anticancer drug induced-cardiotoxicity in its earliest phase, long before any reduction in LVEF has occurred.[77] Troponin is now the gold-standard biomarker for myocardial injury from any cause.[83] Its evaluation during high-dose chemotherapy allows for the early identification of patients who are at risk of developing cardiac dysfunction, the stratification of risk for cardiac events after chemotherapy, and the opportunity for a preventive therapy in selected high-risk patients.[19,84,85] Indeed, it has been demonstrated that prophylactic treatment with enalapril in adult patients who have an early increase in troponin after chemotherapy prevents cardiac dysfunction and associated cardiac events in patients who receive high-dose anthracyclines (Fig. 1).[85] More recently, increases in troponin levels have been observed in patients who received standard anthracycline doses and in patients who received newer antitumor agents.[74,77,78,86] Moreover, in trastuzumab-treated patients, by identifying myocardial cell necrosis, troponin may help us to distinguish between reversible and irreversible cardiac injury.[70]

In the published studies, there is wide variation in the sampling protocols for the measurement of troponins, with increased levels detected at various time intervals after chemotherapy, possibly because of diverse troponin release kinetics in response to cardiotoxic injury with different agents. Thus, currently, most research surveillance protocols have deemed it necessary to collect blood samples several times to document a potential increase in troponin levels.[77] This represents a possible limitation for using the marker in clinical practice; however, the measurement of troponin only immediately before and immediately after each cycle of cancer therapy may be sufficient, and such a protocol would be more easily transferable from the research setting to actual clinical practice.[70] This biomarker-based protocol is likely to be cost-effective when negative values allow for the exclusion of most patients from a long-term monitoring program based on more expensive imaging methods. However, the standardization of routine troponin measurement in the clinical setting to maximize single-time-point assay sensitivity and specificity is needed and should be an important focus for future research. Furthermore, additional vascular biomarkers, such as endothelial growth factors, may be important in identifying those at risk for vascular toxicity with newer antiangiogenic-based treatment, although, currently, those are speculative.[87]

Finally, although our focus is on chemotherapy-related HF, the long-term effects of radiation therapy on the heart can be quite profound.[88] Typically, there is a long period of latency and then the complexity is significant. Peripheral vascular and coronary artery disease are major issues that are classically asymptomatic until a major clinical event occurs. Consideration of appropriate screening tests in high-risk individuals is imperative. For example, carotid ultrasound screening is highly appropriate for patients who have received mantle or head and neck radiation, whereas cardiac stress testing is important in survivors who received radiation to the mediastinum. It also is important to factor in radiation scatter to these

regions from radiotherapy primarily directed toward the spine and upper abdomen. Cardiac valvular structures also are affected by mediastinal radiation, and 2D ECHO is the most appropriate screening test for this condition.

Treatment of Cardiotoxicity

American perspective

The treatment of cardiac toxicity is greatly influenced by the comorbidities that exist in a given patient and the context in which that damage is detected. For example, if a patient is acutely ill from a hematologic-based malignancy, then there may be transient LV dysfunction from a variety of causes, including stress cardiomyopathy or sepsis; and, after a period of stabilization, the patient may be able to resume cardiotoxic chemotherapy if that is necessary for the optimal treatment of their cancer. Alternatively, a patient who had no prior cardiac disease, received anthracycline-based therapy 4 years ago, and now has severe LV dysfunction may not currently be considered for chemotherapy if cancer treatment is needed. The general principles that apply to the treatment of LV dysfunction in all patients are equally important in cancer survivors: 1) dietary adjustments, especially sodium limitation; 2) carefully monitored exercise and weight management; 3) maximally tolerated doses of renin-angiotensin system inhibitors (ACE-Is, ARBs, and beta-blockers); 4) selective use of aldosterone antagonism; 5) appropriate use of implantable cardiac defibrillators or biventricular pacing; and 6) other prevention-based therapies (aspirin, statins, and avoidance of alcohol/smoking).[89] Nevertheless, data supporting the efficacy of these interventions are limited, specifically among cancer survivors and especially among childhood cancer survivors.

European perspective

There are no well established recommendations for the treatment of cancer patients who develop HF as a result of anticancer treatment. Typically, these patients have been excluded from large randomized trials evaluating the effectiveness of novel HF therapies, and the use of ACE-I and beta-blockers in this particular clinical setting remains a matter of debate. One of the more challenging features of this form of cardiac dysfunction is that it usually remains asymptomatic for a very long time.[90] Many American and European authors have recommended screening programs to look for overt HF, as highlighted by Yoon et al,[91] because many cancer patients who develop cardiac dysfunction do not appear to be receiving optimal treatment and often are treated only if symptomatic. This is probably because there are special concerns related to the use of ACE-I and beta-blockers, even if these medications may be highly effective in treating therapy-related HF, possibly because cancer patients are considered frail, and the tendency is not to treat them aggressively. A recently published prospective study that included the largest population of anthracycline-related cardiomyopathy patients to date (N = 201 adult patients, including many still actively receiving anticancer therapy) demonstrated that the time elapsed from the end of chemotherapy to the start of HF therapy (the time to treatment) with ACE-I and with beta-blockers, when tolerated, is a crucial variable for the recovery of cardiac dysfunction.[92] Indeed, the likelihood of obtaining complete LVEF recovery was greater for patients who had treatment initiated within 2 months from the end of chemotherapy. After 2 months, this proportion progressively decreased, and no complete LVEF recovery was observed among those who had therapy initiated only after 6 months (Fig. 2). Notably, in that study, the clinical benefit was more evident in asymptomatic patients than in symptomatic patients. Therefore, monitoring of cardiotoxicity exclusively based on symptom evaluation may miss the opportunity to detect early cardiac injury that is still in a reversible stage. At least among adult cancer patients, this emphasizes the crucial importance of early detection of cardiotoxicity and suggests that an aggressive pharmacologic approach, based on ACE-Is, possibly in combination with beta-blockers, should always be considered, and attempted in all cases of anthracycline-related

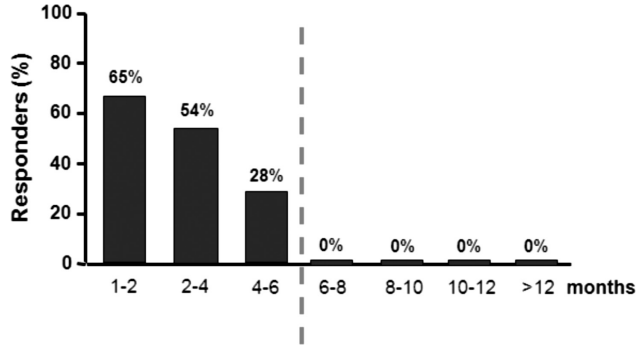

Figure 2. The reversibility of left ventricular dysfunction (both symptomatic and asymptomatic) in patients undergoing treatment with anthracyclines depends critically on the timing of the initiation of cardioprotection therapy with beta-blockers and angiotensin-converting enzyme inhibitors. If initiation of therapy is delayed longer than 6 months since the time of anthracycline exposure, then the likelihood that patients will respond to therapy is greatly reduced. (Adapted from Cardinale D, Colombo A, Lamantia G et al Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;55:213-220.[92]).

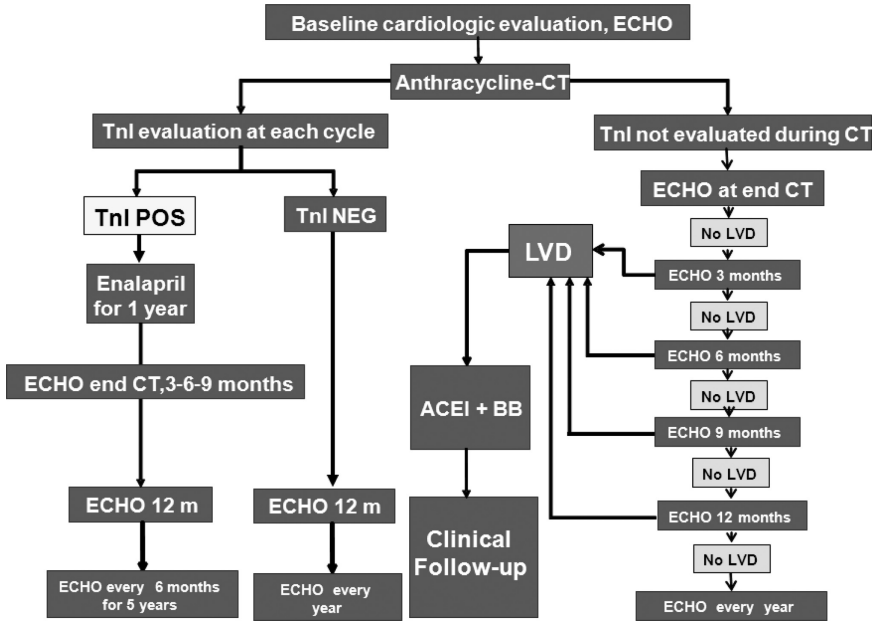

Figure 3. A suggested algorithm for screening for cardiotoxicity during and after chemotherapy with anthracyclines is illustrated. ECHO indicates echocardiography; CT, chemotherapy; TnI, troponin I; LVD, left ventricular dysfunction. (Adapted from Cardinale D. Cardiac dysfunction after cancer treatment. In: Bonow RO, Zipes DP, Libby P, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Ninth ed. Philadelphia, PA: Saunders Elsevier; 2012.[93]).

cardiomyopathy (Fig. 3).[93] Data on the efficacy of ACE-Is among childhood cancer survivors are much more limited, and no recommendations can be made.[90] The length of therapy required once a cancer patient has developed LV dysfunction and HF remains uncertain, but at least some data suggest that treatment should be long-term.[94]

Prevention

American and European perspectives

Because cardiomyopathy may occur even many months or years later, it is crucial to consider cardiac issues for a long time, because it is known that these patients are at high risk for subsequent serious events. True prevention of late cardiotoxicity in cancer patients begins before chemotherapy administration: a baseline assessment of cardiovascular health and effective treatment of cardiovascular risk factors is needed to prevent most late cardiac toxicities. Aspirin, control of hypertension and dyslipidemia, and tobacco cessation all are interventions that should be aggressively pursued where appropriate.[16,49,95,96]

Strategies for primary prevention also have been proposed, balancing the need to preserve therapeutic efficacy while minimizing adverse late effects. Refinements in treatment protocols and radiotherapy delivery have led to decreased rates of cardiovascular disease among select survivor cohorts over time.[97] Continued improvements in technology (eg the advent of intensity-modulated and proton radiotherapy) have the potential to reduce radiation scatter to critical organs even further for some patients.[40] Effective primary strategies also exist to reduce anthracycline-related cardiotoxicity (at least among adults), including the use of less cardiotoxic anthracycline derivatives, prolonging infusion time, and concurrent administration of a cardioprotectant, such as dexrazoxane.[27,50,98-101] Summary risk estimates based on randomized trial data (mostly adult patients with breast cancer) suggest that dexrazoxane is associated with a significantly decreased risk of both clinical and subclinical HF without affecting tumor response rates and without being associated with increased noncardiac side effects compared with conventional anthracyclines.[50,100,101] Currently, it is approved for use by the US Food and Drug Administration only among women with metastatic breast cancer who have received 300 mg/m^2 of doxorubicin and who may benefit from further anthracycline-based therapy.[102] The American Society of Clinical Oncology similarly recommends consideration of dexrazoxane in adults (with any histology) who have already received 300 mg/m^2 of anthracyclines.[103] Data among children are limited,[104-106] and concerns regarding the possible association of dexrazoxane with an increased risk of second cancers[101,107,108] have limited more widespread use among children, and

the European Medicines Agency has specifically recommended that children not receive dexrazoxane.[109]

Conclusions

All patients with cancer who are treated with potentially cardiotoxic chemotherapy represent a high-risk group for the development of HF. Adults, at least, should be treated with ACE-Is and/or beta-blockers, in accordance with the 2009 AHA/ACC guidelines for the treatment of stage A congestive HF, especially when and if the LVEF is reduced to <55%.[61,110] Increased collaboration between cardiologists and oncologists is needed to determine the best treatment combinations and the best preventive strategies that will improve the cardiac health of our patients. To foster this collaboration, new societies based in both Europe and the United States, such as the Italian Association of Cardio-Oncology (AICO) (www.aicocardiologia.it) and the International CardiOncology Society (ICOS) (www.cardioncology.com [accessed January 22, 2013]), have been formed that bring together interested researchers and clinicians from both fields. Finally, childhood cancer survivors need dedicated research, because findings relevant to adult-onset cancer survivors may not necessarily apply to this population.

Key Gaps

Although much progress has been made in better understanding and treating cardiac disease and toxicity associated with cancer therapy, multiple issues remain. These include: 1) the need to develop internationally accepted and uniform definitions of cardiac toxicity to make results across studies more comparable; 2) further study of potential interactions between known treatment risk factors and novel agents as well as a better understanding of possible genetic influences on risk; 3) refinement of screening tests, both serum-based and imaging-based biomarkers, and the optimal timing and interval between tests; 4) additional clinical studies that determine the best treatment strategies both for survivors with asymptomatic LV dysfunction and for those with symptomatic HF; and 5) continued development of strategies that allow for delivery of effective cancer therapy while minimizing unintended toxicity to the heart and the cardiovascular system as a whole.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572-1582.
2. Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA*. 2020;304:172-179.
3. Sun CL, Francisco L, Kawashima T, et al. Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood* 116:3129-3139, 2010; quiz 3377.
4. Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol*. 2000;18:1725-1732.
5. Hull MC, Morris CG, Pepine CJ, et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA*. 2003;290:2831-2837.
6. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol*. 2003;42:743-749.
7. Lenihan DJ, Cardinale D, Cipolla CM. The compelling need for a cardiology and oncology partnership and the birth of the International CardiOncology Society. *Prog Cardiovasc Dis*. 2010;53:88-93.
8. Hequet O, Le QH, Moullet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol*. 2004;22:1864-1871.
9. van der Pal HJ, van Dalen EC, Hauptmann M, et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. *Arch Intern Med*. 2010;170:1247-1255.
10. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol*. 2007;25:3991-4008.
11. Chen MH, Colan SD, Diller L. Cardiovascular disease: cause of morbidity and mortality in adult survivors of childhood cancers. *Circ Res*. 2011;108:619-628.
12. Galper SL, Yu JB, Mauch PM, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood*. 2011;117:412-418.
13. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed May 28, 2009.
14. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259.
15. Lenzen MJ, Scholte op Reimer WJ, Boersma E, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. *Eur Heart J*. 2004;25:1214-1220.
16. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007;25:3808-3815.
17. Chen J, Long JB, Hurria A, et al. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol*. 2012;60:2504-2512.
18. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer:

retrospective analysis of the Childhood Cancer Survivor Study cohort [serial online]. *BMJ*. 2009;339:b4606.
19. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004;109:2749-2754.
20. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys*. 2007;67:10-18.
21. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2012;23(suppl 7):vii155-vii166.
22. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? *J Clin Oncol*. 2008;26:1201-1203.
23. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res*. 2009;14:14-24.
24. Martin M, Esteva FJ, Alba E, et al. Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. *Oncologist*. 2009;14:1-11.
25. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2011;13:1-10.
26. Bovelli D, Plataniotis G, Roila F. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2010;21(suppl 5):v277-v282.
27. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol*. 2005;23:7811-7819.
28. Perez EA, Suman VJ, Davidson NE, et al. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. *J Clin Oncol*. 2004;22:3700-3704.
29. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast*. 2004;13:173-183.
30. O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol*. 2004;15:440-449.
31. Smith I, Procter M, Gelber RD, et al. Two-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369:29-36.
32. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673-1684.
33. Ryberg M, Nielsen D, Cortese G, et al. New insight into epirubicin cardiac toxicity: competing risks analysis of 1097 breast cancer patients. *J Natl Cancer Inst*. 2008;100:1058-1067.
34. Sawaya H, Plana JC, Scherrer-Crosbie M. Newest echocardiographic techniques for the detection of cardiotoxicity and heart failure during chemotherapy. *Heart Fail Clin*. 2011;7:313-321.
35. Tarantini L, Cioffi G, Gori S, et al. Trastuzumab adjuvant chemotherapy and cardiotoxicity in real-world women with breast cancer. *J Card Fail*. 2012;18:113-119.
36. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989;244:707-712.
37. Andrulis IL, Bull SB, Blackstein ME, et al. Neu/erbB-2 amplification identifies a poor-prognosis group of women with node-negative breast cancer. Toronto Breast Cancer Study Group. *J Clin Oncol*. 1998;16:1340-1349.
38. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659-1672.
39. Gianni L, Herman EH, Lipshultz SE, et al. Anthracycline cardiotoxicity: from bench to bedside. *J Clin Oncol*. 2008;26:3777-3784.
40. Travis LB, Ng AK, Allan JM, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. *J Natl Cancer Inst*. 2012;104:357-370.
41. Sawyer DB, Peng X, Chen B, et al. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? *Prog Cardiovasc Dis*. 2010;53:105-113.
42. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med*. 2012;18:1639-1642.
43. Tan C, Tasaka H, Yu KP, et al. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. *Cancer*. 1967;20:333-353.
44. Sorensen K, Levitt GA, Bull C, et al. Late anthracycline cardiotoxicity after childhood cancer: a prospective longitudinal study. *Cancer*. 2003;97:1991-1998.
45. Andersson A, Naslund U, Tavelin B, et al. Long-term risk of cardiovascular disease in Hodgkin lymphoma survivors—retrospective cohort analyses and a concept for prospective intervention. *Int J Cancer*. 2009;124:1914-1917.
46. Hershman DL, McBride RB, Eisenberger A, et al. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:3159-3165.
47. Du XL, Xia R, Liu CC, et al. Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer. *Cancer*. 2009;115:5296-5308.
48. Blanco JG, Sun CL, Landier W, et al. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes—a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30:1415-1421.
49. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*. 2007;99:365-375.
50. van Dalen EC, Michiels ME, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients [serial online]. *Cochrane Database Syst Rev*. 2010;(5):CD005006.
51. Goldberg MA, Antin JH, Guinan EC, et al. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood*. 1986;68:1114-1118.
52. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. *J Natl Compr Canc Netw*. 2011;9:243-249.
53. de Korte MA, de Vries EG, Lub-de Hooge MN, et al. 111Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: a clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. *Eur J Cancer*. 2007;43:2046-2051.
54. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2008;356:125-134.
55. Richards CJ, Je Y, Schutz FA, et al. Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib. *J Clin Oncol*. 2011;29:3450-3456.
56. Visscher H, Ross CJ, Rassekh SR, et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol*. 2012;30:1422-1428.
57. Fan L, Goh BC, Wong CI, et al. Genotype of human carbonyl reductase CBR3 correlates with doxorubicin disposition and toxicity. *Pharmacogenet Genomics*. 2008;18:621-631.
58. Bains OS, Karkling MJ, Grigliatti TA, et al. Two nonsynonymous single nucleotide polymorphisms of human carbonyl reductase 1 demonstrate reduced in vitro metabolism of daunorubicin and doxorubicin. *Drug Metab Dispos*. 2009;37:1107-1114.
59. Hilbers FS, Boekel NB, van den Broek AJ, et al. Genetic variants in TGFbeta-1 and PAI-1 as possible risk factors for cardiovascular disease after radiotherapy for breast cancer. *Radiother Oncol*. 2010;102:115-121.
60. Bhatia S. Role of genetic susceptibility in development of treatment-related adverse outcomes in cancer survivors. *Cancer Epidemiol Biomarkers Prevent*. 2011;20:2048-2067.
61. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis

and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration with the International Society for Heart and Lung Transplantation [serial online]. *J Am Coll Cardiol*. 2009;53:e1-e90.
62. Geiger S, Lange V, Suhl P, et al. Anticancer therapy induced cardiotoxicity: review of the literature. *Anticancer Drugs*. 2010;21:578-590.
63. Heart Failure Society of America; Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline [serial online]. *J Card Fail*. 2010;16:e1-3194.
64. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol*. 2004;22:4979-4990.
65. Skinner R, Wallace WH, Levitt GA. Long-term follow-up of people who have survived cancer during childhood. *Lancet Oncol*. 2006;7:489-498.
66. Sieswerda E, Postma A, van Dalen EC, et al. The Dutch Childhood Oncology Group guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors. *Ann Oncol*. 2012;23:2191-2198.
67. Jones AL, Barlow M, Barrett-Lee PJ, et al. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer*. 2009;100:684-692.
68. Tocchetti CG, Ragone G, Coppola C, et al. Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge. *Eur J Heart Fail*. 2012;14:130-137.
69. Murray LJ, Ramakrishnan S, O'Toole L, et al. Adjuvant trastuzumab in routine clinical practice and the impact of cardiac monitoring guidelines on treatment delivery. *Breast*. 2010;19:339-344.
70. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol*. 2010;28:3910-3916.
71. Altena R, Perik PJ, van Veldhuisen DJ, et al. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol*. 2009;10:391-399.
72. Jenkins C, Leano R, Chan J, et al. Reconstructed versus real-time 3-dimensional echocardiography: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr*. 2008;20:862-868.
73. Walker J, Bhullar N, Fallah-Rad N, et al. Role of 3-dimensional echocardiography in breast cancer: comparison with 2-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. *J Clin Oncol*. 2010;28:3429-3436.
74. Sawaya H, Sebag IA, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *Am J Cardiol*. 2011;107:1375-1380.
75. Geisberg CA, Sawyer DB. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. *Curr Hypertens Rep*. 2010;12:404-410.
76. Ky B, Carver JR. Biomarker approach to the detection and cardioprotective strategies during anthracycline chemotherapy. *Heart Fail Clin*. 2011;7:323-331.
77. Cardinale D, Sandri MT. Role of biomarkers in chemotherapy-induced cardiotoxicity. *Prog Cardiovasc Dis*. 2010;53:121-129.
78. Lipshultz SE, Miller TL, Scully RE, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. *J Clin Oncol*. 2012;30:1042-1049.
79. Lenihan D MM, Baysinger KB, et al. Superior detection of cardiotoxicity during chemotherapy using biomarkers [abstract]. *J Card Fail*. 2007;S151. Abstract 265.
80. Fallah-Rad N, Walker JR, Wassef A, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol*. 2011;57:2263-2270.
81. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:348-371.
82. US Food and Drug Administration. Genentech US BL 103792 supplement: Trastuzumab—Genentech I. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf. Accessed January 7, 2013.
83. O'Brien PJ. Cardiac troponin is the most effective translational safety biomarker for myocardial injury in cardiotoxicity. *Toxicology*. 2008;245:206-218.
84. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36:517-522.
85. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114:2474-2481.
86. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;26:5204-5212.
87. Gerszten RE, Asnani A, Carr SA. Status and prospects for discovery and verification of new biomarkers of cardiovascular disease by proteomics. *Circ Res*. 2011;109:463-474.
88. Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. *J Clin Oncol*. 2012;30:3657-3664.
89. Lenihan DJ. Statins in preparation for chemotherapy: "do these medications help your fitness for battle?" *J Am Coll Cardiol*. 2012;60:2391-2392.
90. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol*. 2004;22:820-828.
91. Yoon GJ, Telli ML, Kao DP, et al. Left ventricular dysfunction in patients receiving cardiotoxic cancer therapies are clinicians responding optimally? *J Am Coll Cardiol*. 2010;56:1644-1650.
92. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;55:213-220.
93. Cardinale D. Chapter 90: Cardiovascular Complication of Cancer Therapeutic Agents. In: Bonow RO, Zipes DP, Libby P, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia, PA: Saunders Elsevier; 2012.
94. Shukla A, Yusuf SW, Daher I, Lenihan D, Durand JB. High mortality rates are associated with withdrawal of beta blockers and ACE inhibitors in chemotherapy-induced heart failure [abstract]. *Circulation*. 2008;118:S797. Abstract 2942.
95. Armenian SH, Sun CL, Shannon T, et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood*. 2011;118:6023-6029.
96. Meacham LR, Chow EJ, Ness KK, et al. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19:170-181.
97. Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst*. 2005;97:419-424.
98. Minotti G, Menna P, Salvatorelli E, et al. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*. 2004;56:185-229.
99. Ewer MS, Martin FJ, Henderson C, et al. Cardiac safety of liposomal anthracyclines. *Semin Oncol*. 2004;31:161-181.
100. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials [serial online]. *BMC Cancer*. 2010;10:337.
101. van Dalen EC, Caron CH, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patient receiving anthracyclines [serial online]. *Cochrane Database Syst Rev*. 2011;(6): CD003917.

102. US Food and Drug Administration (FDA). FDA Statement on Dexrazoxane. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm263729.htm, 2011. Accessed October 25, 2012.
103. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27:127-145.
104. Wexler LH, Andrich MP, Venzon D, et al. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. *J Clin Oncol*. 1996;14:362-372.
105. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med*. 2004;351:145-153.
106. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. *Lancet Oncol*. 2010;11:950-961.
107. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol*. 2007;25:493-500.
108. Vrooman LM, Neuberg DS, Stevenson KE, et al. The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. *Eur J Cancer*. 2011;47:1373-1379.
109. European Medicines Agency. Science Medicines Health [agency website]. Available at: http://www.ema.europa.eu/ema/, 1995-2012. Accessed October 25, 2012.
110. Lenihan DJ. Progression of heart failure from AHA/ACC stage A to stage B or even C: can we all agree we should try to prevent this from happening? *J Am Coll Cardiol*. 2012;60:2513-2514.

Original Article

Interventions to Promote Energy Balance and Cancer Survivorship

Priorities for Research and Care

Catherine M. Alfano, PhD[1]; Alessio Molfino, MD, PhD[2]; and Maurizio Muscaritoli, MD, FACN[2]

The growing population of cancer survivors worldwide and the growing epidemics of obesity and physical inactivity have brought increased attention to the role that interventions to promote exercise and a healthy body weight may play in mitigating the chronic and late effects of cancer. In this light, the authors describe the similarities and differences in research and clinical priorities related to energy balance interventions among post-treatment cancer survivors in Europe versus North America. Randomized controlled trials that targeted nutrition, exercise, and weight are reviewed to determine the affect on survivorship outcomes. Interventions focused on improving prognosis or survival are investigated along with the emerging literature on the interventions targeting pathways and mechanisms of prognosis or survival. Current North American and European guidelines for diet, exercise, and weight control among cancer survivors also are investigated along with the implications of the current state of this science for clinical care. Finally, the authors delineate future European and American priorities for research and care involving energy balance among survivors. It is hoped that this dialogue launches an international conversation that will lead to better research and care for all post-treatment cancer survivors. ***Cancer*** **2013;119(11 suppl):2143-50.** © *2013 American Cancer Society.*

KEYWORDS: cancer; survivorship; research; Europe; United States; diet; exercise; obesity.

INTRODUCTION

Thanks to earlier detection and better, targeted, and multimodal cancer treatment, many individuals diagnosed with cancer can now expect to live for years beyond their treatment. Recent data have demonstrated that an estimated 28 million individuals worldwide had a history of cancer as of 2008,[1] the most recent year for which worldwide data are available. That number represents 5-year prevalence, so it is a dramatic underestimate of the total number of cancer survivors. Furthermore, the number of cancer survivors will increase significantly in the coming years with the aging of the Baby Boomer generation (those born from 1946 to 1964). For example, in the United States alone, it is estimated that there will be over 18 million survivors by 2022, 11 million of whom will be older adults.[2]

Although the increase in the number of cancer survivors is good news, it also means that more individuals than ever before are living with the chronic and late effects of cancer treatment. Chronic effects are problems present during treatment that may persist for months or years after treatment and include fatigue; neuropathy and pain syndromes; depression, anxiety, and distress; lymphedema; problems with cognition; incontinence; altered body image; and sexual dysfunction.[3] Late effects are not present during treatment but emerge during the post-treatment period and include cardiovascular disease; endocrine dysfunction; diabetes; osteoporosis; upper or lower quadrant mobility issues and functional limitations; and increased risk of recurrence, second cancers, and disability.[3] Research attention in the last 15 years on both sides of the Atlantic has focused on identifying risk factors for physical and psychosocial chronic and late effects of

Corresponding author: Maurizio Muscaritoli, MD, FACN, Department of Clinical Medicine, Sapienza University of Rome, Viale dell'Università, 37−00185 Rome, Italy; Fax: (011) 39 06 4997 2016; maurizio.muscaritoli@uniroma1.it

[1]Office of Cancer Survivorship, National Cancer Institute/National Institutes of Health, Bethesda, Maryland; [2]Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28062, **Received:** July 27, 2012; **Revised:** November 29, 2012; **Accepted:** November 30, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

cancer treatment and on developing and testing interventions to prevent or reduce the risk of these negative sequelae. One important line of this research has focused on the role of obesity and energy balance, as determined by dietary intake and energy expenditure, in determining the risk of chronic and late effects and the role that interventions to promote exercise and a healthy body weight may play in mitigating these problems.

Worldwide, physical inactivity and obesity are common. In the United States, >33% of adults are obese, and another 33% are considered overweight.[4] Fifty-three percent of US men and 60% of women do not engage in recommended levels of physical activity,[5] whereas >33% of adults are considered inactive. Rates of obesity[6,7] and inactivity[7] are slightly better in Canada than in the United States. In Europe, the prevalence of obesity varies by country from 4% to 37%, and the prevalence is lower in the western and northern regions and is more akin to US estimates in the eastern, central, and southern areas.[8] The prevalence of inactivity in Europe also differs by country, with Sweden, Finland, Austria, Ireland, and the Netherlands reporting lower levels of inactivity than the United States and Belgium and Mediterranean countries reporting inactivity levels equivalent to those in the United States.[9]

Cancer, inactivity, and obesity also are related. Physical inactivity and obesity are associated with an increased risk of many cancers[10] and with an increased risk of cancer progression and poor prognosis.[11] Preclinical studies have suggested that excess body weight and inactivity may affect cell growth, differentiation, and apoptosis to promote primary tumor growth and also affect tissue invasion and angiogenesis, leading to tumor progression.[12] Compounding the problem of cancer survivors being likely to be obese and inactive, individuals diagnosed with cancer often decrease their physical activity levels, eat poor-quality diets, and gain weight over the course of treatment, as noted especially among breast cancer survivors.[13,14] The result of these factors is that the weight gain tends to be gains in fat mass with a corresponding loss of lean (muscle) mass. This problem, called sarcopenic obesity, may adversely affect the risk of chronic and late effects and poor prognosis.

For this commentary, our objective was to describe the similarities and differences in research and clinical priorities related to energy balance interventions among post-treatment cancer survivors in Europe versus North America. This was not intended to be an exhaustive review of these topics but, rather, a tool to initiate an international dialogue about these issues, which we hope will lead to better science and care for cancer survivors worldwide. We focus here on physical activity, weight, and diet as they contribute to obesity and sarcopenic obesity, but we do not cover the immense research on dietary components, isolates, or supplements and cancer. We present the problem of body composition changes among survivors as 2 sides of the same coin: greater overall body weight and/or elevated body mass index (BMI) values, which can obscure the presence of muscle wasting/cachexia.

Randomized, Controlled Trials Targeting Nutrition, Exercise, and Weight to Affect Survivorship Outcomes

The last 5 years have brought a considerable increase in the number of studies that develop and test interventions aimed at helping survivors to improve their exercise or diet or to lose weight. Most of these studies have been conducted in the United States or Canada, perhaps because of the increased prevalence of obesity and inactivity there, but the reasons for the greater interest here are unknown. Some of these studies have been "proof-of-concept" studies, ie, testing whether the intervention in fact does improve physical activity or reduce weight. However, a growing body of work has targeted survivorship outcomes, aiming to improve quality of life, reduce chronic effects of treatment, improve specific aspects of physical functioning, or reduce the risk of late effects of cancer.

Systematic reviews and meta-analyses of the literature on physical activity interventions for cancer survivors have indicated that these interventions significantly reduce depression[15-17] and fatigue[16-25] and improve cardiorespiratory fitness, muscle strength, body composition and physical functioning,[17,22-26] body image,[16]and quality of life.[16,17,24-27] Resistance training can improve cardiopulmonary and muscle function, peak oxygen uptake, strength,[28]and quality of life.[29] It is noteworthy that weight training has been shown to increase muscle mass and decrease body fat, thereby improving sarcopenic obesity.[30] Exercise interventions that include strength training also may preserve bone health in cancer survivors.[31] Indeed, the available evidence demonstrates that exercise is 1 of the most important therapies to improve functioning and quality of life of cancer survivors. In contrast to the recent burgeoning number of exercise trials, trials are just beginning to evaluate weight loss among cancer survivors. These interventions have been conducted almost exclusively among women with breast cancer. A recent review of this literature suggests that weight loss interventions may improve body composition (especially when

combined with exercise), physical functioning, and quality of life.[32]

Lymphedema

Another major focus of research in the last 10 years has been investigating the role of energy balance in the risk of lymphedema (LE) and the role of exercise and weight loss interventions in reducing the risk or exacerbations of LE. LE, which can occur after surgery for breast cancer and for other malignancies, has major physical consequences (discomfort, swelling, increased risk for infections and secondary malignancies) and psychological consequences (depression, body image disorders) that can decrease quality of life and may affect survival. In most patients (approximately 75%), LE develops within 1 year of breast surgery; however, because of its insidious onset, LE carries a lifetime risk for breast cancer survivors.[33] It has been widely recognized that preoperative BMI increases the risk of LE,[34-37] with BMI values >30 kg/m^2 doubling the risk.[38] Despite the well established relation between preoperative overweight and postoperative risk of LE, few studies have evaluated the role of body weight reduction with either reduced-energy diets or exercise on the risk of developing or exacerbating LE in breast cancer survivors. Two British studies of breast cancer survivors demonstrated that weight loss through hypocaloric or low-fat diet can significantly reduce breast cancer-related LE.[39,40] A review of strength training studies conducted with survivors who had LE demonstrated that slowly progressive strength training was safe and did not exacerbate LE symptoms.[41] It has been observed that strength training interventions in the United States decreased the severity and exacerbations of LE symptoms among breast cancer survivors[42] and decreased the likelihood of increased arm swelling among women at high risk for LE.[43] In summary, the role of weight loss, physical exercise, dietary restrictions, and nutritional counseling in the prevention or control of LE in long-term breast cancer survivors remains largely unexplored both in the United States and in Europe, underscoring the urgent need for large multicenter trials addressing this relevant clinical issue.

Interventions Focused on Improving Prognosis/Survival

Whether exercise and/or weight loss may favorably influence prognosis or overall survival is a matter of great interest in North America. Such trials must include large sample sizes and lengthy follow-up periods; thus, they have not been completed to date. However, a study funded by The National Cancer Institute of Canada is currently conducting a survival trial testing whether exercise can favorably influence disease-free survival among individuals diagnosed with higher risk colorectal cancer (the Colon Health and Life-Long Exercise Change [CHALLENGE] trial).[44] A study testing the effects of weight loss on survival from estrogen receptor-positive breast cancer (Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer [LISA]; P. Goodwin, principal investigator; clinicaltrials.gov identifier NCT00463489) also was being conducted in Canada; however, that study was terminated early because of lost funding.

Two diet intervention studies among breast cancer survivors in the United States have been carried out. The Women's Intervention Nutrition Study (WINS) tested the effects of a low-fat diet among 2437 women with early stage breast cancer on relapse. An interim analysis conducted with 5 years of follow-up revealed marginally significantly lower relapse-free survival in the low-fat diet arm, and subgroup analyses indicated a significantly lower relapse rate among women who had estrogen receptor-negative breast cancers.[45] However, it is not known whether these effects were because of the low-fat diet or because of the average 6-pound weight loss experienced by women in the intervention group. The Women's Healthy Eating and Living (WHEL) study tested the effects of a low-fat, high fruit and vegetable/fiber diet on cancer outcomes in 3088 women with breast cancer. Women in the intervention arm reduced their fat intake but did not lose weight, and there was no difference between the intervention and control arms in recurrence-free survival.[46] However, subgroup analyses revealed that prognosis was improved among women in the intervention group who did not report hot flashes (who likely had higher circulating estrogen levels).[47]

Interventions Focused on Improving Biomarkers of Prognosis or Survival

In the absence of trials targeting survival, some investigators in the United States and Canada have begun to investigate whether physical activity, diet, or weight change can favorably influence intermediate biomarkers of prognosis/survival, including sex hormones, insulin or insulin-like growth factors or their binding proteins, insulin resistance, glucose metabolism, leptin and other adipokines, immunologic or inflammatory factors, oxidative stress and DNA damage or repair capacity, angiogenesis, or prostaglandins. For example, Pakiz et al investigated the effect of a weight loss intervention (regular physical activity and reduced energy intake) on inflammation and

vascular endothelial growth factor in overweight or obese breast cancer survivors. Weight loss was associated with reduced cytokine levels, and increased energy expenditure was associated with a significant reduction in circulating levels of interleukin-6.[48] Befort et al demonstrated that a low-calorie diet and physical activity reduced body weight and improved fasting insulin and leptin levels in rural American breast cancer survivors.[49] Allgayer and colleagues in Germany documented the effects of exercise on DNA damage[50] and inflammation[51] in colorectal cancer survivors (for a complete summary, please see recent reviews of this emerging literature[52,53] and the recent US Institute of Medicine report on this topic[11]). It is noteworthy that, although this has been a topic of emphasis in North America, aside from the work by Allgayer et al cited above and a recently closed clinical trial in the United Kingdom,[54] it has not been a priority among European investigators. Future studies are needed to clarify the role of weight loss and physical activity on biomarkers of prognosis or survival among cancer survivors, including the dose and type of these interventions needed to garner protective effects.

Guidelines and Care Implications

United States

The American Cancer Society (ACS) provides guidelines on nutrition and physical activity for cancer survivors.[55] These guidelines state that, during the post-treatment phase, setting and achieving life-long goals for weight management, a physically active lifestyle, and a healthy diet are important tools to promote overall health and quality and quantity of life. These guidelines are based on the consideration that individuals who have been diagnosed with cancer are at a significantly higher risk of developing second primary cancers and chronic diseases, such as cardiovascular disease, diabetes, and osteoporosis; thus, the guidelines established to prevent those diseases are relevant. In brief, the ACS guidelines advise survivors to achieve and maintain a healthy weight. Overweight or obese survivors should limit consumption of high-calorie foods and beverages and should increase their physical activity to promote weight loss. All survivors should engage in regular physical activity; should avoid inactivity, aiming to exercise at least 150 minutes per week, including strength training exercises at least 2 days per week; and should eat a diet high in vegetables, fruits, and whole grains. These guidelines are consistent with the ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention for the general population. The American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors echoes the ACS guidelines, stating that current national exercise guidelines for the US population are appropriate for cancer survivors.[56]

Europe

The National Cancer Survivorship Initiative-Supported Self-Management Workstream developed in 2010 in the United Kingdom (Department of Health, Macmillan Cancer Support, National Health Service Improvement, 2010) aimed at updating the World Cancer Research Fund (WCRF) report's guidelines.[57] Although the authors recognize gaps in the evidence for lifestyle benefits in cancer survivors, some key lifestyle general recommendations are provided regarding diet (reduce saturated fats, increase fish intake, and consume a varied diet to ensure adequate intakes of vitamins and essential minerals; increase consumption of green and cruciferous vegetables, etc.) and physical activity (at least 30 minutes a day of moderate-intensity physical activity on 5 or more days of the week, although even a modest amount of exercise is considered beneficial and, thus, is encouraged). The role of body composition changes that occur in many cancer patients, depending on tumor localization and treatments, is also emphasized. In particular, the loss of lean body mass (sarcopenia) for patients with head and neck and gastrointestinal cancers is highlighted, and physical exercise is suggested to build lean muscle and prevent post-treatment disability, loss of autonomy, and impaired quality of life. In breast cancer patients, exercise/activity is suggested for controlling body weight and losing fat to combat treatment-related weight gain (which is exacerbated if the prediagnosis BMI is not within the healthy range). Excess weight should be avoided. The recommendation is also given to maintain a stable, healthy weight as opposed to fluctuating between a healthy and unhealthy BMI. Like the US exercise guidelines, the British Association of Sport and Exercise Sciences provides guidance on exercise for cancer survivors, indicating that survivors should follow health-related physical activity guidelines for the general United Kingdom population.[58]

Along with its role in the achievement of energy balance and maintenance of healthy body weight, regular physical exercise should be encouraged to prevent or counteract the loss of muscle mass and function (ie, sarcopenia) that frequently complicates cancer and its therapies. Although it occurs most frequently during the phase of active disease and treatments and in advanced cancer,[59] sarcopenia and the consequent functional impairment may represent a life-long disability for cancer survivors; thus, survivorship care needs to prevent, assess, and treat

this debilitating condition. Permanent impairment in nutritional status secondary to medical or surgical cancer therapy ultimately may lead to skeletal muscle loss that interferes with everyday activities. Overall, little attention has been paid in both US and European guidelines to sarcopenia-related impairment in the quality of life of long-term cancer survivors. In this view, attention to body composition should be improved, because normal/elevated body weight or BMI may well mask an underlying, life-threatening sarcopenia.

Future Priorities for Research and Care Involving Energy Balance Among Survivors: European and American Perspectives

Meeting the needs of the growing population of cancer survivors requires the development of innovative models of care, which may be used to inform and enhance cancer survivorship care in different health care settings.[60] The relevance of researching and optimizing the delivery of care to cancer survivors is being widely recognized in North America and is being progressively recognized in Europe. However, critically reviewing at the available literature, it is apparent that the American and European approaches to cancer survivorship both have pitfalls, particularly concerning noncancer-related health problems, such as promotion of healthy behaviors. Several specific issues have to be addressed and solved by future research in this field to build support for a model of comprehensive survivorship care that meets the needs of all survivors:

1. Although current evidence from cohort and cross-sectional studies suggests that excess body weight and sarcopenic obesity are associated with increased risk of chronic and late effects of cancer, trials should test whether intentional weight loss among cancer survivors results in decreased risk of LE or late effects like cardiovascular disease. Both North American and European investigators have acknowledged this as a priority area.
2. Current guidelines on prescribing exercise, nutrition, and weight control interventions for cancer survivors are based on general public health advice given to the general population. However, achieving the level of healthy behaviors set forth in these recommendations may not be effective for reducing morbidity and mortality among cancer survivors. Randomized clinical trials are needed to generate evidence-based guidelines for cancer survivors.
3. A related direction concerns being able to prescribe appropriately targeted, individualized lifestyle recommendations for cancer survivors. On both sides of the Atlantic, there is interest in conducting trials that establish the intensity and type of intervention needed given an individual survivor's unique disease, psychosocial, behavioral, and genetic profile.
4. The extent to which psychosocial issues like depression or diminished social support play a role in eating behavior and exercise after cancer treatment has received little attention in the literature on both sides of the Atlantic. For example, research should test whether ongoing psychosocial issues or effects of cancer treatments change the hormones that govern appetite (eg leptin, ghrelin).
5. Given the demands of the cancer survivor population on the health care system and the projected dramatic increase in the number of cancer survivors in the future, trials are needed to establish a risk-stratification system for triaging survivors into appropriate levels of lifestyle interventions. For example, many survivors may be able to exercise safely without medical supervision. However, others may need intense oversight and targeted exercise prescription based on cardiovascular functioning parameters along the lines of current supervised cardiac rehabilitation programs in the United States. Investigators in the United States[61] and the United Kingdom[62] have begun work on this kind of risk stratification. More research is needed to identify those individuals who need different levels of lifestyle intervention and to guide the development and delivery of interventions.
6. We need to focus on the promotion of long-term maintenance of healthy behavior changes. The few studies available on this topic suggest that survivors do not maintain their healthy behavior changes over time.[11] Current interest in Europe and North America is focusing on how to keep individuals exercising, eating well, and avoiding weight regain once the intervention ends. For example, studies are investigating the predictors of maintaining behavior changes using behavioral theory.[63,64]
7. Another future direction concerns dissemination of these lifestyle interventions to all survivors who need them. Given the large geographic area of the United States, there is great interest in using technology and telemedicine approaches to increase the reach of behavioral change interventions to allow minorities and underserved populations to benefit from these interventions. For example, Morey and colleagues have observed that a home-based diet and exercise program using telephone counseling can reduce the rate of physical decline in at-risk cancer survivors.[65] Befort and colleagues have used conference call technology to

significantly decrease weight among overweight, rural breast cancer survivors.[49] Similar initiatives are still lacking in Europe.

8. A final area of emerging interest and debate in the United States concerns bariatric surgery for cancer survivors. Bariatric surgery can result in much greater weight loss than behavioral interventions and is associated with better maintenance of weight loss.[11] Furthermore, bariatric surgery studies with the general population indicate that weight loss is associated with reductions in biomarkers of cancer prognosis.[11] However, to date, studies have not addressed the safety and efficacy of bariatric surgery specifically in cancer survivors. In Europe, to our knowledge, there is not yet any discussion about whether bariatric surgery should be used for cancer survivors.

Conclusions

Research interests and priorities related to exercising, maintaining healthy weight, and losing weight in overweight and obese cancer survivors in Europe versus North America are more alike than different. Much of the research in this area has been conducted in North America, but a growing body of research also is being conducted in Europe. Where differences exist between the 2 continents, these are likely because of geographic-specific factors. For example, the interest in the areas of bariatric surgery for weight loss among very obese survivors and telemedicine approaches to delivering energy balance interventions to underserved communities in the United States but in not Europe likely reflects the larger obesity epidemic and greater geographic area of the United States. However, because current obesity trends in Europe suggest an imminent surge in the epidemic,[8] and given the geographic variation between European Union countries (eg Northern and Southern Europe), it is likely these largely US-focused debates will be relevant to Europe in the near future.

Cancer survivors on both sides of the Atlantic face some of the same barriers to receiving adequate intervention programs to promote a healthy energy balance. Although this is changing now in the United Kingdom, for the most part, energy balance interventions are not delivered routinely on either continent as part of post-treatment survivorship care. The lack of a risk-stratification system makes it impossible for health care providers to know which survivors should be referred to which types of lifestyle interventions. Weight, diet, and exercise guidelines on both continents are based on guidelines for the general population and may not be sufficient to achieve optimal health and well being in certain subgroups of survivors. Finally, focus on the assessment of BMI but not body composition may be leading to missed diagnoses of sarcopenia and missed opportunities to prevent or ameliorate this debilitating condition. That these problems are universal underscores the need for international efforts to identify and implement their solutions. We hope that this dialogue launches an international conversation that will lead to better research and care for all post-treatment cancer survivors.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2,. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer, 2010. Available at: http://globocan.iarc.fr. [Accessed November 15, 2012].
2. American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2012-2013. Atlanta, GA; American Cancer Society; 2012.
3. Hewitt M, Greenfield S, Stovall. E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press; 2006.
4. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA.* 2012;307:491-497.
5. Eheman C, Henley SJ, Ballard-Barbash R, et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer.* 2012;118:2338-2366.
6. Shields M, Carroll MD, Ogden CL. Adult obesity prevalence in Canada and the United States. *NCHS Data Brief.* 2011;56:1-8.
7. Hart TL, Craig CL, Griffiths JM, et al. Markers of sedentarism: the joint Canada/US survey of health. *J Phys Act Health.* 2011;8: 361-371.
8. Berghofer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. Obesity prevalence from a European perspective: a systematic review [serial online]. *BMC Public Health.* 2008;8:200.
9. Martinez-Gonzalez MA, Varo JJ, Santos JL, et al. Prevalence of physical activity during leisure time in the European Union. *Med Sci Sports Exerc.* 2001;33:1142-1146.
10. World Cancer Res. Fund/American Institute for Cancer Res., Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research; 2007.
11. Institute of Medicine. The Role of Obesity in Cancer Survival and Recurrence: Workshop Summary. Washington, DC: The National Academies Press; 2012.

12. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer.* 2011;11:886-895.
13. Saquib N, Flatt SW, Natarajan L, et al. Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the Women's Healthy Eating and Living (WHEL) study. *Breast Cancer Res Treat.* 2007;105:177-186.
14. Irwin ML, Crumley D, McTiernan A, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer.* 2003;97:1746-1757.
15. Craft LL, Vaniterson EH, Helenowski IB, Rademaker AW, Courneya KS. Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2012;21:3-19.
16. Duijts SF, Faber MM, Oldenburg HS, van Beurden M, Aaronson NK. Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors—a meta-analysis. *Psychooncology.* 2011; 20:115-126.
17. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials [serial online]. *BMJ.* 2012;344:e70.
18. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2011;20:123-133.
19. McMillan EM, Newhouse IJ. Exercise is an effective treatment modality for reducing cancer-related fatigue and improving physical capacity in cancer patients and survivors: a meta-analysis. *Appl Physiol Nutr Metab.* 2011;36:892-903.
20. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull.* 2008;134:700-741.
21. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. *Clin Oncol (R Coll Radiol).* 2010;22:208-221.
22. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv.* 2010;4:87-100.
23. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1588-1595.
24. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ.* 2006;175:34-41.
25. Spence RR, Heesch KC, Brown WJ. Exercise and cancer rehabilitation: a systematic review. *Cancer Treat Rev.* 2010;36:185-194.
26. Wolin KY, Ruiz JR, Tuchman H, Lucia A. Exercise in adult and pediatric hematological cancer survivors: an intervention review. *Leukemia.* 2010;24:1113-1120.
27. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. *Ann Behav Med.* 2011;41:32-47.
28. De Backer IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: a systematic review. *Int J Sports Med.* 2009;30:703-712.
29. Cramp F, James A, Lambert J. The effects of resistance training on quality of life in cancer: a systematic literature review and meta-analysis. *Support Care Cancer.* 2010;18:1367-1376.
30. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev.* 2005;14:1672-1680.
31. Winters-Stone KM, Schwartz AL, Hayes SC, Fabian CJ, Campbell KL. A prospective model of care for breast cancer rehabilitation: bone health and arthralgias. *Cancer.* 2012;118(8 suppl):2288-2299.
32. Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer.* 2012; 118(8 suppl):2277-2287.
33. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer.* 2001; 92:1368-1377.
34. Johansson K, Ohlsson K, Ingvar C, Albertsson M, Ekdahl C. Factors associated with the development of arm lymphedema following breast cancer treatment: a match pair case-control study. *Lymphology.* 2002;35:59-71.
35. Kwan ML, Darbinian J, Schmitz KH, et al. Risk factors for lymphedema in a prospective breast cancer survivorship study: the Pathways study. *Arch Surg.* 2010;145:1055-1063.
36. Ridner SH, Murphy B, Deng J, et al. A randomized clinical trial comparing advanced pneumatic truncal, chest, and arm treatment to arm treatment only in self-care of arm lymphedema. *Breast Cancer Res Treat.* 2012;131:147-158.
37. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. *Breast Cancer Res Treat.* 2011;130:981-991.
38. Helyer LK, Varnic M, Le LW, Leong W, McCready D. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. *Breast J.* 2010;16:48-54.
39. Shaw C, Mortimer P, Judd PA. A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer.* 2007;110:1868-1874.
40. Shaw C, Mortimer P, Judd PA. Randomized controlled trial comparing a low-fat diet with a weight-reduction diet in breast cancer-related lymphedema. *Cancer.* 2007;109:1949-1956.
41. Kwan ML, Cohn JC, Armer JM, Stewart BR, Cormier JN. Exercise in patients with lymphedema: a systematic review of the contemporary literature. *J Cancer Surviv.* 2011;5:320-336.
42. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med.* 2009;361: 664-673.
43. Schmitz KH, Ahmed RL, Troxel AB, et al. Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. *JAMA.* 2010;304:2699-2705.
44. Courneya KS, Booth CM, Gill S, et al. The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. *Curr Oncol.* 2008;15: 279-285.
45. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst.* 2006;98:1767-1776.
46. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA.* 2007;298:289-298.
47. Gold EB, Pierce JP, Natarajan L, et al. Dietary pattern influences breast cancer prognosis in women without hot flashes: the Women's Healthy Eating and Living trial. *J Clin Oncol.* 2009;27:352-359.
48. Pakiz B, Flatt SW, Bardwell WA, Rock CL, Mills PJ. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. *Int J Behav Med.* 2011;18:333-341.
49. Befort CA, Klemp JR, Austin HL, et al. Outcomes of a weight loss intervention among rural breast cancer survivors. *Breast Cancer Res Treat.* 2012;132:631-639.
50. Allgayer H, Owen RW, Nair J, et al. Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment. *Scand J Gastroenterol.* 2008;43:971-978.
51. Allgayer H, Nicolaus S, Schreiber S. Decreased interleukin-1 receptor antagonist response following moderate exercise in patients with colorectal carcinoma after primary treatment. *Cancer Detect Prev.* 2004;28:208-213.
52. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst.* 2012;104:815-840.

53. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective [published online ahead of print May 17, 2012]. *Brain Behav Immun*. 2012.
54. Saxton JM, Daley A, Woodroofe N, et al. Study protocol to investigate the effect of a lifestyle intervention on body weight, psychological health status and risk factors associated with disease recurrence in women recovering from breast cancer treatment [ISRCTN08045231] [serial online]. *BMC Cancer.* 2006;6:35.
55. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin.* 2012;62:243-274.
56. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc.* 2010;42:1409-1426.
57. Bekkering T, Beynon R, Davey Smith G, et al. A Systematic Review of RCTs Investigating the Effect of Dietal and Physical Activity Interventions on Cancer Survival, Updated Report. London, United Kingdom: World Cancer Research Fund; 2006. Available at: http://www.detandcancerreport.org. [Accessed November 15, 2012].
58. Campbell A, Stevinson C, Crank H. The BASES Expert Statement on exercise and cancer survivorship. *J Sport Sci.* 2012;30:949-952.
59. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* 2011; 12:489-495.
60. Chubak J, Tuzzio L, Hsu C, et al. Providing care for cancer survivors in integrated health care delivery systems: practices, challenges, and research opportunities. *J Oncol Pract.* 2012;8:184-189.
61. Jones LW. Evidence-based risk assessment and recommendations for physical activity clearance: cancer. *Appl Physiol Nutr Metab.* 2011; 36(suppl 1):S101-S112.
62. Maher J, McConnell H. New pathways of care for cancer survivors: adding the numbers. *Br J Cancer.* 2011;105(suppl 1):S5-S10.
63. Courneya KS, Stevinson C, McNeely ML, et al. Effects of supervised exercise on motivational outcomes and longer-term behavior. *Med Sci Sports Exerc.* 2012;44:542-549.
64. Loprinzi PD, Cardinal BJ, Si Q, Bennett JA, Winters-Stone KM. Theory-based predictors of follow-up exercise behavior after a supervised exercise intervention in older breast cancer survivors. *Support Care Cancer.* 2012;20:2511-2521.
65. Morey MC, Snyder DC, Sloane R, et al. Effects of home-based diet and exercise on functional outcomes among older, overweight long-term cancer survivors: RENEW: a randomized controlled trial. *JAMA.* 2009;301:1883-1891.

Original Article

Employment Challenges for Cancer Survivors

Anja Mehnert, PhD[1,2]; Angela de Boer, PhD[3]; and Michael Feuerstein, PhD, MPH[4,5]

There is a considerable body of evidence about the adverse effects of cancer and cancer treatments on employment, work ability, work performance, and work satisfaction among cancer survivors. There is also a growing consensus that cancer survivorship research needs to address the large variety of short-term and long-term work-related problems and that programs to support return to work and employment should be developed and integrated into the follow-up survivorship care of cancer patients. Cancer survivorship and employment can be considered from the perspective of the cancer survivor, the caregiver and the family, the employer and coworkers, the health care providers, and the community or society—elements that comprise many similarities but also differences between Europe and the Unites States and that may affect employment and return to work among cancer survivors in different ways. Previous research has specifically addressed the likelihood and timeliness of work return, including factors that promote and hinder return to work and work performance, and intervention studies and programs that focus on psychological, physical, pharmacologic, or multidisciplinary approaches to work. The area of work disability has emerged as an international field with research from areas throughout the globe. In this article, the authors provide an overview of the current state of scientific research in these areas and further provide a cancer survivorship and work model that integrates significant individual cancer-related, treatment-related, and work-related factors and outcomes. The report concludes with a discussion of European and American contributions and possible future directions for the enhancement of current efforts. ***Cancer*** **2013;119(11 suppl):2151-59.** *© 2013 American Cancer Society.*

KEYWORDS: cancer; employment; work; disability; survivorship.

INTRODUCTION

More individuals are surviving cancer than ever before, particularly in the high-income countries, because of early diagnosis and improvements in multimodal cancer treatments. Breast, prostate, lung, and colorectal cancers are the most common forms of cancer among women and men worldwide. In Europe, the 5-year prevalence includes a total of 8.5 million individuals.[1] In the United States, the number of cancer survivors increased in the last 30 years from 3 million in 1971 to 11.7 million in 2007, an increase from 1.5% to 4% of the US population.[2] Annual cancer incidence data from Europe and the United States indicate that an estimated 43% to 44% of all cancer patients are diagnosed between ages 15 and 64 years, and between 56% and 57% are diagnosed between ages 15 and 69 years,[1] an age when work life plays an important role.

Given the reality that life expectancy has continually increased in European countries and in the United States—countries with a high Human Development Index[3]—in addition to the traditional age range of the labor force, more and more older individuals are expected to remain in the workforce. Thus, surviving cancer leads to new challenges with regard to employment and work that can play a significant role in the global economy given the growing needs of cancer survivors in both the short-term impact and the long-term impact of cancer and treatment. Cancer survivorship and employment can be considered from different perspectives: 1) the cancer survivor (eg health, quality of life, work ability, job satisfaction, return to work, employment discrimination), 2) the caregiver and the family (eg the burden of care, partnership

Corresponding author: Anja Mehnert, PhD, Section of Psychosocial Oncology, Department of Medical Psychology and Medical Sociology, University Medical Center Leipzig, Philipp-Rosenthal-Strasse 55, 04103 Leipzig, Germany; Fax: (011) 49-341-97-18809; anja.mehnert@medizin.uni-leipzig.de

[1]Section of Psychosocial Oncology, Department of Medical Psychology and Medical Sociology, University Medical Center Leipzig, Leipzig, Germany; [2]Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Coronel Institute of Occupational Health, Academic Medical Center, Amsterdam, the Netherlands; [4]Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences, Bethesda, Maryland; [5]Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28067, **Received:** July 27, 2012; **Revised:** November 29, 2012; **Accepted:** December 3, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

issues, financial problems, risk for poverty), 3) the employer and coworkers (eg working conditions, work load, working arrangements), 4) the health care provider (eg supportive care and rehabilitation needs, effective support programs and interventions), and 5) the community or society (eg economic and policy changes).

Between Europe and the United States, there are several differences in terms of health care provision and social security that affect employment and return-to-work in cancer survivors. With regard to legislation on sick leave and sickness benefits, all European countries provide several types of social insurance systems for employees and, in some countries, self-employed individuals as well.[4] However, there are major differences among countries in terms of solutions for employees with chronic health conditions and the unemployed. The Nordic European countries provide a very comprehensive social system for employees with chronic illness, whereas the majority of Continental/Mediterranean countries ensure no specific protection for the unemployed.[4] In most European countries, the amount of benefit is related to the earnings or income of the employee; in some countries, such as Belgium and the United Kingdom, a lump sum or a flat rate benefit is paid. Also, the duration of sickness benefit differs across European countries from a minimum of 6 months to a maximum of unlimited duration.[4] Alternative measures and policies to sick pay allowance can be divided into 3 categories: 1) measures aimed at adapting the workplace and work activity to workers' reduced capacity, 2) measures aimed at fostering life-long learning, and 3) measures aimed at removing individuals from the workplace whose reduced work capacity does not allow them to perform the assigned tasks (or any other task).[4]

In the United States, the health and social network for those who are work-disabled consists of numerous programs, including Social Security (eg, retirement, survivors, and disability insurance), Medicare, unemployment insurance, and supplemental security income. Concerning general health insurance, the employee is often insured by the employer. However; insurance for both health care and indemnity (lost time or 100% work disabled) is also provided through federal programs to which the employee contributes during their working years.

Related to the matter of paid sick leave, there is no national policy related to standard coverage for employees. Clearly this is not the case in countries within the European Union. This policy variation between the United States and the European Union certainly can influence decisions regarding work status at the time of treatment for cancer; however, the US federal government, by implementing the Family and Medical Leave Ac, at least provides 12 weeks of unpaid, job-protected leave.[5] We are unaware of comparisons to date across countries of the effects of such discrepancies on work disability in cancer survivors. However, in relation to this matter, there is anecdotal evidence that, even with short-term disability coverage, cancer patients are deciding not to initiate such coverage and report wanting to work during treatment and/or to use sick leave benefits to cover time lost related to treatment for cancer and its long-term effects.

Employment and Return to Work

Over the past 2 decades, a considerable amount of research has demonstrated the significant physical, emotional, and social impact of cancer and its treatment on patients and their families. However, as the increase in cancer incidence and the improvement in survival rates have led to a growing number of cancer survivors, the importance of work ability, (re-)employment and social reintegration have gradually emerged as critical topics within psycho-oncologic and cancer survivorship research.

Because returning to work has great importance for patients and society, the majority of studies that have specifically addressed cancer and work outcomes have been focusing on the likelihood and timeliness of work return. The work participation of cancer survivors typically has been assessed by measurements like employment status (yes/no)[6] or the length of sick leave, as reflected by the number of days off work after diagnosis.[7] Several review articles from both the United States and the European Union have summarized return-to-work studies and have reported average return-to-work rates of approximately 64%, with a wide range between 24% and 94%.[8-13] However, a meta-analysis by de Boer et al[10] indicated that the unemployment risk was 1.48 times higher (95% confidence interval, 1.15-1.98) in the United States than in European countries. Overall, studies have indicated a steady increase in return to work with increasing time intervals after a cancer diagnosis (Table 1).[13] These results were based mainly on populations with early stage breast cancer or mixed populations with breast cancer, gynecologic cancers, and a variety of other tumor entities, such as gastrointestinal, hematologic, and urologic, cancers.[13-24] Roelen et al[25] demonstrated that, 2 years after a cancer diagnosis, the highest percentage of patients who had fully returned to work were those who had female genital cancer, male genital cancer, skin cancer, and breast cancer. The lowest percentage of patients who returned to work were those who had lung cancer and gastrointestinal cancers.[25] Moreover, advanced cancer stages and palliative treatment

TABLE 1. Percentages of Patients Who Returned to Work After Cancer Diagnosis

Time After Diagnosis	Percentage of Patients (Range)
RTW 6 mo after diagnosis	40 (24-72)
RTW 12 mo after diagnosis	62 (50-81)
RTW 18 mo after diagnosis	73 (64-82)
RTW 24 mo after diagnosis	89 (84-94)
RTW 5 y after diagnosis	67 (1 study)

Abbreviations: RTW, returned to work.
[a]Based on data from: Mehnert A. Employment and work-related issues in cancer survivors. *Crit Rev Oncol Hematol*. 2011;77:109-130.[13]

intention were associated with lower return-to-work rates.[26]

Research has indicated that the risk of unemployment was associated with extensive surgery and advanced tumor stage.[15,22,26-29] Also, a range of tumor entities has been associated with a greater risk of unemployment and job loss, including liver, lung, and brain cancers; hematologic malignancies; gastrointestinal and pancreatic cancers; as well as head and neck and gynecologic cancers.[10,27,28,30-32]

Perceived employer accommodation for cancer-related and treatment-related symptoms and side effects, long-term or late effects, and follow-up medical visits has been identified as a strong predictor of return to work.[8,22,26] In cancer survivors, a return-to-work meeting with the employer as well as advice from a physician about work, flexible working conditions, counseling, miscellaneous training services, job replacement services, job search assistance, and maintenance services were factors significantly associated with a greater likelihood of being employed among cancer survivors in both the United Kingdom and the United States.[17,26,33,34] Studies from European countries, such as Finland, Germany, and the Netherlands, identified younger age, higher levels of education, absence of surgery, fewer physical symptoms, shorter duration of sick leave, male gender, and Caucasian ethnicity as variables that were predictive of or associated with return to work.[13,17,19,21,31,35-37]

In addition to return-to-work and sick leave duration outcomes, the performance of the cancer survivor once back at work has not been regularly investigated. Breast cancer survivors[38] and brain tumor survivors[39] self-reported significantly lower work productivity than their peers who never had cancer, whereas breast cancer survivors had a mean reduction in productivity of 2.5 hours of work over 2 weeks.[40] All of those studies were conducted in the United States. Studies focusing on work ability indicate that higher levels of fatigue or cognitive limitations are associated with decreased work ability.[9,16,27,41-46] These findings have been reported in research both on American and European cancer survivors. In a recent Norwegian study, 31% of the employed cancer survivors (80% were engaged in nonmanual work) reported a reduction in physical work ability because of cancer, whereas 23% reported a reduction in mental work ability.[47]

Some qualitative studies conducted in the United Kingdom, the United States, and Canada using interviews and focus groups have examined the impact of cancer on the survivor's subjective experience of work life. Patients who were 1 to 10 years postdiagnosis reported that they had difficulties coping and concentrating, and they were worried about their reduced work capability.[46] Returning to work after treatment for cancer can alter the patient's job position. Breast cancer survivors reported experiencing unwanted changes in their jobs and job responsibilities, in addition to changes in their relationships with coworkers and employers[48]; these women also reported a change in their feelings about the importance of work. This latter study was reported from Canada and in a province with strong organized labor.

Other qualitative studies on subjective experiences of cancer patients also have indicated that their cancer had influenced their priority of work relative to other aspects of their lives[49] or had deteriorated their job satisfaction and career prospects.[21] Currently, there are few quantitative studies from either the United States or the European Union that provide information about how cancer survivors experience the quality of their working life in terms of job-related well being, work pleasure, and the extent to which work experiences are rewarding, fulfilling, and devoid of stress and other negative personal consequences.[47]

Conceptual Framework

Developing a better understanding of cancer and treatment-induced, work-related problems and the specific targets for work-related interventions and rehabilitation programs will facilitate cancer survivorship research and practice in the area of work and cancer. Figure 1 is a cancer survivorship and work model adapted from Feuerstein et al[12] and Mehnert[13] that illustrates the range of individual and interpersonal factors and the short-term, long-term, and late effects of cancer treatments as well as the work environment and overall legal, organizational, and financial policies and procedures that may affect employment and return to work. Specific interventions and rehabilitation programs should to be further developed, evaluated, and implemented that address a variety of individual and

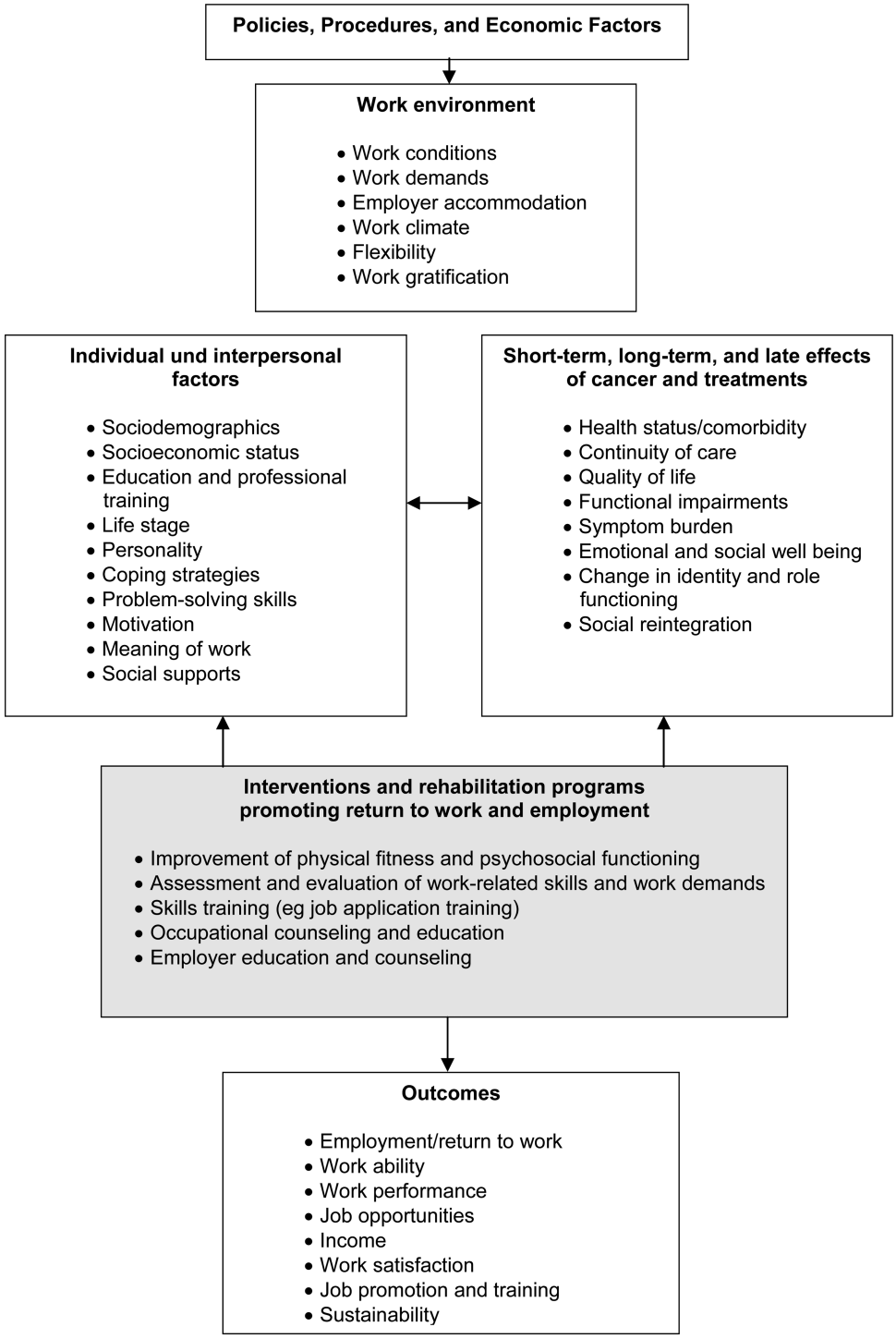

Figure 1. The cancer survivorship and work model is shown.

treatment-related factors and that are tailored to the individual needs of a patient. On the basis of existing research, such programs should focus on the evaluation and targeted intervention related to physical and psychosocial function, symptom burden, work environment, and organization-related and policy-related factors. This approach has the potential to address work-related outcomes, such as employment, work ability, or work performance.

Rather than pointing out differences in the 2 conceptualizations, we thought that it would be more useful to integrate the 2 frameworks. Merging concepts from both of these models, in which both frameworks are based on evidence from studies conducted on both continents, made sense given a focus on parsimony and applicability. The integrated model emphasizes 4 major areas, including individual and interpersonal factors (eg sociodemographics, education and professional training, meaning of work); short-term, long-term, and late effects of cancer and cancer treatments (eg functional impairments, symptom burden); the work environment (eg working conditions); and outcomes, such as employment or work performance (Fig. 1). An intervention element was included to highlight various approaches that can improve work outcomes. The focus on several work outcomes is consistent with potential outcomes in the work disability area.[50,51] Other work-related outcomes that have been considered in the cancer survivor literature include changes in work ability, career choices, work productivity, and work retention or sustainability. Figure 1 provides a more complete list of possible work outcomes.

Intervention Studies and Programs

Given the importance of employment for cancer survivorship and quality of life, it is necessary to provide employed cancer survivors with programs to support the return-to-work process, work retention, and other outcomes, as listed in Figure 1. In the past 2 decades, interventions have focused on either psychological, physical, pharmacologic, or multidisciplinary approaches to work or on modifying various problem areas in cancer survivorship that can influence work outcomes.[50,51] In the United States and in European regions, programs to enhance labor participation of cancer survivors have been reported. These initiatives typically focus on providing strategies that often are focused on the cancer survivor rather than the broader workplace, economic, or related policy areas. Future interventions should more centrally include the perspective of coworkers and employers with regard to the structuring of work organization, the deployment of workers, work-related training, skills training opportunities, and professional development to learn adaptive ways of dealing with new demands and unfamiliar work situations in working with individuals who have cancer and other chronic health conditions.

In a recent *Cochrane Review*, the effectiveness of interventions that constituted randomized controlled trials to improve work outcomes was reported.[6] Until now, the research on evidence-based interventions to achieve changes in various work outcomes has been very modest. This work was conducted with cancer survivors from both the United States and Europe. There were no interventions identified in which the primary focus was to improve return-to-work outcomes or, for that matter, any work-related outcome. Modest evidence indicated that multidisciplinary interventions involving physical, psychological, and vocational components led to higher return-to-work rates than care as usual. Two of the effective multidisciplinary interventions were conducted more than 30 years ago by an oncology nurse in the hospital setting.[52,53] However, to our knowledge, there are no data on the cost of such efforts.

In the early United Kingdom study by Maguire et al,[52] patients with breast cancer were advised by an oncology nurse on exercise, were encouraged to return to work and become socially active, and were counseled on feelings. The nurse began the intervention in the hospital early after surgery and followed the patient every 2 months to monitor their progress until the patient "adapted" psychologically and socially to the new situation. Twelve to 18 months after surgery, those who were helped by the nurse had greater social recovery, return to work, and adaptation to breast loss than those without the nurse's support.[52] Berglund et al[53] developed an intervention in Sweden for patients with breast cancer in which the patients received information and performed physical training supplemented by coping skills training provided by an oncology nurse who specialized in psychosocial matters. In a randomized trial, patients with breast cancer in that program had improved return-to-work outcomes, but no statistically significant differences were observed when those patients were compared with controls who received either a single information session or no intervention.

Various occupational rehabilitation interventions have been developed in Europe. A Dutch program,[54] in which the medical specialist provided a 10-step plan with advice to the patient on returning to work, demonstrated that patients adhered to 7 of the 10 suggestions in the leaflet, and half of the occupational physicians perceived that the guidance they provided was helpful.[54] In a more recent intervention, a psycho-oncology nurse supported cancer patients with returning to work in a work-directed intervention consisting of 4 meetings with a nurse at the treating hospital to start early vocational rehabilitation and supply work-related and legal information; 1 meeting with the participant, occupational physician, and supervisor at work (line manager) and letters from the treating physician to the occupational physician to enhance

communication.[55] A randomized controlled trial evaluating the effects of this intervention is currently underway. In the United Kingdom, a self-management tool for employees affected by cancer (entitled "Work It Out") was recently developed. This empowerment-based approach enables individuals affected by cancer to find solutions in making a timely return to work or to maintain employment during diagnosis and treatment. The project used intervention mapping, which is a process for developing theory-based and evidence-based health education programs, and a Delphi consensus method[56] to develop and test the tool. A feasibility study demonstrated that most participants considered the information and advice on the impact of treatment on work ability most valuable. Most participants felt that specialist cancer nurses and consultants were best placed to deliver return-to-work interventions.[57]

The Spanish Association Against Cancer, in coordination with the Employment Service in Andalusia, has been working since 2005 on a job placement program to promote social-labor integration of cancer patients. The program emphasizes modifying factors in the job placement process, especially those related to cancer. For the early detection of those factors, an adapted Job Placement Psychological Factors Questionnaire is employed. Analysis of those elements, along with a customized employability diagnosis, provides the adoption of specific strategies for each cancer patient.[58] The program's job placement rate is 62.5%. This is probably a relatively good outcome, because the program is focused on individuals who have problems returning to work and need help with their labor integration. In an average population of cancer patients, the return to work is 62% after 12 months.[13]

Vocational rehabilitation services are available in both the United States and the United Kingdom for patients with cancer and are currently being evaluated. In Scotland, patients receiving employment support are allocated a case manager who conducts a telephone assessment of supportive care needs to facilitate remaining in or returning to work. On the basis of this initial assessment of each individual's personal goals and health status, the case manager directs participants to appropriate support services, including physiotherapy, occupational therapy, occupational health specialists, counselors/psychological therapy, and complementary therapy. Thus, each individual may receive a different intervention or a combination of interventions. A randomized pilot study has begun to evaluate the effects of this intervention.[59]

Young adult cancer survivors had lower levels of occupational development and were less ready to pursue employment compared with their noncancer survivor counterparts. In the United States, vocational services were offered by vocational counselors to young cancer survivors, although very few were involved in a state-federal rehabilitation program.[60] Despite this, the provision of certain vocational rehabilitation services was related to increased employment in these young adult survivors. Those who received job search assistance and on-the-job support were 4 times more likely to be employed after receiving such services.[60]

On the basis of social laws in Germany, cancer patients have a legal right to participate in a 3-week inpatient cancer rehabilitation program at specialized institutions.[61] Access to rehabilitation programs is usually facilitated by hospital physicians and social workers immediately after patients complete their primary treatment or at a later stage during the course of cancer. Rehabilitation costs are covered mainly by pension and health insurance. The cancer rehabilitation program has a multidimensional, therapeutic approach that includes patient education, exercise, and physical therapy to regain physical fitness and vitality along with relaxation training and psychosocial as well as occupational counseling to enhance coping skills and facilitate return to work at the earliest possible time. Specific programs for gradual reintegration into the working life are provided.

Research in the United Kingdom indicates that line managers and employers also need support to help their employees affected by cancer. For example, 1 study reported that 73% of employers in the United Kingdom had no formal policy for managing employees diagnosed with cancer, and only approximately 33% of organizations ensured that relevant staff had a good understanding of cancer and the impact of treatment on an individual's working role. The effect of this is that insufficient support and information are made available by employers to employees with cancer.[62] Furthermore, line managers treated referral to occupational health physicians differently for employees who had cancer compared with employees who had other diagnoses, with 45% of respondents indicating that referral may take place too late to be effective in securing a return to work.[63]

To overcome these barriers, the Danish Cancer Society is supporting employers by developing an employer's guide containing information, legislation, and practical advice about how to support employees affected by cancer. The guide is currently being adapted for other European countries. A similar guide has been developed by Macmillan Cancer Support in the United Kingdom,[64] but neither guide has been evaluated. A measure that

assesses a supervisor's level of support, referred to as the Supervisors to Support Return to Work measure, recently has been developed in the United Kingdom. This is a potentially valuable tool in research and in organizational settings, both during long-term sick leave and after employees have returned to work.[65]

European and American Contributions and Perspectives on Work and Cancer: Future Directions

Perhaps because of the global economy in the 21st century and the ease of communication among investigators in diverse countries with differing languages, health care systems, and social safety nets, there are many similar constructs and approaches to cancer survivorship and work. There also are conceptual frameworks that possess many of the same empirically supported and hypothetical associations.[12,13,66-68] Furthermore, in 2006, a group of researchers and clinicians interested in the impact of cancer on work and employment met in London and then again a year later in Spain at the International Psychosocial Oncology Society meetings to discuss this field, its current status, and future directions of this area of research. Many themes discussed in these initial meetings have been reflected in the subsequent research of the individuals who were in attendance. Beyond cancer, there has also been an increasing international focus on the field of work disability in general as well as how it applies to many types of chronic illnesses.[69] With regard to cancer survivorship research, previous studies have mainly focused on breast and gynecologic cancers, including mainly women. Future research should more strongly focus on patients with other cancer entities, such as gastrointestinal cancers or blood cancers, and on different age populations, such as childhood or adolescent cancer survivors.

Clearly, there are differences between the broad geographic areas of the United States and Europe in terms of the European research emphasis on many elements of the workplace rather than the worker.[70,71] This distinction has a long history in the area of work disability in general; however, investigators in the United States could learn from their European colleagues in terms of studying and addressing various aspects of the work environment and organization of work in those with various health problems. Another difference noted in the research between the 2 different entities is the use of work ability as an outcome measure in much of the European research and as more of a focus on measures of productivity in the United States. Although, at this point, both involve the perception of the affected worker and are not independent measures of perceived ability or productivity, the difference is interesting to point out. Perhaps the focus on performance at work is more consistent with the US culture, which focuses on output or productivity to a greater degree than quality of work life. Finally, the lack of research on violations of legal protections for cancer survivors in the workplace in European Union countries versus the United States may reflect a certain level of friction that rises to the level of legal remedy for perceived problems in the workplace in the United States, whereas these problems may be addressed in the routine management of work and health in the European Union.[72] This differential, although speculative, also may reflect a cultural difference in terms of the relative value of the quality of work life.

There are many similarities in terms of the factors associated with work problems across many countries, and these factors are robust despite differences in social systems, health care systems, language, and culture. Research on work disability and a variety of health problems has reported similar challenges and has identified many of the same factors related to work disability among many chronic health problems.[51] For example, problems in the area of work and cancer survivors share many concerns with research on work and disorders, and those studying cancer and work can learn from the decades of research in that area.[73] Cost-effective primary, secondary, and tertiary prevention efforts that address the many problems that serve as barriers to returning to work or work sustainability need to be pursued with vigor. Although we must learn more about the etiology and the impact of work disability among cancer survivors to titrate our interventions, now is the time to design and systematically evaluate various approaches based on our current understanding of cancer survivorship and work and the broad research base on work disability from other chronic illnesses.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional Assessment of Long-Term Cancer Survivors Including Discovery of Genetic Bases of Susceptibility, Depressive Stage, Prevention of Affective Disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. GLOBOCAN (IARC). Section of Cancer Information, 2008. Available at: http://globocan.iarc.fr/factsheet.asp. Accessed December 4, 2012.

2. Centers for Disease Control and Prevention (CDC). Cancer survivors—United States, 2007. MMWR. 2011;60:269-272.
3. Klugman J. Sustainability and Equity: A Better Future for All. New York: United Nations Development Program; 2011.
4. Crepaldi C, Barbera M, Ravelli F, Apostoli P, Naaf S. Cancer and in General Long-Term Illnesses at Workplaces. Brussels, Belgium: European Parliament Employment and Social Affairs Committee; 2008.
5. Blanck P, Myhill W, Solstad Vedeler J, Perlman P. Individuals with cancer in the workforce and their federal rights. In: Feuerstein M, ed. Work and Cancer Survivors. New York: Springer;2009:255-276.
6. de Boer AG, Taskila T, Tamminga SJ, Frings-Dresen MH, Feuerstein M, Verbeek JH. Interventions to enhance return-to-work for cancer patients. *Cochrane Database Syst Rev.* 2011;(2):CD007569.
7. Roelen CA, Koopmans PC, de Graff JH, Balak F, Groothoff JW. Sickness absence and return to work rates in women with breast cancer. *Int Arch Occup Environ Health.* 2009;82:543-546.
8. Spelten ER, Sprangers MA, Verbeek JH. Factors reported to influence the return to work of cancer survivors: a literature review. *Psychooncology.* 2002;11:124-131.
9. Taskila T, Lindbohm ML. Factors affecting cancer survivors' employment and work ability. *Acta Oncol.* 2007;46:446-451.
10. de Boer AG, Taskila T, Ojajarvi A, van Dijk FJ, Verbeek JH. Cancer survivors and unemployment: a meta-analysis and meta-regression. *JAMA.* 2009;301:753-762.
11. Steiner JF, Nowels CT, Main DS. Returning to work after cancer: quantitative studies and prototypical narratives. *Psychooncology.* 2010;19:115-124.
12. Feuerstein M, Todd B, Moskowitz M, et al. Work in cancer survivors: a model for practice and research. *J Cancer Surviv.* 2010;4:415-437.
13. Mehnert A. Employment and work-related issues in cancer survivors. *Crit Rev Oncol Hematol.* 2011;77:109-130.
14. Spelten E. Cancer, fatigue and the return of patients to work—a prospective cohort study. *Eur J Cancer.* 2003;39:1562-1567.
15. Bradley C, Neumark D, Bednarek H, Schenk M. Short-term effects of breast cancer on labor market attachment: results from a longitudinal study. *J Health Econ.* 2005;24:137-160.
16. de Boer AG, Verbeek JH, Spelten ER, et al. Work ability and return-to-work in cancer patients. *Br J Cancer.* 2008;98:1342-1347.
17. Pryce J, Munir F, Haslam C. Cancer survivorship and work: symptoms, supervisor response, co-worker disclosure and work adjustment. *J Occup Rehabil.* 2007;17:83-92.
18. Bieri S, Roosnek E, Helg C, et al. Quality of life and social integration after allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2008;42:819-827.
19. Verbeek J, Spelten E, Kammeijer M, Sprangers M. Return to work of cancer survivors: a prospective cohort study into the quality of rehabilitation by occupational physicians. *Occup Environ Med.* 2003;60:352-357.
20. Johnsson A, Fornander T, Rutqvist L, Vaez M, Alexanderson K, Olsson M. Predictors of return to work ten months after primary breast cancer surgery. *Acta Oncol.* 2009;48:93-98.
21. Amir Z, Moran T, Walsh L, Iddenden R, Luker K. Return to paid work after cancer: a British experience. *J Cancer Surviv.* 2007;1:129-136.
22. Bouknight RR, Bradley CJ, Zhehui L. Correlates of return to work for breast cancer survivors. *J Clin Oncol.* 2006;24:345-353.
23. Balak F, Roelen CA, Koopmans PC, Berge EE, Groothoff JW. Return to work after early-stage breast cancer: a cohort study into the effects of treatment and cancer-related symptoms. *J Occup Rehabil.* 2008;18:267-272.
24. Johnsson A, Fornander T, Olsson M, Nystedt M, Johansson H, Rutqvist LE. Factors associated with return to work after breast cancer treatment. *Acta Oncol.* 2007;46:90-96.
25. Roelen CA, Koopmans PC, Groothoff JW, van der Klink JJ, Bultmann U. Sickness absence and full return to work after cancer: 2-year follow-up of register data for different cancer sites. *Psychooncology.* 2011;20:1001-1006.
26. Mehnert A, Koch U. Predictors of employment among cancer survivors after medical rehabilitation—a prospective study. *Scand J Work Environ Health.* 2013;39:76-87.
27. Short PF, Vasey JJ, Tunceli K. Employment pathways in a large cohort of adult cancer survivors. *Cancer.* 2005;103:1292-1301.
28. Choi KS, Kim E, Lim J, et al. Job loss and reemployment after a cancer diagnosis in Koreans—a prospective cohort study. *Psychooncology.* 2007;16:205-213.
29. Ahn E, Cho J, Shin DW, et al. Impact of breast cancer diagnosis and treatment on work-related life and factors affecting them. *Breast Cancer Res Treat.* 2009;116:609-616.
30. Schultz PN, Beck ML, Stava C, Sellin RV. Cancer survivors. *Work related issues. AAOHN J.* 2002;50:220-226.
31. Taskila-Brandt T, Martikainen R, Virtanen SV, Pukkala E, Hietanen P, Lindbohm M. The impact of education and occupation on the employment status of cancer survivors. *Eur J Cancer.* 2004;40:2488-2493.
32. Park J, Park E, Park J, Kim S, Lee S. Job loss and re-employment of cancer patients in Korean employees: a nationwide retrospective cohort study. *J Clin Oncol.* 2008;26:1302-1309.
33. Chan F, Strauser D, da Silva Cardoso E, Xi Zheng L, Chan JY, Feuerstein M. State vocational services and employment in cancer survivors. *J Cancer Surviv.* 2008;2:169-178.
34. Cooper AF, Hankins M, Rixon L, Eaton E, Grunfeld EA. Distinct work-related, clinical and psychological factors predict return to work following treatment in 4 different cancer types [published online ahead of print March 21, 2012]. Psychooncology. 2012.
35. Hensel M, Egerer G, Schneeweiss A, Goldschmidt H, Ho A. Quality of life and rehabilitation in social and professional life after autologous stem cell transplantation. *Ann Oncol.* 2002;13:209-217.
36. Molina Villaverde R, Feliu Batlle J, Villalba Yllan A, et al. Employment in a cohort of breast cancer patients. *Occup Med.* 2008;58:509-511.
37. Verdonck-de Leeuw IM, van Bleek WJ, Leemans CR, de Bree R. Employment and return to work in head and neck cancer survivors. *Oral Oncol.* 2010;46:56-60.
38. Hansen JA, Feuerstein M, Calvio LC, Olsen CH. Breast cancer survivors at work. *J Occup Environ Med.* 2008;50:777-784.
39. Feuerstein M, Hansen J, Calvio L, Johnson L, Ronquillo J. Work productivity in brain tumor survivors. *J Occup Environ Med.* 2007;49:803-811.
40. Lavigne JE, Griggs JJ, Tu XM, Lerner DJ. Hot flashes, fatigue, treatment exposures and work productivity in breast cancer survivors. *J Cancer Surviv.* 2008;2:296-302.
41. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. *Br J Cancer.* 2004;91:822-828.
42. Yabroff K, Lawrence W, Clauser S, Davis W, Brown M. Burden of illness in cancer survivors: findings from a population-based national sample. *J Natl Cancer Inst.* 2004;96:1322-1330.
43. Bradley CJ, Oberst K, Schenk M. Absenteeism from work: the experience of employed breast and prostate cancer patients in the months following diagnosis. *Psychooncology.* 2006;15:739-747.
44. Gudbergsson SB, Fossa SD, Borgeraas E, Dahl AA. A comparative study of living conditions in cancer patients who have returned to work after curative treatment. *Support Care Cancer.* 2006;14:1020-1029.
45. Steinbach JP, Blaicher H, Herrlinger U, et al. Surviving glioblastoma for more than 5 years: the patient's perspective. *Neurology.* 2006;66:239-242.
46. Kennedy F, Haslam C, Munir F, Pryce J. Returning to work following cancer: a qualitative exploratory study into the experience of returning to work following cancer. *Eur J Cancer Care.* 2007;16:17-25.
47. Torp S, Nielsen RA, Gudbergsson SB, Dahl AA. Worksite adjustments and work ability among employed cancer survivors. *Support Care Cancer.* 2011;20:2149-2156.
48. Maunsell E, Brisson C, Dubois L, Lauzier S, Fraser A. Work problems after breast cancer: an exploratory qualitative study. *Psychooncology.* 1999;8:467-473.
49. Main DS, Nowels CT, Cavender TA, Etschmaier M, Steiner JF. A qualitative study of work and work return in cancer survivors. *Psychooncology.* 2005;14:992-1004.
50. Pransky GS, Loisel P, Anema JR. Work disability prevention research: current and future prospects. *J Occup Rehabil.* 2011;21:287-292.

51. Boot CR, Koppes LL, van den Bossche SN, Anema JR, van der Beek AJ. Relation between perceived health and sick leave in employees with a chronic illness. *J Occup Rehabil.* 2011;21: 211-219.
52. Maguire P, Brooke M, Tait A, Thomas C, Sellwood R. The effect of counselling on physical disability and social recovery after mastectomy. *Clin Oncol.* 1983;9:319-324.
53. Berglund G, Bolund C, Gustafsson UL, Sjoden PO. One-year follow-up of the "Starting Again" group rehabilitation programme for cancer patients. *Eur J Cancer.* 1994;30:1744-1751.
54. Nieuwenhuijsen K, Bos-Ransdorp B, Uitterhoeve LL, Sprangers MA, Verbeek JH. Enhanced provider communication and patient education regarding return to work in cancer survivors following curative treatment: a pilot study. *J Occup Rehabil.* 2006;16:647-657.
55. Tamminga SJ, de Boer AG, Verbeek JH, Taskila T, Frings-Dresen MH. Enhancing return-to-work in cancer patients, development of an intervention and design of a randomised controlled trial [serial online]. *BMC Cancer.* 2010;10:345.
56. Linstone HA, Turoff M. The Delphi Method. Reading, MA: Addison-Wesley; 1975.
57. Bains M, Munir F, Yarker J, Steward W, Thomas A. Return-to-work guidance and support for colorectal cancer patients: a feasibility study. *Cancer Nurs.* 2011;34:E1-E12.
58. Rio M, Cano C, Tudela FV, Sanchez MC. Insercion laboral en mujeres despues de un cancer de mama: una ayuda de la integracion social. *Psicooncologia.* 2010;7:143-152.
59. Kyle RG, Culbard B, Evans J, Gray NM, Ayansina D, Hubbard G. Vocational rehabilitation services for patients with cancer: design of a feasibility study incorporating a pilot randomised controlled trial among women with breast cancer following surgery [serial online]. *Trials.* 2011;12:89.
60. Strauser D, Feuerstein M, Chan F, Arango J, da Silva Cardoso E, Chiu C. Vocational services associated with competitive employment in 18-25 year old cancer survivors. *J Cancer Surviv.* 2010;4: 179-186.
61. Hellbom M, Bergelt C, Bergenmar M, et al. Cancer rehabilitation: a Nordic and European perspective. *Acta Oncol.* 2011;50:179-186.
62. Chartered Institute of Personnel and Development (CIPD)/Cancerbackup. Working with cancer. Survey report, 2006. London, United Kingdom: CIPD; 2006. Available at: http://www.cancerbackup.org.uk/News/Mediacentre/Pressreleases statements/2006/Newguidancetoaddresslackofsupportforemployees affectedbycancer/Surveyfinal.pdf. [Accessed November 23, 2012].
63. Amir Z, Wynn P, Chan F, Strauser D, Whitaker S, Luker K. Return to work after cancer in the UK: attitudes and experiences of line managers. *J Occup Rehabil.* 2010;20:435-442.
64. Macmillian Cancer Support. Managing cancer in the workplace: an employers guide to supporting staff affected by cancer. Available at: http://www.macmillan.org.uk/Cancerinformation/Livingwithandaftercancer/Workandcancer/Supportformanagers/Employersguide/Employersguide.aspx. [Accessed November 23, 2012].
65. Munir F, Yarker J, Hicks B, Donaldson-Feilder E. Returning employees back to work: developing a measure for supervisors to support return to work (SSRW). *J Occup Rehabil.* 2012;22:196-208.
66. Hoffman B. Cancer survivors at work: a generation of progress. *CA Cancer J Clin.* 2005;55:271-280.
67. Feuerstein M, Harrington CB. Recommendations for the US National Occupational Research Agenda: research on cancer survivorship and musculoskeletal disorders and work disability. *J Occup Rehabil.* 2006;16:1-5.
68. Steiner JF, Cavender TA, Nowels CT, et al. The impact of physical and psychosocial factors on work characteristics after cancer. *Psychooncology.* 2008;17:138-147.
69. Feuerstein M. Introduction: the world challenge of work disability. *J Occup Rehabil.* 2005;15:451-452.
70. Gudbergsson S, Fossa S, Lindbohm M, Dahl A. Received and needed social support at the workplace in Norwegian and Finnish stage 1 breast cancer survivors: a study from the Nordic Study Group of Cancer and Work (NOCWO). *Acta Oncol.* 2009;48:67-75.
71. Roelen CA, Koopmans PC, Groothoff JW, van der Klink JJ, Bultmann U. Return to work after cancer diagnosed in 2002, 2005 and 2008. *J Occup Rehabil.* 2011;21:335-341.
72. Feuerstein M, Luff G, Harrington CB. Patterns of workplace disputes in cancer survivors: A population study of ADA claims. *J Cancer Surviv.* 2007;1:185-192.
73. Feuerstein M. Handbook of Cancer Survivorship. Springer: New York; 2007.

Original Article

Informal Caregiving for Cancer Patients

Francesca Romito, PhD[1]; Gil Goldzweig, PhD[2]; Claudia Cormio, PhD[1]; Mariët Hagedoorn, PhD[3]; and Barbara L. Andersen, PhD[4]

According to the recent worldwide estimation by the GLOBOCAN project, in total, 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008. The worldwide number of cancer survivors within 5 years of diagnosis has been estimated at be almost 28.8 million. Informal caregivers, such as family members and close friends, provide essential support to cancer patients. The authors of this report provide an overview of issues in the study of informal caregivers for cancer patients and long-term survivors in the United States and Europe, characterizing the caregivers commonly studied; the resources currently available to them; and their unmet needs, their psychosocial outcomes, and the psychosocial interventions tailored to their special circumstances. A broad overview of the state of research and knowledge, both in Europe and the United States, and observations on the directions for future research are provided. ***Cancer*** **2013;119(11 suppl):2160-9.** *© 2013 American Cancer Society.*

KEYWORDS: cancer; survivorship; health care delivery; nonclinical distribution; Europe.

INTRODUCTION

The estimated number of cancer survivors worldwide who are within 5 years of diagnosis is approximately 28.8 million.[1,2] Informal caregivers, such as partners, close family members, or friends, provide essential support to cancer patients along the illness trajectory. During diagnosis and the first phases of the illness, these individuals may offer practical help by accompanying the patient during the diagnostic steps and also psychological support for coping with uncertainty and fear. In the advanced phases of the illness, caregivers may provide assistance and self-care and give emotional support.

The burden of cancer is likely considerable across all cultures. Some have suggested that the experience of caregiving is not influenced by aspects like race and ethnicity,[3] but others have observed racial differences among the type of and level of involvement in the caregiving task.[4]

In reality, there are aspects related to race and ethnicity and also aspects related to cultural values, beliefs, and family systems that may account for caregivers in different countries experiencing their role in different ways. For example, in some geographic areas, families live close to their families of origin; and, in these cases, more help may come from the extended family. In other areas, however, the nuclear family may be the only resource for caregiving. For example, if families, such as those in Mediterranean countries, are closely involved in their relative's care, then this may negatively impact diagnosis disclosure from oncologists to cancer patients despite ethical and legal obligations to the contrary,[5] creating a discrepancy between norms and real medical practice.[6,7] Similarly, different approaches to end-of-life care, from diagnosis disclosure, to the practice of euthanasia, to the role of family members and the availability of hospices, have been documented among European countries.[8] Thus, there is no unique, "western" way of providing care to a patient with cancer.

Corresponding author: Francesca Romito, MD, Experimental Unit of Psycho-Oncology, Department of Critical Area and Surgery, National Cancer Research Center Istituto Tumori "Giovanni Paolo II," Via Orazio Flacco 65, 70126 Bari, Italy; Fax: (011) 39-080-5555328; francescaromito@yahoo.com

[1]Experimental Unit of Psycho-Oncology, Department of Critical Area and Surgery, National Cancer Research Center Istituto Tumori "Giovanni Paolo II,", Bari, Italy; [2]Department of Psychology, School of Behavioral Sciences, Tel-Aviv-Yaffo Academic College, Tel-Aviv, Israel; [3]Health Psychology Section, Department of Health Sciences, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [4]Department of Psychology, The Ohio State University, Columbus, Ohio.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28057, **Received:** July 27, 2012; **Revised:** November 29, 2012; **Accepted:** November 30, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

The objective of the current discussion is to provide readers with an outline of the cancer caregiver literature, in both the United States and Europe, and to offer some comparisons. The focus is only on caregivers of adult cancer patients, because caregiving a child or an adolescent poses particular strains for families. We performed a nonsystematic literature search using the PubMed and Web of Knowledge databases using the following search terms: *caregiving*, *caregiver*, *significant other*, *next of kin*, *spouse*, *partner*, *son*, *daughter*, *relative*, *cancer*, and *oncology*. We also considered exemplar studies from reviews authored by US or European researchers. The variety of content in the 2 literatures reflects the extant differences identified.

Defining Cancer Caregiving

First, it is useful to consider how the research literature has defined "caregiver." Unfortunately, there is no universal definition (and, at times, no definition is provided), so there is variation across studies. We asked the following questions: Is an individual a caregiver based on the provision of psychological aid or behavioral assistance, such as preparing a meal? Is the extent of support in hours per day or economic costs incurred more relevant in defining who is or is not a caregiver? Is anyone living with a cancer patient assumed to be caregiving? The American Cancer Society's (ACS) National Quality of Life Survey for Caregivers (NQOL-CG), for example, combined elements like these and defined a caregiver as a "family-like" individual, nominated by the patient, and the 1 individual providing consistent help.[9] Similarly, we observed that some literature reported only using "caregiver" or "carer"[10] as search terms, whereas others used broader terms like "family," "significant other," or "next of kin."[11,12] Still, it is important to note that different studies and reviews can be compared or integrated only if they have a common definition of caregivers or at least if the definitions are clearly stated.

Cancer Caregiving in the United States

The National Alliance for Caregiving (NAC) estimates that 4 million individuals are caring for an adult cancer patient; this estimate accounts for roughly 8% of all caregivers in the United States. In fact, the 8% estimate exceeds the numbers of caregivers (6%) for the number 1 killer of Americans: heart disease.[13] Data suggest that, for those with cancer, the periods of care are predominantly during the first year or 2 after diagnosis (currently, 1.6 million individuals are diagnosed annually[14]) or when an individual is declining and dying of cancer (currently, 600,000 Americans die annually[14]). By comparison, there are fewer studies of caregivers at other times in the cancer trajectory, but the available data indicate low rates of caregiving (eg 16% at 5 years postdiagnosis[15]) when survivors are disease free. This suggests there is a bimodal distribution of caregiving (ie, care at diagnosis/treatment, care at end of life) across the cancer trajectory. Considering the numbers of patients at both time points, roughly 2.2 million individuals may be caregiving at any 1 time. The overview of US caregiver research and data has implications for both policy makers and researchers. First, considering the numbers of caregivers (estimated at 2.2 million), their time and effort expended, and their personal financial costs (including lost wages), policy makers might consider these "hidden" costs to the United States. Absent proper guidance and skills, caregivers also may become a burden on the health care and public welfare systems. Specifically, there is a pressing need for caregiver support and education to become a part of the patient discharge plan, much like what is done for caregivers of stroke or cardiac patients.

Who is caregiving?

Although there are millions, describing the population of cancer caregivers is not straightforward. To date, studies have used a 2-step sampling process: first, identifying and sampling patients and, second, asking the patient to identify (nominate) his/her caregiver who, in turn, is surveyed. Of course, each stage is subject to sampling problems and biases, as illustrated by analyses from the first ACS Study of Cancer Survivors (ACS SCS-I), which is described below. By using this sampling strategy, Kim et al[9] reported that patient factors, such as age, sex, ethnicity, and type of cancer, predicted the nomination of a caregiver for further study. Women (especially those diagnosed with ovarian or breast cancer) were more likely to nominate a caregiver than men. Also, racial groups other than African Americans were equally likely to nominate caregivers.

Regarding the caregiver participants, Kim et al[15] and Kim and Spillers[16] report that they ranged in age from 18 to 90 years (mean age, approximately 55 years), and most (65%) were women. The majority (66%) were spouses, and others were offspring (17%), siblings (7%), parents (4%), or 3% friends. Thus, it is important for population-based studies like ACS SCS-I to have an adequate representation of cancer types and disease stages. However, the nominated caregivers who eventually were surveyed were primarily Caucasian, middle-aged, women who were spouses.[17] Acknowledging the limitations of sampling strategies like these, the ACS NQOL-CG,

which is described below, is the most comprehensive study of US caregivers to date.

A different sampling strategy was used by the NAC in collaboration with the American Association of Retired Persons. Data were collected from anyone who was caregiving (not only cancer caregivers).[13] Even so, the resultant sample was similar to that obtained in the ACS NQOL-CG, although somewhat older (aged ≥65 years). The coresidence caregivers (spouses) usually were the sole caregivers, but the majority (68%) also reported receiving help from additional unpaid caregivers, although not their adult children, as might be assumed. Thus, few studies have sampled nonspousal caregivers, such as daughters or sons (although there are examples[9,17]) or the offspring of older caregivers.[18] To our knowledge, there are no studies sampling other relatives or close friends. In the future, recruiting caregivers through community sampling (rather than patient nomination) would achieve a more representative caregiver sample and would be feasible considering the millions of cancer caregivers in the United States.

Caregivers' unmet needs, tasks, and burdens

Caregivers' tasks are multifaceted and change along the trajectory of illness in concordance with patients' medical and emotional needs. Measures have been developed for assessing quality-of-life outcomes and support needs. In considering the measures used in the broader literature, Wen and Gustafson[19] note that existing measures are varied in the domains assessed and whether or not they are conceptually grounded. Of course, supplying the right resources for caregivers depends on an accurate assessment of needs. Although there is general agreement between researchers on the broad categories of needs (eg information), there is less agreement on the elements within categories. Caregivers participating in the NQOL-CG, for example, estimated the frequency of providing 4 types of support: emotional, instrumental (eg information, obtaining medical services), tangible (eg household chores), and medical (eg administering medication).[17] Patients had been diagnosed for a mean of 25 months; at that time, approximately half of the caregivers reported giving all types of support, and the most common was emotional support.

The daily burdens leave caregivers with their own needs for support and assistance that, when left unmet, lead to a poorer quality of life and higher levels of distress.[20] Even 2 years after the patient's diagnosis, at least 33% of caregivers may need assistance in coping with their own concerns: the patient's emotional distress as well as their own, communication with the patient about concerns, changes in lifestyle, and how to get their information needs about cancer met.[21] Five years after diagnosis, a significant proportion of caregivers (21%) still needed assistance in helping with the patients' continuing distress. At the same time, 12% of caregivers needed help with their own emotional distress, their relationship with the patient, and determining whether their medical and insurance coverage was sufficient.[21]

Research by Kim et al[21] provides a useful categorization of caregivers' many needs and concerns. Those authors identified 5 domains: psychosocial, financial, medical, and activities of daily living.[21] They considered these key areas when surveying caregivers 2 months, 2 years, and 5 years after the patients' diagnoses (N =162, N =896, and N =608, respectively). The prevalence of unmet psychosocial needs was 68% at 2 months and 36% at 5 years. Unmet medical, financial, or daily activity needs at 2 months remained elevated for the next 5 years. Also, unmet needs were correlated with age, sex, education, and ethnicity. That is, younger caregivers reported greater unmet needs than older caregivers, women reported greater unmet psychosocial needs than men, and Caucasian caregivers reported the fewest unmet needs at 5 years compared with non-Caucasian caregivers. Caregivers with higher education reported greater unmet needs in psychosocial and daily activity aspects at the early phase of the survivorship, but not at later phases.[21]

Caregiver outcomes

Hundreds of studies describe the untoward effects of cancer caregiving,[12] with the consensus message that caregiving adversely affects quality of life. However, there is less agreement about the nature and extent of negative outcomes. In a comprehensive review, Kim and Given[22] note that the majority of studies to date have focused on psychological distress, usually that occurring within 2 years after diagnosis; considering the data described above, this is certainly the most challenging period. For caregivers, similar to cancer patients, the negative impacts are experienced to a greater or lesser extent, depending on the sociodemographic characteristics of the caregivers. Psychological distress among caregivers was higher among women, younger individuals, employed caregivers, and those with lower socioeconomic status.[22] Other major life areas, such as social relationships, occupational circumstances, etc, have received little study. Stenberg et al note that anxiety, sexual problems, and a broad spectrum of physical problems (eg sleep disturbance, fatigue) are common areas of disruption among caregivers.[12]

After the first 2 years, caregivers generally adapt well. The ACS NQOL-CG[16] was used to assess mental health, physical health, psychological distress, and spirituality of caregivers 2 years postdiagnosis. The results indicated that both the mental health and the physical health of caregivers were comparable to those of the US population. Only spirituality needs were heightened among the caregivers. Regarding individual differences, women and younger caregivers had higher levels of psychological distress and poorer mental health, whereas older caregivers reported poorer physical health. These results are in concordance with findings indicating a 63% higher mortality rate among older caregivers compared with noncaregivers.[23]

In the 5-year follow-up of the ACS NQOL-CG,[9] the mental health of former caregivers (because the patient either was disease-free or had died) was comparable to the mean mental health of the general US population. However, caregivers who continued to provide care and those who were bereaved had the highest distress. The physical health of both current and former caregivers was comparable to US norms. Caregivers' age was positively correlated with lower psychological distress and better mental functioning. Nonspousal caregiving was associated with better mental functioning. For the former caregivers of patients who had remained disease free, the women caregivers, higher levels of caregiver esteem, and caring for patients with less severe disease were associated with better mental functioning. Finally, the data suggest that adult daughter caregivers, in contrast to the patient's spouse, report the highest level of caregiver stress; and it is noteworthy that caregiver sons report the lowest level of distress.[18] However, this finding regarding sons may be an artifact of existing sex differences in the reporting of distress.

There is broad agreement that cancer caregiving is stressful. Considering caregivers as a group, younger women who are caregivers may be at greater risk. In the population, there will be more women caregivers than men because of the differential survival rates for the sexes; thus, it is not surprising that study samples include predominantly women. Consequently, we know much less about the experience and needs of male caregivers. Regardless of sex, older caregivers may be doubly burdened by their distress and the risk for new or worsening physical symptoms and illnesses.

Experts have concluded[22] that data are needed regarding the long-term effects of caregiving, such as poor caregiver health, caregiving for patients with recurrent disease, and caregivers' bereavement. For the next generation of data, recruiting caregivers through community sampling would be a step forward and may be more feasible than might be expected when considering the millions of cancer caregivers in the population. In addition to the individual differences that have been identified in the literature, there surely are others, such as ethnicity, relational ties (spousal vs other), and combined vulnerabilities. Within a conceptual framework, an understanding of these kinds of factors can lead to a tailoring of interventions for caregivers in the greatest need.

Intervention studies and trials

In an important meta-analysis of interventions with family caregivers, Northouse et al[24] summarized results from 29 randomized clinical trials of interventions that included caregivers. Of the interventions analyzed, the majority (63%) were interventions for patient-caregiver dyads. The interventions were psychosocial, behavioral, or cognitive and included psychoeducation, skills training, or therapeutic counseling. The most frequently studied outcomes were appraisal of caregiver burden and benefit, coping strategies, self-efficacy, quality of life (distress, anxiety, depression, and physical health), social functioning, and others. In general, interventions had small treatment effects (eg, 0.11-0.26 for physical functioning, 0.16-0.29 for distress and anxiety, 0.04-0.20 for marital/family relationships, 0.20-0.29 for self-efficacy) and had no effect on relief from depressive symptoms. The authors emphasized that the focus of many of these programs was patient care and that few protocols were designed to help caregivers, per se. These data suggest that, although some efforts are best addressed within the patient-caregiver unit, more robust gains likely would be achieved for interventions tailored to caregivers' needs.

Couple or family interventions can be important. To date, however, there have been few interventions tailored for caregivers, although there is agreement that such interventions should be introduced at early stages, such as when the patient begins or continues in treatment. Specific, empirically based intervention protocols are needed to address the tasks, needs, and coping efforts of caregivers as well as any adverse effects that may occur.

Resources: Nonprofit organizations and government programs

Although a full discussion of resource and policy issues is beyond the scope of the current article, 2 salient sources of support are considered. Many nonprofit organizations (NPOs) founded with the mission to aid cancer patients have recently broadened their scope or expanded previous efforts to address caregiver needs. In the United States, the ACS and the Cancer Support Community,[25,26] for

example, offer emotional support and support groups through online or local (state or community) affiliates. Another example, the Family Caregiver Alliance,[27] offers discussion groups, legal advice, and financial advice and connects caregivers to local resources through a Family Care Navigator program. These and other NPOs are working to build more substantive programming and resources for family members in general and caregivers in particular.

Compared with emotional support or tips and advice, it is more difficult to locate financial and instrumental support resources. Expenses are incurred for months, and they are considerable. On the basis of ACS NQOL-CG data, caregivers provided help for an average of 17 months after diagnosis, providing care for an average of 8.8 hours per day. Yabroff and Kim[17] estimated that the average cost of caregiving during 2 years after diagnosis was $47,710, with the highest cost incurred from caring for a patient with lung cancer ($72,702) and the lowest cost incurred from caring for a patient with breast cancer ($38,334). Some NPOs may be able to provide modest funds or connect patients with other organizations that have similar resources. There are peripheral, "virtual" sources to identify financial support. For example, 1 search engine is that available through the Cancer Financial Assistance Coalition, which includes 14 different member organizations for the education of cancer patients and caregivers about existing financial resources.[28] Although these resources are potentially useful, older caregivers, for example, may not have adequate Internet navigation skills to take advantage of them.

Of course, many caregivers seek governmental (federal) support, like that available through Medicare (for which all are eligible) and Medicaid, the specific US program for individuals with little to no financial means. Medicare operates "Ask Medicare,"[29] which is a source of information for caregivers, including that for financial issues. Some Medicaid waiver programs provide funds to pay family members for providing care that otherwise may have been provided by paid professionals or more expensive facilities, such as assisted living facilities.[30] Still, programs like these are not available to all and may be difficult to obtain simply because of the time, expertise, and personal resources needed to seek the assistance (eg computer access, availability of social workers and related professionals), which are required to successfully navigate complex health care systems in the United States.

In an historical review of public policies on family and informal caregivers for older individuals, Scharlach[30] noted that, 2 decades ago (1993), the United States became 1 of the few countries to grant workers the right to unpaid leave to care for a parent, spouse, or child with a serious health condition through the federal Family and Medical Leave Act. Since then, Scharlach has noted that an integrated, comprehensive long-term care system has not been developed that considers informal caregivers as both care partners and service recipients in their own right.[30] Indeed, there are no "umbrella" organizations or coordination efforts enabling caregivers to learn about and access all available resources. Navigating the current maze is made more difficult for caregivers who have limited facility with or access to the Internet. However, there is hope that this circumstance will improve, because caregiving is embedded in the Patient Protection and Affordable Care Act (P.L.111-148), which promotes patient-centered and family-centered care.

Cancer Caregiving in Europe

Recent data from the EUROFAMCARE (Services for Supporting Family Carers of Elderly People in Europe: Characteristics, Coverage, and Usage)[31] and SHARE (Survey of Health, Ageing, and Retirement in Europe)[32] studies estimate that approximately 19 million individuals are providing care to an older individual in Europe.[33] Such an estimate includes caregivers of those who have different disabling conditions, such as adult disabled children, frail elderly individuals, or individuals with mental health problems. One study examined the problems of caregivers of nonelderly individuals, including data from England, Belgium, the Netherlands, Austria, and Italy. The data[34] suggest that the majority of caregivers are women aged >45 years who cohabit with the care recipient and are physically and emotionally strained from the caregiving. To date, specific data on the prevalence of cancer caregivers in Europe are lacking, including information about the tasks caregivers are required to fulfill according to the different needs of cancer patients at various stages of the disease.

Caregivers' unmet (information) needs

The European literature on unmet needs focuses on the necessity of more information for families coping with cancer. A review of 34 studies (including 20 European studies) examining the degree to which information needs of family members are fulfilled by health care professionals highlights the need for better access to information from such professionals and for health care professionals who can communicate with them in a more caring and compassionate manner.[35] To date, only investigations among recently diagnosed patients that had small samples

and/or that were limited only to patients with breast or prostate cancer have been carried out. An exception is the 2003 report by Isaksen et al, who surveyed a mixed group of cancer survivors (<10 years after diagnosis) and their family members (N = 473).[36] Although the majority of patients (67%) in their study reported satisfaction with the support and information received, close family members did not. Less than 30% of the family members were satisfied with either the information or the support and encouragement received from health care professionals.

Data from surveyed Icelandic family members (N = 223) of cancer patients indicating an average of 6.2 unmet needs of 20 needs surveyed, and 12 important needs were unmet in 40% to 56% of the sample.[37] Follow-up analyses of individual differences indicated that unmet needs were significantly greater among caregivers who were women, younger, a relative other than a spouse, and/or helping patients with metastatic cancer. In contrast, family members of disease-free cancer survivors at ≥5 years after diagnosis reported very few unmet needs (2.7 unmet of 34 possible needs).[38] Also, the needs noted were those most relevant for long-term survivors, ie, information about familial risk and ways to manage the fear of recurrence.

Caregiver outcomes

Health.

In general, studies of the physical problems of caregivers have highlighted fatigue, sleep disturbances, and loss of weight and appetite,[12] although few of those studies were from Europe. There is some indication that these physical problems are observed in caregivers throughout the disease process.[39] Caregivers of the newly diagnosed have reported the occurrence of symptoms like as sleep disruption, headaches, and fatigue.[40] Physical problems like these may result in more health care use. For instance, a Swedish study that included 11,000 partners reported increased health care costs and inpatient health care use in the 1 to 2 years after the patient was diagnosed with cancer compared with the 2 years before diagnosis.[41]

In contrast, when patients remain disease free, close family members or partners have health (eg mobility, health care use, pain or discomfort) similar to that of the general European population.[38] However, the experience of caregiving may vary considerably, depending on both the intensity and the nature of the caregiving tasks as well as the caregiver's perception of the burden. To our knowledge, there are no studies of objective and subjective burden in relation to caregivers' physical health. Measuring the burden of care may provide a better understanding of the aspects of caregiving that pose the greatest strain on caregivers' physical health.

Psychological distress.

Overall, the picture arises that most family members adapt well and may not evidence any elevated rate of emotional distress.[42] Studies using self-report measures of psychological morbidity (usually symptoms of anxiety or depression) suggest that the prevalence of clinically significant distress among caregivers is 20 to 30%. Not surprisingly, studies that use diagnostic interviews provide lower rates of approximately 10%.[43] Unfortunately, there are few studies comparing prevalence rates for caregivers versus the rate in a comparison sample.[42] An exception is a report by Hagedoorn et al[44] in which the authors also evaluated a control group of healthy couples. One recent study from the United Kingdom, however, sampled 257 family members of long-term cancer survivors and reported percentages for anxiety and depression (9% and 3%, respectively) similar to those observed in the general European population.[38] An exception is in the case of caregivers for patients receiving palliative or end-of-life care, in which caregiver distress is considerably higher and is also higher compared with distress in the general European population.[45,46] Across all studies, there is the common difference with regard to sex, in which spouses who are women report more distress than spouses who are men.[42-44]

Social activities and relationships.

Despite the importance of social ties to mortality,[47-49] there has been little study of the negative impact of caregiving on social relationships, with the exception of studies of marital distress. Two Italian studies are available. In 2003, Rossi Ferrario et al observed that 60% of caregivers were unable to maintain their friendships or engage in recreational activities or hobbies.[50] In 2007, Giorgi Rossi et al studied caregivers of terminal patients; in that study, 68% of caregivers reported that it was either very difficult or quite difficult to manage any social or leisure activities, and some even needed to move into the patients' home. Leisure activities were more disrupted more than employment, as may be expected.[51] Future research is needed to learn more about the influence on caregivers' social activities and relationships apart from the family.

Most of the research on relationship outcomes focuses on marital stress and strain. For example, it has been observed that cancer survivors and their partners are not at greater risk of divorce than members of the general population (except for women who are diagnosed with cervical cancer).[52] Moreover, partners have reported

positive changes in relationship satisfaction compared with healthy controls.[53] However, the effect of cancer and its treatment on the caregiver-patient relationship may be different for spouses and nonspousal caregivers, such as children or other family members. For example, in a mixed sample of significant other caregivers of patients with lung cancer, only 15% reported an improvement in relationship quality during the disease trajectory, whereas a considerable proportion (38%) reported a (temporary) decline in relationship quality.[54] Those who did report improvement were more likely to be spouses rather than significant others. The findings of the latter study also may have been influenced by the palliative illness phase. That is, the need to provide palliative care may pose extra strain on relationships. Future research might consider the phase of cancer or the nature of caregiving tasks as moderators of relationship distress in couples as well as other dyads (eg parent-child).

The sexual life of couples also has been studied, including many studies of patients with genitourinary cancers[55] (eg prostate, bladder, kidney, testicular, or penile cancer). For example, sexual satisfaction, but not marital satisfaction, reportedly is lower for couples in which 1 partner is a survivor of testicular cancer compared with couples that are cancer free.[56] In the future, additional studies on sexual satisfaction and functioning among couples coping with cancer other than genitourinary cancers will be needed.

During the last decade, attention has shifted to studying relationship consequences, emotional outcomes, and benefit finding in dyads.[57-59] Instead of examining patients and partners or caregivers separately, data from patient-partner pairs are able to account for their interdependent relationships. The dyadic approach views couples reacting to the distress caused by cancer as an emotional system rather than as individuals. Thus, partners (or caregivers) have to deal with their own and the patients' emotions and responses to the cancer, and vice versa. It is believed that the dynamics and the (prior) functioning of the pair play an important role in maintaining or even improving the relationship during the disease trajectory.[42] Hagedoorn et al,[59] for example, reported that both healthy partners and patients were able to maintain their relationship satisfaction even if their spouses were currently not responsive to their needs, but this was the case only if they perceived that past spousal supportiveness was high. In the future, dyadic studies that include the testing of mediator and moderator factors will provide further insight into relational processes, eg clarifying which dyads (including patient-nonspouse dyads) are able to maintain relationship satisfaction and emotional well being and under which conditions.

Benefit finding

To our knowledge, only 2 European studies have been conducted on benefit finding, and both came from Switzerland. In a small qualitative study, women who were partners of patients with head and neck cancer reported positive changes with respect to attitudes toward life, personal strength, and relationships with others; they also reported more positive changes within the partnership compared with the affected spouses.[60] Another study with a large sample (224 couples) indicated that patient and partner growth covaried, especially in couples that included a patient who was a man and a woman partner. This suggests that patients and partners may experience parallel growth.[57] Obviously, more research is needed, including studies on nonspousal caregivers. Future studies should investigate which mechanisms are involved in the perception of growth in patient-caregiver dyads when the caregiver is the partner and also when the caregiver is not the intimate partner of the patient. Cancer-related factors (eg prognosis) may moderate the association between patient and caregiver perceptions of growth, but interpersonal processes within patient-caregiver dyads also may stimulate benefit finding in both members of the dyad.

Financial issues

Although health care systems in Europe are socialized, financial costs for individuals and families still may be substantial. Some medications, nursing assistance, and/or physician home visits are costs usually not included in state-funded health care. For example, 2 large studies from the United Kingdom reported that between 16% and 32% of participants stated a need for more financial help.[61,62] In an Italian study, of the 1249 bereaved caregivers studied, 26% used all or most of their savings in providing care for their loved one.[51]

Employment-related problems also are common, particularly for caregivers of terminally ill patients. For example, 49% of Italian caregivers of working age (<65 years) had difficulties in managing their regular employment in the last months of terminal care.[51] Research on the financial/employment problems among caregivers of patients in other phases of the illness and at the end of life would be important. In such research, objective outcome measurements, such as the amount of expenses or reduced incomes, would be more direct measures of adverse financial impact.

Intervention studies and trials

To date, the research literature on interventions for caregivers is limited. In a recent review,[63] 8 of 33 studies were from Europe, specifically the United Kingdom and Sweden. The majority (7 of 8 studies) focused on caregivers of patients in advanced or palliative phases, and 2 of 8 studies focused on bereaved caregivers. None of the studies was intended for patient/carer dyads.

Similarly, according to a recent review, few European-based studies of psychosocial interventions are specifically designed for couples.[64] Only 3 of 14 studies reviewed originated from European countries—the Netherlands,[65] Greece,[66] and the United Kingdon[67]—and each had a unique focus. From the Netherlands, the efficacy of a brief counseling intervention to restore relational equity among partners was examined. The intervention was identified as effective in improving relationship quality, but psychological distress was reduced only in patients and not in partners. From Greece, the efficacy of a combination of couple and sex therapy was tested postmastectomy: patients' depression levels improved after the intervention, such as their satisfaction with body image and their relational and sexual life. In the United Kingdom, a case report qualitatively described an attachment theory-based psychotherapeutic intervention that was used for a partner and a patient with breast cancer aged 83 years who was terminally ill; the intervention helped the couple cope with bereavement.

A recent German longitudinal study on 72 couples indicated that a dyadic-skills intervention, mainly based on training in communication skills and dyadic coping, was more effective in reducing avoidance in communication within the couple and enhancing relationship skills during the first 16 months after diagnosis with respect to a control psychoeducational intervention.[68]

Taken together, the literature on caregiver interventions is limited. Consistent with a developing literature, there is heterogeneity of topics and modest methods (eg small samples, short-term qualitative outcomes, unknown long-term benefits of the interventions, etc). Expansion of the literature to include caregivers across the cancer continuum also is needed.

Web-based resources

Across Europe, each country may have its own resources for helping caregivers through the web. The web-based resources of the 2 countries of the European authors of this report, however, have been analyzed by way of example. In both Italy and the Netherlands, there are some associations dedicated to cancer patients who offer information, advice, and support for various aspects of illness, treatments, and patients' life during the trajectory of disease. These groups also may provide information on health care use and facilities for both patients and caregivers. Some have created discussion forums for caregivers or information booklets with some advice on coping with an ill relative. In Italy, no web-based resource for caregivers of cancer patients was identified except for bereaved relatives.

Summary and General Conclusions

To paraphrase an observation of Leo Tolstoy, each family with cancer has cancer in its own way. Still, there are many similarities between the United States and Europe in caregivers and caregiving. For example, most cancer patients are supported by informal caregivers along the trajectory of the illness. Of these, the majority of caregivers are women, usually spouses. Also, caregiving exacts emotional, social, and physical health tolls.

Yet, the overview revealed broad differences and gaps of knowledge that may serve as directions for future research in the respective regions. One prominent difference is the lack of "basic" data concerning caregivers in Europe compared with data available in the United States, indicating a need for European data concerning demographics, tasks, and resources for caregivers. We suspect this is partially because of the obvious differences in the feasibility of data collection; much of the US data come from the ACS NQOL-CG, which samples cancer survivors identified through a national cancer registry. The task of gathering basic data concerning caregivers of cancer patients is beyond the capabilities of an individual research team. Thus, a combined effort of national and international cancer registries may be useful and may facilitate survey efforts in Europe. Data coming from such surveys provide 1 basis for decisions made by policy makers and eventually may facilitate collaborative research between the 2 continents.

There is also a lack of data concerning specific populations (eg minorities) in the United States and in northern and eastern European countries. Strategic decisions by policy makers may help to channel appropriate funding and resources for such studies. Data are lacking both in Europe and in the United States concerning long-term adaptation of disease-free cancer survivors and their caregivers. Although there is evidence that long-term cancer survivors and their caregivers adapt well, it remains important to learn whether caregivers cope with residual physical or emotional consequences. There is also a need for more studies in both the United States and Europe

concerning caregiving for patients with progressive disease or at the end of life, and more studies are needed on cultural differences regarding variations in family structure and caregivers' coping, burdens, and outcomes. Such studies also may have implications for understanding resilience and protective factors and how interventions can build on positive aspects of adjustment and coping. In conclusion, international and cross-cultural collaborations and comparisons will provide a better understanding of the basic principles of the cancer experience for survivors and caregivers.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

Dr. Andersen's efforts were facilitated by support from the National Cancer Institute (K05 CA098133).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127:2893-2917.
2. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*. 2013;132:1133-1145.
3. Martin MY, Sanders S, Griffin JM, et al. Racial variation in the cancer caregiving experience: a multisite study of colorectal and lung cancer caregivers. *Cancer Nurs*. 2012;35:249-256.
4. Siefert ML, Williams AL, Dowd MF, Chappel-Aiken L, McCorkle R. The caregiving experience in a racially diverse sample of cancer family caregivers. *Cancer Nurs*. 2008;31:399-407.
5. Menaca A, Evans N, Andrew EV, et al. End-of-life care across Southern Europe: a critical review of cultural similarities and differences between Italy, *Spain and Portugal Crit Rev Oncol Hematol*. 2012;82:387-401.
6. Surbone A. The information to the cancer patient: psychosocial and spiritual implications. *Support Care Cancer*. 1993;1:89-91.
7. Thomsen OO, Wulff HR, Martin A, Singer PA. What do gastroenterologists in Europe tell cancer patients? *Lancet*. 1993;341:473-476.
8. Gysels M, Evans N, Menaca A, et al. Project PRISMA. Culture and end of life care: a scoping exercise in 7 European countries [serial online]. *PLoS One*. 2012;7:e34188.
9. Kim Y, Spillers RL, Hall DL. Quality of life of family caregivers 5 years after a relative's cancer diagnosis: follow-up of the national quality of life survey for caregivers. *Psychooncology*. 2012;21:273-281.
10. Northfield S, Nebauer M. The caregiving journey for family members of relatives with cancer: how do they cope? *Clin J Oncol Nurs*. 2010;14:567-577.
11. Bee PE, Barnes P, Luker KA. A systematic review of informal caregivers' needs in providing home-based end-of-life care to people with cancer. *J Clin Nurs*. 2009;18:1379-1393.
12. Stenberg U, Ruland CM, Miaskowski C. Review of the literature on the effects of caring for a patient with cancer. *Psychooncology*. 2010; 19:1013-1025.
13. National Alliance for Caregiving (NAC) in Collaboration With AARP. Caregiving in the US. Available at: http://www.caregiving.org/pdf/research/Caregiving_in_the_US_2009_full_report.pdf. Accessed March 29, 2012.
14. American Cancer Society. Cancer Facts & Figures. Available at: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Accessed March 29, 2012.
15. Kim Y, Kashy DA, Kaw CK, Smith T, Spillers RL. Sampling in population-based cancer caregivers research. *Qual Life Res*. 2009;18: 981-989.
16. Kim Y, Spillers RL. Quality of life of family caregivers at 2 years after a relative's cancer diagnosis. *Psychooncology*. 2010;9:431-440.
17. Yabroff KR, Kim Y. Time costs associated with informal caregiving for cancer survivors. *Cancer*. 2009;115(18 suppl):4362-4373.
18. Kim Y, Baker F, Spillers RL. Cancer caregivers' quality of life: effects of gender, relationship, and appraisal. *J Pain Symptom Manage*. 2007;34:294-304.
19. Wen KY, Gustafson DH. Needs assessment for cancer patients and their families. *Health Qual Life Outcomes*. 2004;26:2-11.
20. Printz C. Cancer caregivers still have many unmet need. *Cancer*. 2011;117:1331-1331.
21. Kim Y, Kashy DA, Spillers RL, Evans TV. Needs assessment of family caregivers of cancer survivors: 3 cohorts comparison. *Psychooncology*. 2010;19:573-582.
22. Kim Y, Given BA. Quality of life of family caregivers of cancer survivors: across the trajectory of the illness. *Cancer*. 2008;112 (11 suppl):2556-2568.
23. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA*. 1999;282:2215-2219.
24. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. *CA Cancer J Clin*. 2010;60:317-339.
25. American Cancer Society. Caregivers. Available at: http://www.cancer.org/Treatment/Caregivers/index?from=CSN/ Accessed April 5, 2012.
26. Cancer Support Community. Caregiving. Available at: http://www.cancersupportcommunity.org/MainMenu/Family-Friends/Caregiving. Accessed April 5, 2012.
27. Family Caregiver Alliance. Fact Sheet. Available at: http://www.caregiver.org/caregiver/jsp/home.jsp. Accessed April 5, 2012.
28. Cancer Financial Assistance Coalition (CFAC). CFAC Resource Directory. Available at: http://www.cancerfac.org/. Accessed April 5, 2012.
29. Centers for Medicare and Medicaid Services. Ask Medicare Home. Available at http://www.medicare.gov/caregivers/index.html. Accessed April 5, 2012.
30. Scharlach A. Historical overview. *Am J Nurs*. 2008;108(9 suppl):16-22.
31. EUROFAMCARE. Services for Supporting Family Carers of Elderly People in Europe: Characteristics, Coverage, and Usage. Available at: http://www.uke.de/extern/eurofamcare/. Accessed April 20, 2012.
32. Survey of Health, Ageing and Retirement in Europe (SHARE). SHARE program website. Available at: http://www.share-project.org/. Accessed April 20, 2012.
33. Grammenos S. Implications of Demographic Ageing in the Enlarged EU in the Domains of Quality of Life, Health Promotion and Health Care. Available at: http://ec.europa.eu/employment_social/social_situation/docs/lot5_health_summary_en.pdf. Accessed May 20, 2012.
34. Glendinning C, Arksey H, Tjadens F, Moree M, Moran N, Nies H. Care provision Within Families and its Socioeconomic Impact on Care Providers Across the European Union. Research Works, 2009-2005. York, United Kingdom: Social Policy Research Unit, University of York; 2009.
35. McCarthy B. Family members of patients with cancer: what they know, how they know and what they know. *Eur J Oncol Nurs*. 2011;15:428-441.

36. Isaksen A, Thuen F, Hanestad B. Patients with cancer and their close relatives: experiences with treatment care and support. *Cancer Nurs*. 2003;26:68-74.
37. Fridriksdottir N, Saevarsdottir P, Halfdanardottir Svandis I, et al. Family members of cancer patients: needs, quality of life and symptoms of anxiety and depression. *Acta Oncol*. 2011;50:252-258.
38. Turner D, Adams E, Boulton M, et al. Partners and close family members of long-term cancer survivors: health status, psychosocial well being and unmet supportive care needs. *Psychooncology*. 2013; 22:12-19.
39. Grov EK, Valeberg BT. Does the cancer patient's disease stage matter? A comparative study of caregivers' mental health and health related quality of life. *Palliat Support Care*. 2012;22:1-8.
40. Pellegrino R, Formica V, Portarena I, et al. Caregiver distress in the early phases of cancer. *Anticancer Res*. 2010;30:4657-4663.
41. Sjovall K, Attner B, Lithman T, et al. Influence on health of the partner affected by tumour disease in the wife or husband based on a population-based register study of cancer in Sweden. *J Clin Oncol*. 2009;27:4781-4786.
42. Hagedoorn M, Sanderman R, Bolks H, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. *Psychol Bull*. 2008;134:1-30.
43. Pitceathly C, Maguire P. The psychological impact of cancer on patients' partners and other key relatives: a review. *Eur J Cancer*. 2003;39:1517-1524.
44. Hagedoorn M, Buunk BP, Kuijer R, Wobbes T, Sanderman R. Couples dealing with cancer: role and gender differences regarding psychological distress and quality of life. *Psychooncology*. 2000;9:232-242.
45. Ostlund U, Wennman-Larsen A, Persson G, Gustavsson P, Wengstrom Y. Mental health in significant others of patients dying from lung cancer. *Psychooncology*. 2010;19:29-37.
46. Grov EK, Dahl AA, Moum T, et al. Anxiety, depression, and quality of life in caregivers of patients with cancer in late palliative phase. *Ann Oncol*. 2005;16:1185-1191.
47. Bloom JR. Improving the health and well-being of cancer survivors: past as prologue. *Psychooncology*. 2008;17:525-532.
48. Reynolds P, Boyd PT, Blacklow RS, et al. The relationship between social ties and survival among black and white breast cancer patients. National Cancer Institute Black/White Cancer Survival Study Group. *Cancer Epidemiol Biomarkers Prev*. 1994;3:253-259.
49. Kroenke CH, Kubzansky LD, Schernhammer ES, Holmes MD, Kawachi I. Social networks, social support, and survival after breast cancer diagnosis. *J Clin Oncol*. 2006;24:1105-1111.
50. Rossi Ferrario S, Zotti AM, Massara G, et al. A comparative assessment of psychological and psychosocial characteristics of cancer patients and their caregivers. *Psychooncology*. 2003;12:1-7.
51. Giorgi Rossi P, Beccaro M, Miccinesi G. Dying of cancer in Italy: impact on family and caregiver. The Italian Survey of Dying of Cancer. *J Epidemiol Commun Health*. 2007;61:547-554.
52. Carlsen K, Dalton SO, Frederiksen K, et al. Are cancer survivors at an increased risk for divorce? A Danish cohort study. *Eur J Cancer*. 2007;43:2093-2099.
53. Kuijer RG, Buunk BP, Ybema JF. Are equity concerns important in the intimate relationship when 1 partner of a couple has cancer? *Soc Psych Quart*. 2001;64:267-282.
54. Wennman-Larsen A, Persson C, Ostlund U, et al. Development in quality of relationship between the significant other and the lung cancer patient as perceived by the significant other. *Eur J Oncol Nurs*. 2008;12:430-435.
55. Aerts L, Enzlin P, Vergote I, et al. Sexual, psychological, and relational functioning in women after surgical treatment for vulvar malignancy: a literature review. *J Sex Med*. 2012;9:361-371.
56. Tuinman MA, Fleer J, Sleijfer DT, et al. Marital and sexual satisfaction in testicular cancer survivors and their spouses. *Support Care Cancer*. 2005;13:540-548.
57. Zwahlen D, Hagenbuch N, Carley MI, et al. Posttraumatic growth in cancer patients and partners—effects of role, gender and the dyad on couples' posttraumatic growth experience. *Psychooncology*. 2010; 19:12-20.
58. Hagedoorn M, Puterman E, Sanderman R, et al. Is self-disclosure in couples coping with cancer associated with improvement in depressive symptoms? *Health Psychol*. 2011;30:753-762.
59. Hagedoorn M, Dagan M, Puterman E, et al. Relationship satisfaction in couples confronted with colorectal cancer: the interplay of past and current spousal support. *J Behav Med*. 2011;34:288-297.
60. Ruf M, Buchi S, Moergeli H, et al. Positive personal changes in the aftermath of head and neck cancer diagnosis: a qualitative study in patients and their spouses. *Head Neck*. 2009;31:513-520.
61. Cartwright A. Social class differences in health and care in the year before death. *J Epidemiol Commun Health*. 1992;46:54-57.
62. Addington-Hall J, McCarthy M. Dying from cancer: results of a national population-based investigation. *Palliat Med*. 1995;9:295-305.
63. Harding R, List S, Epiphaniou E, Jones H. How can informal caregivers in cancer and palliative care be supported? An updated systematic literature review of interventions and their effectiveness. *Palliat Med*. 2012;26:7-22.
64. Baik OM, Adams KB. Improving well-being of couples facing cancer: a review of couple-based psychosocial interventions. *J Marital Fam Ther*. 2011;37:250-266.
65. Kuijer RG, Buunk BP, De Jong GM, Ybema JF, Sanderman R. Effects of a brief intervention program for patients with cancer and their partners on feelings of inequity, relationship quality and psychological distress. *Psychooncology*. 2004;13:321-334.
66. Kalaitzi C, Papadopoulos VP, Michas K, Vlasis K, Skandalakis P, Filippou D. Combined brief psychosexual intervention after mastectomy: effects on sexuality, body image, and psychological well-being. *J Surg Oncol*. 2007;96:235-240.
67. McWilliams AE. Couple psychotherapy from an attachment theory perspective: a case study approach to challenging the dual nihilism of being an older person and someone with a terminal illness. *Eur J Cancer Care (Engl)*. 2004;13:464-472.
68. Heinrichs N, Zimmermann T, Huber B, Herschbach P, Russell DW, Baucom DH. Cancer distress reduction with a couple-based skills training: a randomized controlled trial. *Ann Behav Med*. 2012; 43:239-252.

Original Article

Current Perspectives and Emerging Issues on Cancer Rehabilitation

Michael D. Stubblefield, MD[1]; Gill Hubbard, PhD[2]; Andrea Cheville, MD[3]; Uwe Koch, MD, PhD[4]; Kathryn H. Schmitz, PhD, MPH[5]; and Susanne Oksbjerg Dalton, MD, PhD[6]

Cancer rehabilitation is a rapidly emerging and evolving medical field in both Europe and the United States, in large part because of increases in the number of cancer survivors. Although few argue with the need to restore function and quality of life to patients affected by cancer and its treatments, differences exist between European countries with regard to the funding, accessibility, and even the definition of cancer rehabilitation services. In the United States, there is tremendous variability in the provision of rehabilitation services resulting from a variety of factors, including a lack of highly trained cancer rehabilitation physicians and therapists as well as a lack of comprehensive cancer rehabilitation programs, even at the majority of top cancer centers. Although studies evaluating the effectiveness of rehabilitation programs in the cancer setting, particularly exercise, have influenced clinical decision-making in both Europe and the United States for some time, this emerging evidence base also is now starting to influence guideline and policy making. Coordinated research efforts are essential to establish a robust framework to support future investigation and establish shared initiatives. Determining the best way forward for cancer survivors will require investment in large-scale prospective cohort studies that sufficiently describe their rehabilitation needs through the continuum of the survivorship experience. ***Cancer*** **2013;119(11 suppl):2170-8.** © *2013 American Cancer Society.*

KEYWORDS: cancer; rehabilitation; survivor; exercise.

INTRODUCTION

Preventing and addressing the late and long-term effects of cancer and its treatment are relatively new ideas in the cancer care model and are reflected in often disconnected systems of cancer care and rehabilitation services both in the United States and in Europe. Because of an aging population and successful treatment, the number of Americans and Europeans living with cancer will increase in the coming years. It must be anticipated that the prevalence of cancer survivorship will continue to grow disproportionately in relation to the number of new cancer cases and deaths. In the United States, there were 13.8 million cancer survivors in 2010 compared with 1.5 million new cases of cancer and 569,000 cancer deaths (Fig. 1, top).[1,2] It is estimated that the number of cancer survivors in the United States will grow to 18.1 million by 2020.[1] For the European Union population (ie, in the 27 European Union member states), the estimated number of survivors was 17.8 million in 2008 compared with 2.5 million new cases and 1.2 million deaths (Fig. 1, bottom).[3,4] More than half of European cancer patients diagnosed with 1 of the common forms of cancers today will be alive after 5 years.[5] A recent United Kingdom study estimated that up to 10% of their estimated 2 million cancer survivors will be in the "rehabilitation

Corresponding author: Michael D. Stubblefield, MD, Rehabilitation Medicine Service, Sillerman Center for Rehabilitation, Memorial Sloan-Kettering Cancer Center, 515 Madison Avenue, Fifth Floor, New York, NY10022; Fax: (646) 888-1910; stubblem@mskcc.org

[1]Rehabilitation Medicine Service, Sillerman Center for Rehabilitation, Memorial Sloan-Kettering Cancer Center, New York, New York; [2]Cancer Care Research Center, School of Nursing, Midwifery, and Health, University of Stirling, Highland Campus, Centre for Health Science, Inverness, Scotland, United Kingdom; [3]Physical Medicine and Rehabilitation, Division of Cancer Rehabilitation and Lymphedema Services, Mayo Clinic, Rochester, Minnesota; [4]Medical Faculty, Medical University Center Hamburg-Eppendorf, Hamburg, Germany; [5]Epidemiology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania; [6]Survivorship, Danish Cancer Society Research Center, Copenhagen, Denmark.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28059, **Received:** July 27, 2012; **Revised:** November 21, 2012; **Accepted:** December 3, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

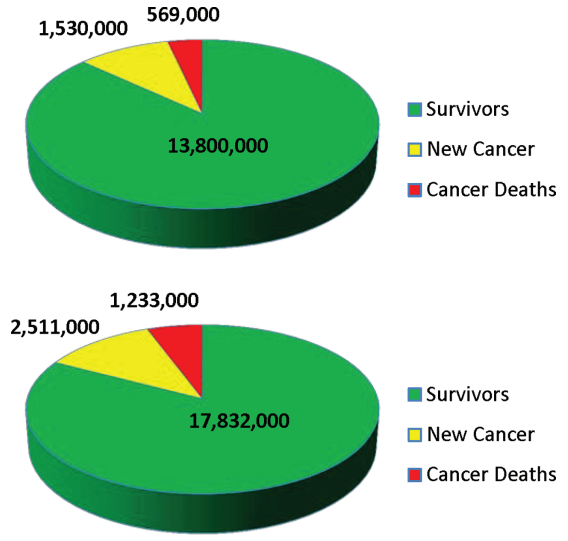

Figure 1. The estimated numbers of cancer survivors in (*Top*) the United States in 2010 and (*Bottom*) the European Union in 2008 are compared with the numbers of new cancer diagnoses and deaths for the same years.[1,3,4,7]

phase," defined as in the second year after diagnosis and without recurrence.[6] The needs of survivors will vary in type, intensity, and duration; thus, the need for planning services that prevent or mitigate the effects of late sequelae effectively and efficiently will be of increasing importance as demand grows over time.

In this article, we highlight some of the differences between American and European approaches to the rehabilitation of cancer survivors. The ultimate goal of this report is to provide a snapshot of the large-scale work already done in European and US cancer rehabilitation. We hope that increasing awareness of the important gains made to date and identifying barriers to continued progress will encourage collaboration between clinicians in different countries and will help foster the continued growth and development of this emerging but critically important field.

State-of-the-Art: Europe

Despite the common objectives of various European countries regarding the goals of rehabilitation, rehabilitation concepts differ considerably between nations.[7] Europe is a continent composed of countries with vastly varied geopolitical and economic systems that have very different health care policies and practices. Thus, it is impossible to provide a whole systemic European perspective. Instead, in this overview, we refer to specific European countries to illustrate key points. Many European countries have included cancer rehabilitation in their national cancer plans, and some have developed or are working on evidence-based recommendations (ie, Finland, Holland, United Kingdom), but differences remain regarding the provision, accessibility, and funding of rehabilitation services.[7] Important principles of most rehabilitation programs are a biopsychosocial understanding of illness and disability, the importance of early rehabilitation measures, the continuity of rehabilitative treatment, and a tailored rehabilitation plan. In some European countries, cancer rehabilitation is mainly provided by the primary health care sector (eg Denmark); although, in most countries, such as Sweden, Holland, and Norway, services are provided by both primary and secondary sectors and are supplemented by private initiatives. In Germany, the historic tradition for rehabilitation as a systematic process (Table 1) is primarily funded by the pension insurance funds.[2]

Both organization and coverage differ between nations, ranging from high coverage in some countries to virtually nonexistent systematic cancer rehabilitation services in others. Researchers, clinicians, and policy officials concerned with cancer rehabilitation from the various European countries came together under the auspices of the European Commission to develop a set of common cancer rehabilitation indicators (the European Cancer Center Health Indicator Project [EUROCHIP]).[4] This was part of a broader European Union agenda to conceptualize care at the European level as opposed to the individual country level.

Challenges arose for this task because of various definitions of cancer rehabilitation (both within and between countries), the availability of national cancer rehabilitation guidelines and action plans, and the availability of data to determine the status of cancer rehabilitation within each country. Despite these challenges, a consensus was reached about a common set of cancer rehabilitation indicators.

The indicators of cancer rehabilitation developed in the EUROCHIP project include: 1) 2-year and 5-year cancer prevalence by age, sex, and cancer type; 2) quality of life of individuals living with cancer using a common instrument for all countries so that direct comparisons can be made (for example, European Organization for Research and Treatment of Cancer [EORTC] questionnaires); 3) the number of cancer survivors returning to work; and 4) the number of consultations with an allied health professional (eg speech therapist, dietician, physiotherapist, clinical psychologist). Whether and how countries will implement these recommendations is unclear,

TABLE 1. Rating the Evidence Base Supporting the American College of Sports Medicine Exercise Guidelines for Cancer Survivors[a]

Variable	Breast (During)	Breast (After)	Prostate	Hematologic (During or After HSCT)	Hematologic (No HSCT)
Safety	A	A	A	A	
Fitness	A	A	A	C	B
Strength	A	A	A	C	
Body composition	B	B	B		
QOL	B	B	B	C	
Fatigue	B	B	A	C	B
Anxiety	B	B			
Flexibility		A			
Physical function		A	B		
Lymphedema		A (is safe)			
Body image		B			

Abbreviations: HSCT, hematologic stem cell transplantation; QOL, quality of life.
[a] This model of the cancer rehabilitation process in Germany was adapted from Schmitz et al.[2] Evaluation of the evidence was based on National Heart, Lung, and Blood Institute categories,[3] in which A indicates overwhelming data from randomized controlled trials; B indicates that few randomized controlled trials exist or that they are small and results are inconsistent; C indicates that results stem from uncontrolled, nonrandomized, and/or observational studies; and D indicates that evidence insufficient for categories A, B, and C. Blanks (as well as the nonlisting of a specific type of cancer) indicate that there was insufficient evidence to rate the data.

although the goal of developing a European perspective on cancer rehabilitation remains.

Evaluating the Effectiveness of Rehabilitation Interventions: Is Country of Origin Important?

Since 2000, several European health departments have commissioned systematic reviews regarding the effectiveness of interventions to aid in the recovery of cancer patients. This demonstrates the importance placed on addressing the rehabilitation needs of individuals affected by cancer by the European health community.[8,9] These reviews included interventions that are irrespective of country of origin, suggesting that country was not considered relevant by the reviewers when assessing the effectiveness of interventions for cancer patients. Thus, an implicit assumption is being made when examining evidence regarding the effectiveness of interventions—that cancer patients have common disease characteristics that render an intervention being tested in Cleveland, Ohio just as relevant for cancer patients in Copenhagen, Denmark. Moreover, reviewers in different countries, because they were drawing on the international evidence base, reached similar conclusions. Among these were the lack of evidence to determine the optimal time in the patient pathway to provide rehabilitation and the optimal duration and intensity of certain rehabilitation activities.

An overview of cancer rehabilitation in the Nordic countries, the Netherlands, and Germany cites several research studies evaluating the impact of ongoing rehabilitation programs.[7] The evidence across these countries on the impact of rehabilitation on quality of life, physical functioning, anxiety, and depression and change in health behaviors indicates that the results are mixed. There is a need to identify those components of rehabilitation that will benefit cancer patients most. There is also a lack of data on the long-term impact of rehabilitation efforts.

Although several European countries draw on international evidence for decision-making regarding the effectiveness of rehabilitation interventions, they recognize the importance of evaluating their rehabilitation programs at the national and local levels. This presents an opportunity for a European and international database of rehabilitation interventions that can be disseminated in Europe and elsewhere. Although it is important to draw on international evidence, the challenge is to translate and transfer interventions that are successful for individual countries, at the local level, and even in smaller subdivisions when necessary.

Future Areas of Research in Europe

Like in all interventions within the health care system, rehabilitation efforts should be based on evidence. Acknowledging that this area of research is a relatively new field, all levels of analytical evidence are needed, including observational, experimental, and qualitative research, to disentangle the complicated challenges of how, when, and which rehabilitation to offer.[10-12] One research priority should be large-scale, prospective European cohorts that sufficiently describe the needs of survivors through the trajectory of disease, from the point of diagnosis to long-term survivorship, to inform the development of timely rehabilitation or preventative efforts. Such population-based follow-up studies can provide us with information on disease characteristics, treatments, the presence of comorbidities, social support, and socioeconomic status to identify and characterize vulnerable

groups at higher risk of developing needs that should be addressed. Important knowledge can be obtained from such longitudinal studies about resilience and growth factors and about the complex interactions between the experience of limitations, needs, and the desire for help.

The building of ambitious, long-term, pan-European follow-up cohort studies has been successfully carried out in other fields of cancer research, such as the (European Prospective Investigation into Cancer and Nutrition (EPIC) study, which included more than 500,000 Europeans and provided knowledge on dietary risk factors for cancer, or the European Cancer Registry-Based Study on Survival and Care of Patients (EUROCARE) studies, which aim to follow survival trends among cancer patients in Europe over time and to detect changes across regions.[13,14] Establishing such European survivor cohorts would provide us with knowledge regarding the origins and evolution of cancer-related impairments to function and quality of life among cancer survivor populations. Evidence from such efforts would point toward ways to increase standards of cancer rehabilitation across Europe by elucidating differences and similarities in outcomes for European cancer patients across nations and diseases.

Comprehensive rehabilitation programs are perhaps most important from the patients' perspective, because they can obtain rehabilitation tailored to their specific needs. However, when testing the effects of rehabilitation efforts, priority must be given to a description of each intervention component to create better rehabilitation initiatives. Comprehensive programs must be rigorously described in terms of aims (prevent or alleviate), target group (disease and patient characteristics), timing (during or after treatment), component (physical training, speech therapy, delivering specialist, intensity, duration, context), and outcomes (baseline, standardized measurements and evaluations, generic or disease/treatment-specific measures). In addition, experimental testing of rehabilitation programs should include evaluation of patient perspectives, investigating the association between expectations, motivation, and needs on subsequent outcomes.

These programs should be tested in sufficiently powered studies applying long-term follow-up. In countries like Germany, legislation hinders randomization of interventions in rehabilitation, but quasiexperimental evidence has been obtained from several outcome and process studies in cancer rehabilitation with very high numbers of patients.[2,15] In many European countries, rehabilitation is not fully integrated into the standard medical care of all cancer patients, and it is possible that we reach only segments of the population (ie, the middle class). We need to know more regarding what motivates different groups of patients to address the question of whether the content of rehabilitation interventions should be reconsidered as well as the format and setting (peer vs professional, group vs individual). In a setting of rehabilitation services in which standards may vary not only between nations but also within nations because the fragmentation of services across health sectors influences accessibility and navigation or because health insurance coverage differs from region to region, 1 of the tasks for future research should be information on the optimal organization of efforts.

When the highest methodological standards are applied, we ensure that replicable interventions have been identified that are transferable across settings, both nationally and/or internationally. By doing this, we will add to the evidence base and ensure that all cancer patients participating in our studies will contribute to better rehabilitation in the future.

The American Perspective: State of the Art

Meeting the challenges of the millions of cancer survivors in the United States will require overcoming a variety of barriers. Many more specialized providers will need training, including cancer rehabilitation physicians and physical and occupational therapists with specialized training other than lymphedema management certification. In addition, oncology and primary care providers will need to be educated about the benefits of cancer rehabilitation services, particularly the indications for referral to cancer rehabilitation services.[16]

Cancer rehabilitation programs should be equipped to contend not only with the complications of cancer and its treatment but also with the medical and degenerative comorbidities that are common in the general population, because these complicate the restoration of function and quality of life in cancer survivors. Ideally, a comprehensive program would include a fellowship-trained cancer rehabilitation physician as well as physical and occupational therapists with experience in the functional restoration of cancer patients. Of the approximately 8300 board-certified physiatrists in the United States, only a small number practice in cancer rehabilitation centers, and there are only 2 fellowship training programs in cancer rehabilitation (Memorial Sloan-Kettering Cancer Center, New York, NY and The University of Texas M. D. Anderson Cancer Center, Houston, Tex), making the paradigm of a comprehensive cancer rehabilitation program difficult to

achieve in the short run, because each of these programs has only 2 fellowship positions.[17]

The reasons why there are so few cancer rehabilitation fellowship training programs are unclear but likely are similar to the reasons why there are so few comprehensive cancer rehabilitation programs. Specific reasons include difficulty clearly defining the role for cancer rehabilitation as a specialty devoted to the functional restoration of cancer patients and survivors at all stages of the cancer experience, from primary treatment though palliative care, with emphasis on the growing and specialized needs of the survivor. All too often, cancer rehabilitation is thought of or acts as a lymphedema and/or fatigue treatment service and, as such, garners little respect at the institution in which it operates. Similarly, convincing hospital administrations to develop a comprehensive cancer rehabilitation program in a climate of ever increasing financial pressure, at best, is difficult. Emphasis on the clear benefit the patient care and also the bottom line in a properly administered program, not only through direct revenue but also by decompressing the oncology staff so that they can be more efficient and less burdened, should help overcome this obstacle. Finally, the difficulty of developing and/or recruiting staff with the specialized skill sets to create a program in cancer rehabilitation is a daunting barrier for many centers. This obstacle is best overcome by striving to reach a critical mass of comprehensive cancer rehabilitation programs that can serve as a foundation on which to develop cancer rehabilitation fellowships and thereby create the a steady supply of well trained cancer rehabilitation physicians.

Many American institutions are now interested in developing a cancer rehabilitation program to qualify for the American College of Surgeons Commission on Cancer (COC) Accreditation Program.[18] For many institutions, obtaining COC accreditation is not just about ensuring quality of care but about setting themselves apart from other cancer centers and practices in a competitive and lucrative market. It is noteworthy that the COC does not set minimal standards of accreditation or provide guidance regarding what constitutes a cancer rehabilitation program. The COC program standards only stipulate that the institution should have a policy or procedure in place that provides patients with access to rehabilitation services either on site or by referral.[18] Regardless of the reasons, requiring rehabilitation as a component of a desired certification—even if its quality has yet to be assured—is a positive development for cancer survivors. The next challenge will be to ensure the quality of rehabilitation and determine the components that are required for it to be comprehensive in an atmosphere in which the inclination of some centers may be to set the bar as low as possible.

Intervention Studies/Intervention Programs in the United States: Evidence and Examples

One area of cancer rehabilitation with deep evidence for efficacy is an exercise program after a cancer diagnosis. There have been multiple systematic reviews and a set of guidelines published on this topic from the American College of Sports Medicine.[19-21] Dozens of randomized controlled exercise trials have demonstrated a variety of benefits for survivors of breast, prostate, and hematologic cancers, including reduction of fatigue, physical function, quality of life, and body composition. There is considerably less research regarding the safety and efficacy of exercise for colorectal and gynecologic cancer survivors, although these are among the more common diagnoses of long-term cancer survivors.[22]

Existing Cancer Rehabilitation Programming in the United States

Comprehensive cancer rehabilitation programs are the exception rather than the rule in the United States. The vast majority of National Cancer Institute-designated cancer centers do not have comprehensive cancer rehabilitation programs. Freestanding cancer wellness centers and commercial or not-for-profit rehabilitative exercise programming are common across multiple urban and some suburban settings but are rare in rural settings.

There are clear pathways for rehabilitation interventions, including inpatient admission for most patients with functional decline because of injury, neurologic, degenerative, and many other function-altering disorders. However, if a decline in functional status caused by the effects of cancer or its treatment, then the likelihood of referral for rehabilitation is significantly reduced. There is evidence that patients with metastatic breast cancer in the United States who have difficulty ambulating may not be referred for rehabilitation services.[23] Centers of excellence do exist at a small number of institutions, including The University of Texas M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, the Rehabilitation Institute of Chicago (Chicago, Ill, and the Mayo Clinic (Rochester, Minn). Each of these programs varies in their offerings with respect to inpatient and outpatient services, interventions offered by rehabilitation medicine, and the overall focus of rehabilitation medicine. Exemplary freestanding cancer wellness or rehabilitative exercise programs also are burgeoning across the United States.

Wellness programs vary widely with regard to cost, quality, and efficacy, and none are currently covered by third-party payers.

Future Areas of Research in the United States

The aforementioned lack of empirical support continues to impede the clinical integration of rehabilitation services into comprehensive cancer care in the United States.[24,25] A recognition that coordinated research efforts are essential to establish a robust framework that can support future investigation has spurred US cancer rehabilitation researchers to establish shared initiatives. Some of the most compelling and clinically pertinent are outlined here.

Measurement

Function, activity, and participation measures are needed across the broad performance range characteristic of patients with cancer. Currently, 3 approaches are being closely evaluated: 1) activity monitors, 2) item response theory (IRT)-based assessment, and 3) objective performance measures and batteries. Activity monitors produce large amounts of objective data at relatively low cost. However, a lack of validated algorithms that can convert their copious output into standardized and relevant information for clinicians, researchers, and end users remains problematic.[26] Consequently, modeling techniques to meaningfully classify physical activities both qualitatively and quantitatively are an area of intense research effort.[27]

IRT-based assessment tools, such as the Patient Reported Medical Information System (PROMIS)[28,29] and the Ambulatory Post Acute Care Computer Adaptive Test (APC)[30] and short forms,[31] may offer the potential to precisely discriminate across a broad range of functional abilities with minimal respondent burden. IRT methodologies have been extensively delineated elsewhere.[32] The enthusiasm for IRT-based measurement lies in part in its capacity to create study-specific or population-specific short forms and computer-adaptive tests that, despite the inclusion of different items, yield comparable scores. To date, efforts have focused on creating item banks rather than examining their validity and responsiveness among patients with cancer. However, the APC has demonstrated responsiveness comparable to that of much longer, fixed-length instruments in both a general outpatient population and in patients with late-stage lung cancer.[33,34]

Objective performance measures and batteries have matured to the point that they are widely integrated into observational databases, clinical practice, and research studies.[35] Their capacity to predict important clinical outcomes is accepted.[36] From this foundation, interest has shifted toward examining whether their use can inform medical decision-making to improve outcomes.[37] Attention has focused on geriatric cancer patients, who enter treatment with greater functional morbidity and who are more likely to develop treatment-related toxicities.[38] The use of performance batteries, such as the Short Physical Performance Battery (SPPB), may provide an objective basis to stratify patients according to risk, gauge their need for reduced treatment intensity, and proactively involve rehabilitation services.

Care delivery strategies

Recognition of a need for more efficient, outcome-based, and patient-centric care delivery has intensified a re-evaluation of comprehensive cancer care. In the United States, the glacial clinical integration of cancer rehabilitation offers a current advantage, in that novel strategies can be implemented without a need to dismantle established infrastructure. However, it is problematic that scant data are available to guide the pragmatic integration of theoretically promising approaches, such as the Prospective Surveillance Model for breast cancer survivors[39] or the preemptive delivery of rehabilitation services to patients with late-stage cancer who are at high risk of becoming disabled. Clinical trials are underway to determine whether treatments that have been established as effective in other populations can benefit patients with cancer.

Characterizing disablement trajectories and rehabilitation needs

In an era of shrinking medical resources, identifying the patients for whom cancer rehabilitation services provide greatest benefit is appropriately becoming a research focus.[40] The heterogeneity of patients with cancer at diagnosis is matched by the dramatic functional transformations that many undergo as they progress through treatment toward advanced disease or long-term survivorship. To date, the characteristics of patients who may or may not become disabled are poorly understood. Patient centricity and cost sensitivity are useful factors for determining whether patients should undergo screening for physical impairments or should automatically receive therapy services.

Examining cancer-related and cancer treatment-related threats to functionality

The relation between physical impairment and disability among cancer patients lacks the direct linearity suggested by many disablement paradigms.[41] This is not surprising

in light of the intense variation in the psychological, symptom, and social dimensions of the cancer experience that catalyze the progression of relatively benign impairments to frank disability.[40,42] Examination of the inevitably complex and nuanced relations between patients' demographics, cancers, treatment exposures, physical impairments, and disabilities has been limited. In addition, the mechanisms by which cancer and cancer treatments produce physical impairments in some patients, and not in others, are a growing research interest, particularly with respect to whether these mechanisms may be amenable to therapeutic intervention.

Many Differences but More Similarities in the Challenges of Developing Comprehensive Cancer Programs in Europe and the United States

Curative cancer care is the primary objective of medical practice in both the United States and Europe, as evidenced by the US-based National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines for breast cancer treatments.[43,44] Patients and survivors should expect a similar primary objective from their rehabilitative care, that is, the restoration of their pretreatment level of function and quality of life. Just as we are not always able to deliver a cure to patients with cancer, we are not always able to successfully meet the goals of rehabilitation. There is considerable room for growth in our evidence base to guide the principles and practice of cancer rehabilitation in both the clinical realm and the academic realm.

Research, by its nature, is reductionist, whereas clinical practice is holistic. Research on cancer rehabilitation will focus on interventions for specific impairments in a specific tumor site at a specific time point along the time course after cancer. By contrast, the clinical practice of cancer rehabilitation will perceive the patient as a whole person for whom cancer mat be 1 of multiple health challenges. Rehabilitation interventions need to be comprehensive, addressing multiple impairments simultaneously or in succession, with various levels of patient education, supervision, and ongoing surveillance for improvement or decrement in function from the time of diagnosis throughout the patients' lives. The challenge of piecing together a coherent, holistic clinical practice from largely reductionist research findings is hardly unique to cancer rehabilitation. However, we acknowledge that it creates a natural tension between the evidence base supporting cancer rehabilitation versus the clinical practice of cancer rehabilitation. The research evidence supporting the efficacy of cancer rehabilitation interventions for adverse treatment effects, as noted above, will not differ between the United States and Europe.

Defining the levels of care required by cancer survivors and designing appropriate services and programs to accommodate them should be a priority irrespective of country. Although some patients may have no discernible impairments (ie, resection of a malignant thyroid nodule), others can be stratified has having mild, moderate, or severe impairments.[45] The effects of cancer treatments can vary widely. For instance, the same dose of a neurotoxic chemotherapeutic agent can leave 1 patient with little or no chemotherapy-induced neuropathy and can leave another patient severely impaired.[46] Similar disparities can be observed in patients treated with radiation who suffer from radiation fibrosis syndrome.[47] The chemotherapy-induced neuropathy observed with taxanes may improve significantly in the majority of patients, whereas the neuropathy resulting from platinum analogues tends to be more durable and may last for the life of the patient.[46] In the case of patients who have radiation fibrosis syndrome, their symptoms may not manifest for months or years after treatment and will progress for the rest of their lives.[47]

The ideal comprehensive cancer rehabilitation program should include a specialized cancer rehabilitation physician with skill and expertise in the evolution and treatment of a wide variety of neuromuscular, musculoskeletal, pain, and functional disorders common to cancer patients and survivors. The program would serve both inpatients and outpatients and would be supported by highly trained physical, occupational, and lymphedema therapists dedicated to treating the unique needs of the cancer population. Clinicians, including not only the primary oncologist, oncologic surgeon, and radiation oncologist but also a variety of specialties, such as medical survivorship, psychology, psychiatry, social work, speech, and swallowing, and medical subspecialties, such as cardiology and endocrinology, among others, need to be readily accessible for consultation and collaboration. By having access to a wide variety of allied clinicians, rehabilitation medicine physicians not only would be able to address functional issues, which are their primary focus and expertise, but also would be able to ensure that other domains, such as the patients' psychological and social well being, are being addressed.

Conclusions

An increase in the number of cancer survivors in Europe and the United States has led to progressive interest in

robust and effective cancer rehabilitation services to help restore function and quality of life to individuals affected not only by direct effects of cancer but also by surgery, chemotherapy, radiation, and other treatments important in effecting cure or prolonged survival. The field of cancer rehabilitation is still very much in development in both Europe and the United States. Basic questions concerning what constitutes a state-of-the-art cancer rehabilitation program, where such programs should reside, how to train clinicians, and which skill sets are critical have yet to be answered. Similarly, which programs are most successful and how to measure success are subjects of debate. The configuration of cancer rehabilitation programs and access to those services varies widely across Europe and the United States, reflecting different funding systems and widening health inequalities. Narrowing not only our knowledge gap but also this socioeconomic chasm will be a major but critical challenge for rehabilitation professionals going forward.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional Assessment of Long-Term Cancer Survivors Including Discovery of Genetic Bases of Susceptibility, Depressive Stage, Prevention of Affective Disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103:117-128.
2. Mehnert A, Koch U. Predictors of employment among cancer survivors after medical rehabilitation: a prospective study. *Scand J Work Environ Health.* 2013;39:76-87.
3. Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer.* 2011;47: 2493-2511.
4. International Agency for Research on Cancer (IARC). GLOBOCAN Fact Sheet. Available at: http://globocan.iarc.fr/factsheets/cancers/all.asp. [Accessed March 12, 2013].
5. Berrino F, De Angelis R, Sant M, et al. Survival for 8 major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. *Lancet Oncol.* 2007;8:773-783.
6. Maher J, McConnell H. New pathways of care for cancer survivors: adding the numbers. *Br J Cancer.* 2011;105(suppl 1):S5-S10.
7. Hellbom M, Bergelt C, Bergenmar M, et al. Cancer rehabilitation: a Nordic and European perspective. *Acta Oncol.* 2011;50:179-186.
8. Dalton SO, Hansen HP, Johansen C, et al. Rehabilitation After Breast Cancer, Colorectal Cancer and Prostate Cancer—A Medical Technology Assessment [in Danish]. Copenhagen, Denmark: National Board of Health, Monitoring and Medical Technology Assessment; 2010.
9. National Cancer Action Team (NCAT). Cancer and Palliative Care Rehabilitation Workforce Project: A Review of the Evidence. London, United Kingdom: NCAT; 2009.
10. Armes J, Crowe M, Colbourne L, et al. Patients' supportive care needs beyond the end of cancer treatment: a prospective, longitudinal survey. *J Clin Oncol.* 2009;27:6172-6179.
11. Ross L, Petersen MA, Johnsen AT, Lundstrom LH, Groenvold M. Are different groups of cancer patients offered rehabilitation to the same extent? A report from the population-based study "The Cancer Patient's World" Support Care Cancer. 2012;20:1089-1100.
12. Holm LV, Hansen DG, Johansen C, et al. Participation in cancer rehabilitation and unmet needs: a population-based cohort study. *Support Care Cancer.* 2012;20:2913-2924.
13. Gonzalez CA. The European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr.* 2006;9:124-126.
14. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer.* 2009;45: 931-991.
15. Poppelreuter M, Weis J, Mumm A, Orth HB, Bartsch HH. Rehabilitation of therapy-related cognitive deficits in patients after hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2008; 41:79-90.
16. Alfano CM, Ganz PA, Rowland JH, Hahn EE. Cancer survivorship and cancer rehabilitation: revitalizing the link. *J Clin Oncol.* 2012; 30:904-906.
17. Stubblefield MD. Commentary on "oncologists' and physiatrists' attitudes regarding rehabilitation for patients with advanced cancer." *PM R.* 2012;4:109-110.
18. American College of Surgeons. Commission on Cancer (COC) Accreditation Program. Chicago, IL: American College of Surgeons; 2012.
19. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv.* 2010;4:87-100.
20. Oldervoll L, Kaasa S, Hjermstad M, Lund JA, Loge JH. Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients? *Eur J Cancer.* 2004;40: 951-962.
21. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc.* 2010;42:1409-1426.
22. Hewitt M GS, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: The National Academies Press; 2006.
23. Cheville AL, Troxel AB, Basford JR, Kornblith AB. Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer. *J Clin Oncol.* 2008;26:2621-2629.
24. Lehmann JF, DeLisa JA, Warren CG, deLateur BJ, Bryant PL, Nicholson CG. Cancer rehabilitation: assessment of need, development, and evaluation of a model of care. *Arch Phys Med Rehabil.* 1978;59:410-419.
25. Guadagnoli E, Mor V. Daily living needs of cancer outpatients. *J Commun Health.* 1991;16:37-47.
26. Freedson P, Bowles HR, Troiano R, Haskell W. Assessment of physical activity using wearable monitors: recommendations for monitor calibration and use in the field. *Med Sci Sports Exerc.* 2012;44:S1-S4.
27. Bassett DR Jr, Rowlands A, Trost SG. Calibration and validation of wearable monitors. *Med Sci Sports Exerc.* 2012;44(1 suppl 1):S32-S38.
28. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol.* 2010;63:1179-1194.
29. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol.* 2007;25:5106-5112.
30. Haley SM, Ni P, Hambleton RK, Slavin MD, Jette AM. Computer adaptive testing improved accuracy and precision of scores over

random item selection in a physical functioning item bank. *J Clin Epidemiol.* 2006;59:1174-1182.
31. Jette AM, Haley SM, Ni P, Moed R. Adaptive short forms for outpatient rehabilitation outcome assessment. *Am J Phys Med Rehabil.* 2008;87:842-852.
32. Thomas ML. The value of item response theory in clinical assessment: a review. *Assessment.* 2011;18:291-307.
33. Jette AM, Haley SM, Tao W, et al. Prospective evaluation of the AM-PAC-CAT in outpatient rehabilitation settings. *Phys Ther.* 2007;87:385-398.
34. Cheville A, Yost K, Larson D, et al. Performance of an item response theory-based computer adaptive test in identifying functional decline. *Arch Phys Med Rehabil.* 2012;93:1153-1160.
35. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci.* 2000;55: M221-M231.
36. Vasunilashorn S, Coppin AK, Patel KV, et al. Use of the Short Physical Performance Battery Score to predict loss of ability to walk 400 meters: analysis from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci.* 2009;64:223-229.
37. Klepin HD, Geiger AM, Tooze JA, et al. The feasibility of inpatient geriatric assessment for older adults receiving induction chemotherapy for acute myelogenous leukemia. *J Am Geriatr Soc.* 2011;59: 1837-1846.
38. Barthelemy P, Heitz D, Mathelin C, et al. Adjuvant chemotherapy in elderly patients with early breast cancer. Impact of age and comprehensive geriatric assessment on tumor board proposals. *Crit Rev Oncol Hematol.* 2011;79:196-204.
39. Stout NL, Binkley JM, Schmitz KH, et al. A prospective surveillance model for rehabilitation for women with breast cancer. *Cancer.* 2012;118:2191-2200.
40. Cheville A, Kornblith A, Basford J. An examination of the causes for the underutilization of rehabilitation services among people with advanced cancer. *Am J Phys Med Rehabil.* 2011;90(5 suppl 1):S27-S37.
41. Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med.* 1994;38:1-14.
42. Bosompra K, Ashikaga T, O'Brien PJ, Nelson L, Skelly J. Swelling, numbness, pain, and their relationship to arm function among breast cancer survivors: a disablement process model perspective. *Breast J.* 2002;8:338-348.
43. National Comprehensive Cancer Network (NCCN). Breast Cancer. NCCN Clinical Practice Guidelines in Oncology. 2 ed. Fort Washington, PA: National Comprehensive Cancer Network; 2001.
44. Aebi S, Davidson T, Gruber G, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2011;22(suppl 6):vi12-vi24.
45. Stubblefield MD, O'Dell MW. Cancer Rehabilitation Principles and Practice. New York: Demos Medical Publishing; 2009.
46. Stubblefield MD, Burstein HJ, Burton AW, et al. NCCN Task Force Report: management of neuropathy in cancer. *J Natl Compr Canc Network.* 2009;7:S1-S26.
47. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. *PM R.* 2011;3: 1041-1054.

Original Article

Survivorship Programs and Care Planning

Mary S. McCabe, RN, MA[1]; Sara Faithfull, PhD, MSc BSc (Hons)[2]; Wendy Makin, MBChB, FRCR, FRCP[3]; and Yvonne Wengstrom, MD[4]

Formal cancer survivorship care is a growing focus internationally. This article provides a broad overview of the national strategies currently in progress for the development of survivorship programs and care plans within the United States and across Europe. The different approaches taken in their implementation, staffing, and clinical focus are highlighted, with an emphasis on how they are incorporated into various models of care. The considerable variation in making survivorship a formal period of care across countries and health care systems is discussed, including the factors influencing these differences. A review of research focused on the evaluation of definitions and outcomes is provided along with a discussion of important areas requiring future research. ***Cancer*** **2013;119(11 suppl):2179-86.** © *2013 American Cancer Society.*

KEYWORDS: survivorship; survivorship programs; care plans; rehabilitation; models of care.

INTRODUCTION

Survivorship programs and care plans are frequently identified as core components in survivorship strategies after the completion of successful cancer treatment. The term "survivorship program" is used to describe a range of planned interventions to promote and support a patient's participation in maximizing their recovery and the adoption of a healthy lifestyle for the future.[1]

The objectives include monitoring by clinicians and patients for possible symptoms of cancer recurrence and late effects, support to optimize quality of life and physical and psychological well-being, and a successful return to employment and other social functions.[1,2] The individual is encouraged to take a more active role in managing their own health care, with particular attention to prevention and screening behaviors.[3,4] A survivor care plan (SCP) refers to an individualized plan of care that is constructed through a holistic assessment and implemented at the conclusion of cancer treatment.[5,6] Although discussions and treatment choices that relate to long-term consequences should be part of the earlier pathway after diagnosis, the SCP is usually based on the end-of-treatment summary. It will also include both immediate and longer-term goals: from recovery and rehabilitation to future monitoring for potential late consequences of treatment or second cancers.[7] The SCP should be provided to the cancer survivor and shared with the primary care provider and other professionals who provide ongoing care, as well as others who may care for the individual in subsequent years.[1]

This article provides an overview of the concepts and ways in which survivorship programs and SCPs are being implemented within the United States and across Europe. The different approaches taken in their development and formulation are explored as is the context in which they are being applied to models of survivorship care. This article also illustrates the considerable variation in the extent to which cancer survivorship is a clearly defined period of care or even acknowledged within health care systems, the different factors that influence models of care, and the extent that these models have been formally tested.

Corresponding author: Mary McCabe, RN, MA Director, Survivorship Program, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065; Fax: (212) 717-3414; mccabem@mskcc.org

[1]Cancer Survivorship Program, Memorial Sloan-Kettering Cancer Center, New York, New York; [2]Faculty of Health and Medical Sciences, University of Surrey, Stag Hill, Guildford, Surrey, United Kingdom; [3]Palliative Medicine and Oncology, The Christie National Health Service Foundation Trust, Manchester, United Kingdom; [4]Department of Neurobiology, Care Science and Society, Division of Nursing, Karolinska Institute, Stockholm, Sweden.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28068, **Received:** August 1, 2012; **Revised:** January 16, 2013; **Accepted:** January 16, 2013, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

Influence of National Strategies and Policy Initiatives on the Development of Survivorship Programs

The current literature reflects international heterogeneity with regard to the extent to which cancer follow-up care is considered a priority requiring a strategic approach in health care with an acknowledgment that there are survivors within the population who will require various degrees of support long after the completion of treatment.

In the United States, cancer survivorship as a formal period of care gained national recognition via 2 key publications in 2004 and 2005. *A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies* was published in 2004 by the Centers for Disease Control and Prevention in collaboration with the LIVESTRONG Foundation.[8] This was followed by the influential Institute of Medicine (IOM) report entitled, *From Cancer Patient to Cancer Survivor: Lost in Transition,*[1] which offered a strong challenge and comprehensive guidance to the broad community of clinicians caring for cancer survivors. The broad set of Institute of Medicine recommendations established a survivorship roadmap for clinical care, research, communication, professional training, and education. It also included a strong recommendation for SCPs for all survivors.

In recent years, all 50 states in the United States have established cancer control plans and 88% of these plans include a focus on survivorship services with the intention of proposing ways to coordinate and communicate cancer efforts. These plans are intended to be a catalyst for community action, engaging health care providers, public health officials, and patient groups. This effort was further enhanced in 2005 with the identification and funding by LIVESTRONG Foundation of a Survivorship Centers of Excellence Network that included a group of National Cancer Institute-designated cancer centers.[9] The goal of this ongoing initiative was to "**. . .** provide a mechanism to bring together these 8 cancer centers and their community partners to address the most pressing issues of cancer survivorship. -the Network sought to harness the expertise, experience, creativity and productivity of leading cancer centers to accelerate progress in survivorship, research care and services."[10] In 2011, LIVESTRONG expanded their scope of activity by publishing a brief on the Essential Elements of Survivorship Care that are relevant to all oncology care settings in the United States.[11]

Across Europe, there is considerable variation both in the recognition of cancer survivorship and how organizations are responding to these identified needs. In 2008, 16 European countries had defined national cancer plans,[12] although to our knowledge very few currently have survivorship services within these plans. European Commission recommendations to reduce the burden of cancer endorse the inclusion of an integrated approach to care across the cancer trajectory.[13] In contrast to the United States, there are no single pan-European templates for care planning and survivor programs. Consequently, some countries are further ahead than others, but the growing number of cancer survivors in the European population will require discussions about the implications of this growth and the resulting expenditure of health care resources.[14] In Scandinavia, where there is a public tax-financed health care system with resources allocated to specific areas including cancer aftercare and rehabilitation, survivorship programs are further developed. Norway has undertaken population surveys through cancer registries to inform the design of rehabilitation programs for survivors.[14,15] Sweden is evaluating the government-funded development of an integrated approach for all cancer survivors.[16] Italy also has free access to medical care and social services; however, a survey in 2003 established that there was variable access to rehabilitation after cancer treatment, although referrals could be made by oncologists or primary care physicians. In response, a research-based approach has been initiated using provider-reported outcomes to demonstrate the benefits of support services to cancer survivors and to the health economy as well.[17] However, even when there is free access to rehabilitation, there is a poor uptake of these services,[18] suggesting that other psychological and social factors to improve implementation are needed for the population to fully benefit from such recovery models.[19]

In the United Kingdom, the landmark development in cancer survivorship was the creation in 2008 of the National Cancer Survivorship Initiative, which is a partnership between the Department of Health (England and Wales) and a major UK charity, Macmillan Cancer Support. The publication of a national strategy, the so-called "National Cancer Survivorship Vision," followed in January 2010.[20] Similar to the IOM recommendations in the United States, this report made the case for identifying the priority developments for survivorship cancer services and research. The document was informed by a health and well-being survey undertaken by Macmillan in 2008, which provided evidence of chronic health care needs among cancer survivors.[21] The following year, the UK government's Cancer Reform Strategy included reference to survivorship for the first time and included specific outcome measures for cancer survivors .[20]

The Health Council of the Netherlands has also promoted a national approach, including the use of SCPs and cancer rehabilitation as a strategic objective[22] with the

inclusion of a detailed quality-of-life assessment of cancer survivors linked to the cancer registry. This approach may be aspirational for other parts of Europe. For example, in Hungary, which has the highest cancer incidence and mortality rates in central Europe, Csikai et al[23] described the challenges for the existing health care system with few health care professionals who are equipped to address the psychological consequences of cancer treatment support and rehabilitation for survivors. This is not just an issue for Eastern Europe; workforce capacity is a contributing factor to the engagement of health care professionals in many countries worldwide in survivorship care.[24,25]

The promotion and development of cancer survivorship care is increasingly influenced by professional societies and organizations in both the United States and Europe. The American Society of Clinical Oncology, the American Cancer Society, the Oncology Nursing Society, and the National Comprehensive Cancer Network all have made survivorship a strategic priority and have launched important initiatives to develop clinical guidance for the identification and management of survivorship issues that occur as a result of the cancer and its treatment. The Organization of European Cancer Institutes is a platform that fosters pan-European collaboration for cancer care, education, and research and includes those issues relating to survivorship. The European Oncology Nursing Society and the European CanCer Organization endeavor to share learning and enhance survivorship models. In parallel, there is a growing patient voice. The European Cancer Patient Coalition, which represents over 300 patient cancer groups across Europe, has identified survivorship care as one of their priorities. Such developments will influence all aspects of cancer service development, including survivorship.

Design of Survivor Programs

In the United States to date, formal survivorship planning is structured around the types of providers and types of facilities in which patients and their families seek cancer treatment and care, and this diversity has resulted in several care models.[25-29] With so much of US medical care currently focused on the specialist rather than the primary care provider, the key provider in these survivorship models has been the cancer specialty team and not the primary care physician, although increasingly a shared care model with the primary care physician is being adopted and is driven by the development of Accountable Care Organizations under the Patient Protection and Affordable Care Act.[30] Although the initial models began in academic cancer centers, they currently are being implemented and adapted in community oncology practices and hospitals.[31] This is an important advancement in survivorship care in the United States because the majority of cancer patients are treated and receive follow-up care in the community.[26,27]

In both the United States and many countries within Europe, nurses have developed the skills to care for cancer survivors and play an increasingly important role in providing follow-up care with particular attention paid to a holistic assessment of the patient; a focus on lifestyle interventions and psychological adjustment; a sharing of follow-up monitoring with the oncologist; and, in addition, the management of patients with late-onset and chronic symptoms.[28,32,33] This expertise supports the construction and use of SCPs. In contrast, the role of the cancer nurse specialist is not well developed in several European countries, thereby limiting their ability to intervene in a patient's care after the completion of treatment.

In the United States, nurse practitioners and physician assistants may see patients either independently or in a collaborative visit with a physician for ongoing survivorship care planning and support. This may take place in cancer centers, hospitals, or community practices. Survivors may also be referred for a 1-time comprehensive survivorship visit although the ongoing care continues to be provided by the oncology team.[28,34] Both models of care include the provision of a treatment summary and care plan; a review of the recommended surveillance for long-term and late effects; and a discussion of health promotion and disease prevention activities, such appropriate cancer screening, diet, exercise, and smoking cessation. For individual problems that may be identified, survivors are referred to medical subspecialists, physical rehabilitation, nutrition counseling, and psychological or psychiatric services. There is emphasis on establishing primary care-based support for the survivor with the expectation that communication between the oncology team and primary care provider will continue.[35] Evaluation of this type of follow-up is currently being conducted both within the United States[36] and Europe.[24,37]

Thus in the United States, the components of the "survivor program" are customized to the individual, provided via targeted referral to specific services, and coordinated by the care planning process, rather than a formal course for a group of patients. To our knowledge to date, there has been limited evaluation of these models, but there is increasing emphasis on the need to do so.[31,34,38]

Another model of a survivor program used in both Europe and the United States and customized to the individual is that of a planned and brief course provided by several experts and accessed by groups of survivors. This approach can harness mutual encouragement and

support, enhance motivation to adopt better lifestyle choices, and promote self-care.[39-41] The group visit model of survivorship care is a means of encouraging survivors to actively participate in the development of their SCP. In Sweden, Grahn[42] developed the "Learning to Live With Cancer" program, which has been evaluated in several European countries.[43-45] Such a model is also often led by nurses and focuses on adaptation to chronic health issues as well as the development of the SCP.[46]

Survivor Program Models Linked to Rehabilitation

The components of what are called survivorship programs in the United States are recognizable within the provision of rehabilitation by several European countries; indeed the term "rehabilitation" may be considered to be a surrogate for "survivorship program" because they have broadly similar aims. Although rehabilitation (physical and vocational) in the United States is most often a separate service used by individuals cared for in a survivorship program, the broad dissemination of these services into the community has been limited.[4] In contrast, rehabilitation is well established within Europe and the elements of survivorship programs can be identified within the context of rehabilitation after cancer treatment, including the promotion of psychological care and exercise.[47,48] Although there are examples of interventions and pathways[49] that relate to these survivorship models, the way in which rehabilitation is implemented as part of cancer survivorship will be shaped within the context of different health care systems, financial support, and cultures across Europe.

Provision of rehabilitation after any significant illness has been long established within the health care and social care systems in Germany and are now financed via the Social Insurance code system. The intention is to enhance recovery after acute illnesses through vocational rehabilitation that promotes a return to employment. The established model is a 3-week to 4-week residential course of intensive rehabilitation training (requiring that individuals remain at the facility) at the conclusion of cancer treatment.[50] Patients apply for funding for this training, which is provided at a rehabilitation hospital or specialist cancer institutions. However, although access to rehabilitation is a legal right, not all patients access these services. For example, Rick et al[51] highlighted that only a few patients used the rehabilitation services provided after resection for lung cancer or treatment of ovarian cancer.[52] Outpatient rehabilitation is currently the exception in Germany, although such services have been shown to be comparable and are more popular with patients.[53] This preference for outpatient services may influence the future development of patient programs and in doing so widen access to those who cannot commit to the standard rehabilitation clinics because of personal circumstances.

In Italy, rehabilitation centers are focused on diagnostic groups other than cancer and cancer rehabilitation protocols are generally not yet established, although there are reports of rehabilitation, particularly after surgery, with a recommendation for wider use in cancer services.[54,55] In the Netherlands, although cancer rehabilitation programs are not yet routinely available to all patients, models of nonresidential programs currently are being developed and evaluated.[56-58] Models of cancer rehabilitation have been well described across Scandinavian countries, but again there is no systematic provision of services and consequently access is variable.[49] The Danish Cancer Society highlighted the importance of rehabilitation in patients with cancer in 1993, after which there was growth noted with regard to residential cancer rehabilitation initiatives.[59] However, only between 5% and 50% of patients (depending on their diagnosis) were admitted to cancer rehabilitation programs.[18,60] Currently, physical and rehabilitation medicine is underdeveloped in relation to oncology in France.[61] In the United Kingdom, although the role of rehabilitation is identified for specific cancer pathways,[62] there has not been widespread implementation of rehabilitation services due to a lack of staff and reimbursement of aftercare.

Cancer survivorship services are therefore developed in parallel with rather than built on a rehabilitation model.[63] Although the focus of rehabilitation appears to be more on physical recovery, there is acknowledgment of the importance of screening survivors for physical, psychological, and social care needs.[57,64] Although rehabilitation has been tailored to the needs of individual patients, some researchers have demonstrated little change in psychological stress in the longer term, identifying the need for the inclusion of other aftercare approaches[65-67] within the rehabilitation model. Clearly there are many rehabilitation initiatives occurring across Europe; however, these are often occurring in selected patient groups and there is no consensus on best approaches or data on long-term effectiveness.

Survivor Programs Adopted From Self-Management Approaches With Other Chronic Conditions

Self-management is an interactive process aimed at enhancing individual responses and behavior by managing the physical and psychosocial consequences of

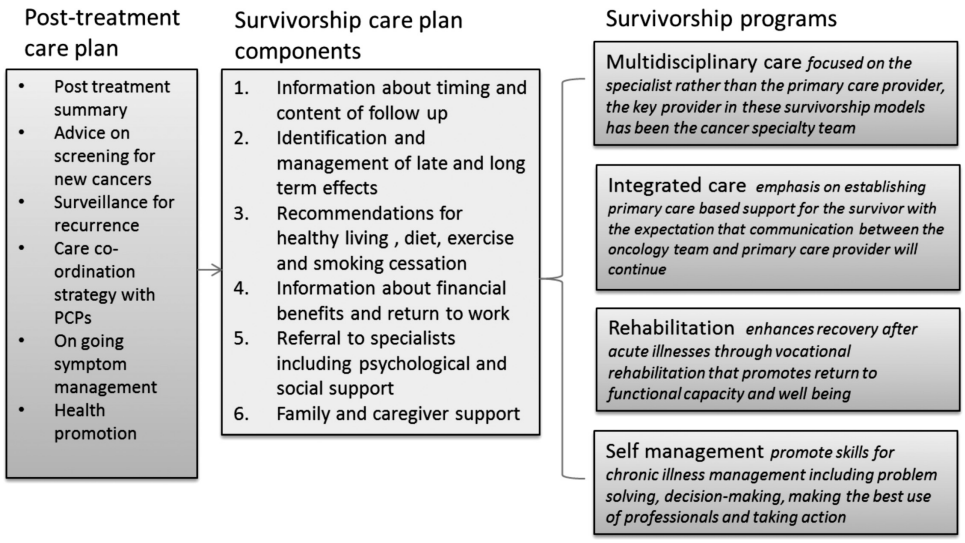

Figure 1. Critical elements of survivorship care planning.

symptoms and treatment.[68] These are supported by a clinician, and often involve cognitive behavioral therapy approaches.[39] The promotion of patient confidence in self-management was launched by the UK Department of Health in 2002 through Expert Patient Programmes[69] and expanded across long-term health conditions. Self-management for cancer patients promotes skills for chronic illness management including problem solving, decision-making, making the best use of professionals, and taking action,[39] and draws on the chronic disease self-management model developed by Lorig et al and Barlow et al.[70,71] This concept has also been used successfully in the United States to promote lifestyle change and psychosocial health.[72] In Norway, a self-management program has been developed for women with breast cancer.[73] It includes a 1-week residential course designed to provide a holistic approach to enhance coping strategies, with an additional 4-day course taking place 2 months later, which was reported to reduce anxiety levels. Evidence from feasibility studies indicated that this targeted self-management approach can reduce long-term symptoms as a consequence of cancer treatment and improve the quality of life in patients with prostate cancer.[74,75] However, further research is needed to adequately power these self-management studies to determine the benefits, if any, for patients with cancer.

Evolution of the SCP

The SCP should be developed at the conclusion of treatment by the principal providers who coordinated the patient's oncology care. In addition to providing a summary of treatment as a source of future reference, this document relates to the unique experience of each patient and should identify requirements for monitoring, encourage self-management, and be clear on when and how to access advice and support. Given the diversity in health care delivery systems and the uniqueness of the differing survivor populations, the lesson thus far is that no "one size fits all" approach can be taken. However, although care planning may differ in focus, organization, and type of provider, each of which has their own implementation challenges, there are commonly agreed on elements that are considered essential (Fig. 1).[7]

In the German studies evaluating rehabilitation programs, there was no reference to individual care plans, although it is evident that rehabilitation itself is based on a holistic assessment of individual function and need. Schnipper-Haasler and Gonschewski[76] describe individualized "discharge papers" directed toward the family physician who is responsible for the patient's future care. The letters generated by the oncologist signaling the completion of treatment and plans for follow-up should also provide information regarding possible long-term problems. It is considered best practice for the patient to hold a copy of such a letter, although not all patients are asked about this or indeed wish to obtain a copy. In the United Kingdom, the National Cancer Survivorship Initiative provides and promotes templates for end-of-treatment summaries, which are accessible via the Web site (ncsi.org.uk). These can form the basis of an SCP but the challenge lies in its adoption into mainstream practice among oncologists for all patients.[77]

Although there is broad support for formal survivorship care planning throughout the United States, 7 years after the publication of the IOM report, the use of SCPs and evaluation of those that are used is limited.[78-81] A recent review by Salz et al[82] reported that although SCPs are accepted in comprehensive cancer centers, only 43% of such centers provided them to survivors of colorectal cancer. Even when used, there appears to be no consistent approach to what should be included.[83] Variations in the content may be due to the broad range of topics to be included, or the clinical team may be unclear about how best to impart this information.[30] There may be a lack of clarity regarding which items in the plan are the responsibility of the oncology team and which are the responsibility of the primary care physician.

Barriers to implementation also exist. For example, putting this information together for a survivor in a busy clinic may be too time-consuming to be practical, the lack of an electronic medical record may make it difficult to pull all the needed information together, and the lack of financial reimbursement for the time it takes to prepare the document is a disincentive.[5] In a recent survey of US oncologists, the majority reported that the SCP should take no more than 20 minutes per patient to complete.[79] Despite all these real challenges, there are several tools that are being used, revised, and evaluated in the United States. The American Society of Clinical Oncology has several SCP templates that can be completed online (asco.org). There are plans to revise and condense these in the near future because of their length and complexity. Another example, called "Journey Forward," includes a simple treatment summary along with modules with recommendations for future care.[6] This tool was developed as a collaboration between the National Coalition for Cancer Survivorship, the UCLA-Cancer Survivorship Center, WellPoint Inc, and Genentech. The LIVE**STRONG** Care Plan is another option that has been developed as an online, patient-oriented tool and can be completed by patients, family members, and providers. It has undergone numerous revisions and has a high satisfaction rating from users.

However, if the generation of individual SCPs is viewed as a hallmark of good practice and required as part of the future accreditation of cancer programs, there is a growing expectation that SCPs will become part of standard oncology practice. Nevertheless, broad adaptation will also require the education and training of practitioners along with evaluation of the usefulness of the various components.[83] As a first step, the American College of Surgeons Commission on Cancer is requiring that the provision of SCPs be phased in as part of accreditation in 2015.[84]

Conclusions

International attention is increasingly focused on the unique care needs of cancer survivors, resulting in the implementation of SCPs and programs. In turn, these will enable new and more flexible models of care to meet the needs of the increasing numbers of cancer survivors. Survivorship is a growing area of research, resulting in a rapid increase in knowledge both across Europe and in the United States, as evidenced in this article. Despite this increase in publications, to the best of our knowledge, evidence remains limited concerning the value of SCP use and whether new models of survivorship care delivery improve health outcomes for survivors. It is now incumbent on the research community to develop an evidence base for the components of survivorship care planning, vigorously evaluate the information and communication value of SCPs, and test models of care for efficiency and quality in the various health care systems in which survivorship programs are operationalized. Few survivorship studies are conducted within the context of controlled trials, and therefore the evidence base is largely descriptive with preintervention and postintervention evaluations. To the best of our knowledge, studies evaluating survivorship programs have rarely defined the theoretical basis for the interventional approach or the components that comprise the program and therefore it is difficult to compare studies across Europe and the United States. In addition, there may be benefits to instituting survivorship programs that begin during treatment with the opportunity to engage patients when they may be strongly motivated and enable them to take charge of their adjustment and recovery, both during treatment and into survivorship.

To better inform survivorship care planning, there are several important questions to be addressed, including understanding the specific relationships between comorbidity and functional ability and how these are manifested in long-term health problems, quality of life, and health service usage. An additional important area that has to our knowledge received little attention to date is research focused on the unique needs of specific at-risk populations that may not necessarily be represented in studies conducted with the general population of cancer survivors. Such individuals often lack the ability to navigate health care systems, confront social and economic barriers to accessing needed services, and are often reluctant to seek assistance. It will be important to demonstrate that future SCPs and survivorship programs can be effective for these survivors as well as for those who are informed, articulate, and self-motivated.

Although the current article provides a valuable source of shared learning, it is important to recognize the

distinct nature of the respective health care systems that shape the approaches to survivorship care internationally. Even as research builds a clinical evidence base, we can expect to see these differences influence the way in which these interventions and services are adopted across health care settings.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Hewitt M, Greenfield S, Stovall E, eds. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press; 2005.
2. Ganz PA. Survivorship: adult cancer survivors. *Prim Care*. 2009;36:721-741.
3. Institute of Medicine. Implementing Cancer Survivorship Care Planning: Workshop Summary. Washington, DC: The National Academies Press; 2006.
4. Alfano CM, Ganz PA, Rowland JH, Hahn EE. Cancer survivorship and cancer rehabilitation: revitalizing the link. *J Clin Oncol*. 2012;30:904-906.
5. Earle CC. Failing to plan is planning to fail: improving the quality of care with survivorship care plans. *J Clin Oncol*. 2006;24:5112-5116.
6. Hausman J, Ganz PA, Sellers TP, Rosenquist J. Journey forward: the new face of cancer survivorship care. *J Oncol Pract*. 2011;7(suppl 3):e50s-e56s.
7. Earle CC, Ganz PA. Cancer survivorship care: don't let the perfect be the enemy of the good. *J Clin Oncol*. 2012;30:3764-3768.
8. Centers for Disease Control and Prevention. A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies. Atlanta, GA: Centers for Disease Control and Prevention, Lance Armstrong Foundation; 2004.
9. Rechis R, Eargle E, Dutchover Y, et al. Defining Survivorship Care: Lessons Learned From the LIVESTRONG Survivorship Centers of Excellence Network. Austin, TX: Lance Armstrong Foundation; 2011.
10. Campbell M, Tessaro I, Gellin M, et al. Adult cancer survivorship care: experiences from the LIVESTRONG centers of excellence network. *J Cancer Surviv*. 2011;5:271-282.
11. Rechis R, Beckjord E. The Essential Elements of Survivorship Care: A LIVESTRONG Brief. Austin, TX: Lance Armstrong Foundation (LIVESTRONG); 2011.
12. Bastos J, Peleteiro B, Goouveia J, Coleman MP, Lunet N. The state of the art of cancer control in 30 European countries in 2008. *Int J Cancer*. 2010;126:2700-2715.
13. Gouveia J, Coleman M, Haward R, et al. Improving cancer control in the European Union: conclusions from the Lisbon round-table under the Portuguese EU Presidency, 2007. *Eur J Cancer*. 2007;44:1457-1462.
14. Simonelli C, Annunziata MA, Chimienti E, Berretta M, Tirelli U. Cancer survivorship: a challenge for the European oncologists. *Ann Oncol*. 2008;19:1216-1217.
15. Gjerset G, Fossa S, Courneya K, Skovlund E, Jacobsen AB, Thorsen L. Interest and preferences for exercise counselling and programming among Norwegian cancer survivors. *Eur J Cancer Care (Engl)*. 2011;20:96-105.
16. Goransson P. Developing and integrating a cancer rehabilitation process in order to acheive a patient focused and coherent cancer care at hallnds hospital Halmstead: a pilot project. *Psychooncology*. 2011;20(Suppl S1):154.
17. Mattioli V, Montanaro R, Romito F. The Italian response to cancer survivorship research and practice: developing an evidence base for reform. *J Cancer Surviv*. 2010;4:284-289.
18. Rix B. A national strategy for cancer rehabilitation and palliative care in Denmark. *Psychooncology*. 2011;20(Suppl S1):236.
19. Stein K, Syrjala K, Andrykowski M. Physical and psychological long-term and late effects of cancer. *Cancer*. 2008;112(suppl 11):2577-2592.
20. Department of Health, Macmillan Cancer Support, NHS Improvement: National Cancer Survivorship Vision, 2010. http.// www.dh.gove.uk/en/publications and statistics_DH123371.
21. Elliott J, Fallows A, Staetsky L, et al. The health and well-being of cancer survivors in the UK: findings from a population survey. *Br J Cancer*. 2011;105(suppl 1):S11-S20.
22. van de Poll-Franse L, Horevoorts N, van Eenbergen M, et al; Profiles Registry Group. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer*. 2011;47:2188-2194.
23. Csikai E, Walsh K, Allen F, et al. Best practices and challenges in psychosocial oncology in Hungary: outcomes of a professional exchange summit. *Psychooncology*. 2009;18(Suppl 2):S253-254.
24. Heins M, Schellevis F, Rijken M, van der Hoek L, Korevaar J. Determinants of increased primary health care use in cancer survivors. *J Clin Oncol*. 2012;30:4155-4160.
25. Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract*. 2007;3:79-86.
26. McCabe M, Baker S, Huffman C, et al. Optimizing survivorship care: academic and community clinic models. In: Feurstein M, Ganz P, eds. Health Services for Cancer Survivors. New York: Springer; 2011:223-238.
27. Oeffinger KC, McCabe MS. Models for delivering survivorship care. *J Clin Oncol*. 2006;24:5117-5124.
28. McCabe MS, Jacobs LA. Clinical update: survivorship care-models and programs. *Semin Oncol Nurs*. 2012;28:e1-e8.
29. Mao JJ, Bowman MA, Stricker CT, et al. Delivery of survivorship care by primary care physicians: the perspective of breast cancer patients. *J Clin Oncol*. 2009;27:933-938.
30. McClellan M, McKethan AN, Lewis JL, Roski J, Fisher ES. A national strategy to put accountable care into practice. *Health Aff (Millwood)*. 2010;29:982-990.
31. Chubak J, Tuzzio L, Hsu C, et al. Providing care for cancer survivors in integrated health care delivery systems: practices, challenges, and research opportunities. *J Oncol Pract*. 2012;8:184-189.
32. Cox K, Wilson E, Heath L, Collier J, Jones L, Johnston I. Preferences for follow-up after treatment for lung cancer: assessing the nurse-led option. *Cancer Nurs*. 2006;29:176-187.
33. Beaver K, Campbell M, Williamson S, et al. An exploratory randomized controlled trial comparing telephone and hospital follow-up after treatment for colorectal cancer. *Colorectal Dis*. 2012;14:1201-1209.
34. Gage EA, Pailler M, Zevon MA, et al. Structuring survivorship care: discipline-specific clinician perspectives. *J Cancer Surviv*. 2011;5:217-225.
35. Mayer DK, Gerstel A, Leak AN, Smith AK. Patient and provider preferences for survivorship care plans. *J Oncol Pract*. 2012;8:e80-e86.
36. Mayer EL, Gropper AB, Neville BA, et al. Breast cancer survivors' perceptions of survivorship care options. *J Clin Oncol*. 2012;30:158-163.

37. Khan NF, Mant D, Rose PW. Quality of care for chronic diseases in a British cohort of long-term cancer survivors. *Ann Fam Med*. 2010;8:418-424.
38. Gilbert SM, Miller DC, Hollenbeck BK, Montie JE, Wei JT. Cancer survivorship: challenges and changing paradigms. *J Urol*. 2008;179:431-438.
39. Cockle-Hearne J, Faithfull S. Self-management for men surviving prostate cancer: a review of behavioural and psychosocial interventions to understand what strategies can work, for whom and in what circumstances. *Psychooncology*. 2010;19:909-922.
40. Berglund G, Petersson LM, Eriksson KC, et al. "Between Men": a psychosocial rehabilitation programme for men with prostate cancer. *Acta Oncol*. 2007;46:83-89.
41. May AM, Korstjens I, van Weert E, et al. Long-term effects on cancer survivors' quality of life of physical training versus physical training combined with cognitive-behavioral therapy: results from a randomized trial. *Support Care Cancer*. 2009;17:653-663.
42. Grahn C. Coping with the cancer experience. Developing an education and support programme for cancer patients and their significant others. *Eur J Cancer Care*. 1996;5:176-181.
43. Berat S, Djurdjevic A, Neskovic-Konstant Z, Vuckovic-Dekic Lj. Implementation of the European educational programme "Learning to live with cancer": how participants evaluate the seminars "Education of educators." *J BUON*. 2008;13:291-293.
44. Grahn G, Danielson M, Ulander K. Learning to live with cancer in European countries. *Cancer Nurs*. 1999;22:79-84.
45. van der Molen B, Hutchison G. Learning to live with cancer: the UK experience of a European patient education and support programme. *Eur J Cancer Care (Engl)*. 1999;8:170-173.
46. Trotter K, Schneider SM. Evaluation of a breast cancer survivorship clinic that uses a group medical appointment model: patient program evaluation and financial analysis. *ASCO Meeting Abstracts*. 2012;30:90.
47. EUROCHIP. Work Package-6 Indicators on Cancer Rehabilitation. Milan, Italy: Fondazione IRCCS "Istituto Nazionale dei Tumori"; 2012.
48. Department of Health: Living With and Beyond Cancer, Cancer Rehabilitation. London, UK: Department of Health; 2011.
49. Hellbom M, Bergelt C, Bergenmar M, et al. Cancer rehabilitation: a Nordic and European perspective. *Acta Oncol*. 2011;50:179-186.
50. Johansen C. Rehabilitation of cancer patients-research perspectives. *Acta Oncol*. 2007;46:441-445.
51. Rick O, Seifart U, Faber G, et al. Lung resection tumour patients and rehabilitation. *Onkologie*. 2011;17:933-939.
52. Schrock R. Rehabilitation of patients with ovarian cancer. *Onkologie*. 2006;12:444-450.
53. Bergelt C, Lehmann C, Beierlein V, et al. Patients assessment of inpatient and outpatient cancer rehabilitation. *Psychooncology*. 2009;18(Suppl 2):S48.
54. Di Fabio F, Koller M, Nascimbeni R, Talarico C, Salerni B. Long-term outcome after colorectal cancer resection. Patients' self-reported quality of life, sexual dysfunction and surgeons' awareness of patients' needs. *Tumori*. 2008;94:30-35.
55. Magrone G, Bozzone A, Romanelli A, et al. Rehabilitation and quality of life in patients undergoing surgery for esophageal cancer. *Rays*. 2006;31:13-16.
56. van de Poll-Franse LV, Nicolaije KA, Vos MC, et al. The impact of a cancer Survivorship Care Plan on gynecological cancer patient and health care provider reported outcomes (ROGY Care): study protocol for a pragmatic cluster randomized controlled trial. *Trials*. 2011;12:256.
57. Dergent T, Troch E, Vandebroek A, et al. Finding a new balance: a cancer rehabilitation program. *Psychooncology*. 2009;18(Suppl 2):S120.
58. Korstjens I, Mesters I, Van Der Peet E, Gijsen B, van den Borne B. Quality of life of cancer survivors after physical and psychosocial rehabilitation. *Eur J Cancer Prev*. 2006;15:541-547.
59. Hansen H, Tjornhoj-Thomsen T. Cancer rehabilitation in Denmark: the growth of a new narrative. *Med Anthropol Q*. 2008;22:360-380.
60. Hansen H, Tjornhoj-Thomsen T, Johansen C. Rehabilitation interventions for cancer survivors: the influence of context. *Acta Oncol*. 2011;50:259-264.
61. Genty M, Ribinik P, Frenay C, et al. Physical medicine and functional rehabilitation and cancer: state of the art and literature review. *Phys Rehab Med*. 2011;54:1877.
62. Robb K. Addressing consequences of treatment-the role of rehabilitation. *Eur J Cancer*. 2011;47:S61-S62.
63. Stubblefield M, O'Dell M. Cancer Rehabilitation: Principles and Practice. New York: Demos Medical Publishing; 2009.
64. Cheville AL, Kornblith AB, Basford JR. An examination of the causes for the underutilization of rehabilitation services among people with advanced cancer. *Am J Phys Med Rehabil*. 2011;90(5 suppl 1):S27-S37.
65. Fors E, Bertheussen G, Thune I, et al. Psychosocial interventions as part of breast cancer rehabilitation programs? Results from a systematic review. *Psychooncology*. 2011;20:909-918.
66. Mehnert A, Koch U. Distress among cancer patients during cancer rehabilitation: a prospective study using the German version of the NCCN distress thermometer. *Psychooncology*. 2011;20(Suppl 2):243.
67. Holzner B, Kemmler G, Kopp M, et al. Quality of life in breast cancer patients-not enough attention for long-term survivors? *Psychosomatics*. 2001;42:117-123.
68. Foster C, Fenlon D. Recovery and self-management support following primary cancer treatment. *Br J Cancer*. 2011;105(suppl 1):S21-S28.
69. Department of Health. The Expert Patient: A New Approach to Chronic Disease Management for the 21st Century. London, UK: Her Majesty's Stationery Office; 2001.
70. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract*. 2001;4:256-262.
71. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. *Patient Educ Couns*. 2002;48:177-187.
72. Trotter K, Frazier A, Hendricks CK, Scarsella H. Innovation in survivor care: group visits. *Clin J Oncol Nurs*. 2011;15:E24-E33.
73. Granstam B, Lindemalm C, Ojutkangas M, et al. Support group intervention after breast cancer treatment: first results of a prospective randomized study. *Eur J Cancer*. 2010;8:80-81.
74. Faithfull S, Cockle-Hearne J, Khoo V. Self-management after prostate cancer treatment: evaluating the feasibility of providing a cognitive and behavioural programme for lower urinary tract symptoms. *BJU Int*. 2011;107:783-790.
75. Penedo FJ, Dahn JR, Molton I, et al. Cognitive-behavioral stress management improves stress-management skills and quality of life in men recovering from treatment of prostate carcinoma. *Cancer*. 2004;100:192-200.
76. Schnipper-Hassler U, Gonschewski R. Therapy of secondary effects in medical rehabilitation. *Gynakologe*. 2008;41:269-274.
77. Maher J, McConnell H. New pathways of care for cancer survivors: adding the numbers. *Br J Cancer*. 2011;105(suppl 1):S5-S10.
78. Stricker CT, Jacobs LA, Risendal B, et al. Survivorship care planning after the institute of medicine recommendations: how are we faring? *J Cancer Surviv*. 2011;5:358-370.
79. Hewitt M, Bamundo A, Day R, Harvey C. Perspectives on post-treatment cancer care: qualitative research with survivors, nurses, and physicians. *J Clin Oncol*. 2007;25:2270-2273.
80. Jacobs LA, Palmer SC, Schwartz LA, et al. Adult cancer survivorship: evolution, research, and planning care. *CA Cancer J Clin*. 2009;59:391-410.
81. Faul LA, Shibata D, Townsend I, Jacobsen PB. Improving survivorship care for patients with colorectal cancer. *Cancer Control*. 2010;17:35-43.
82. Salz T, Oeffinger KC, McCabe MS, Layne TM, Bach PB. Survivorship care plans in research and practice. *CA Cancer J Clin*. 2012;62:101-117.
83. Merport A, Lemon SC, Nyambose J, Prout MN. The use of cancer treatment summaries and care plans among Massachusetts physicians. *Supportive Care Cancer*. 2012;20:1579-1583.
84. American College of Surgeons. Cancer Program Standards 2012, Version 1.1: Ensuring Patient-Centered Care. Chicago, IL: American College of Surgeons; 2012.

Original Article

Health Care Policy and Cancer Survivorship

Katherine S. Virgo, PhD, MBA[1,2]; Julia L. Bromberek, MSPH[1]; Adam Glaser, DM[3]; Denis Horgan, LLM, MSC[4]; Jane Maher, PhD, FRCP[5]; and Otis W. Brawley, MD[2,6]

The United States and the European Union (EU) vary widely in approaches to ensuring affordable health care coverage for our respective populations. Such variations stem from differences in the political systems and beliefs regarding social welfare. These variations are also reflected in past and future initiatives to provide high quality cancer survivorship care. The United States spends considerably more on health care compared to most European countries, often with no proven benefit. In the United States, individuals with chronic illnesses, such as cancer survivors, often experience difficulties affording insurance and maintaining coverage, a problem unknown to EU countries with national health insurance. This article reviews health policy development over time for the United States and EU and the impact for cancer survivors. For the United States, the impact of the Affordable Care Act on improving access to affordable care for cancer survivors is highlighted. For the EU, the importance of multiple-morbidity disease management, cancer plan development, and pan-European data collection for monitoring cancer outcomes is addressed. Given predicted workforce shortages and ever-increasing numbers of aging cancer survivors on both sides of the Atlantic, sharing lessons learned will be critical. ***Cancer*** **2013;119(11 suppl):2187-99.** © *2013 American Cancer Society.*

KEYWORDS: cancer survivorship; Affordable Care Act; Medicaid; uninsured; access to care; insurance mandate; European Union; preventive services; social welfare; chronic illness management.

INTRODUCTION

Unlike major European countries, the United States has never had a national health insurance program. Prior to the 1930s, there was virtually no health insurance in the United States other than limited coverage to replace lost wages due to illness or accident. In the early 1930s, insurance plans were born as individual hospitals as well as groups of hospitals within communities began offering plans. Commercial plans developed independently, but scope of coverage and amounts reimbursed for both types of plans were largely controlled by doctors and hospitals with no limits on amounts charged.[1] Costs slowly began rising and have risen more rapidly than real wages over time in the United States, although many attempts have been made to slow the growth rate. Compared with other countries worldwide, the United States currently ranks second highest at 16.2% (behind Malta at 16.5%) in total health expenditures as a percentage of gross domestic product (GDP), double that of a European country such as Germany at 8.1%.[2]

With such a high percentage of GDP devoted to health care, one might expect that the United States would perform exceedingly well on leading indicators of the health of its people. Unfortunately, there are wide disparities in access to health care services due to the fragmented nature of the US health care system. The US infant mortality rate is 5.98 per 1000 live births (49th when countries are ranked from best to worst) compared with the European Union (EU) as a whole at 4.49 (ranked 33rd) and Germany at 3.51 (ranked 15th). Life expectancy at birth in the United States is 78.5 years, 50th when countries are ranked from best to worst, compared with the EU at 79.8 (ranked 36th) and Germany at 80.2 (ranked 28th).[2]

Corresponding author: Katherine S. Virgo, PhD, MBA, Department of Health Policy and Management, Rollins School of Public Health, Emory University, 1360 Stephens Drive NE, Atlanta, GA 30329; Fax: (404) 965-1556; Email: kvirgo@emory.edu

[1]Health Services Research Program, Intramural Research Department, American Cancer Society, Atlanta, Georgia; [2]Emory University, Atlanta, Georgia; [3]Department of Pediatric Oncology and Hematology, Leeds Teaching Hospital NHS Trust, Leeds, United Kingdom; [4]Office of the Executive Director, European Alliance for Personalized Medicine, Brussels, Belgium; [5]Macmillan Cancer Support and Mount Vernon Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex, United Kingdom; [6]Office of the Chief Medical Officer, American Cancer Society, Atlanta, Georgia.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

The opinions or views expressed in this supplement are those of the authors and do not necessarily reflect the opinions or recommendations of the journal editors, the American Cancer Society, John Wiley & Sons, Inc., or the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari.

DOI: 10.1002/cncr.28066, **Received:** August 1, 2012; **Revised:** November 30, 2012; **Accepted:** December 3, 2012, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

To address inadequacies of the US health care system, comprehensive, sweeping health care reform has been attempted multiple times, beginning with attempts by the administrations of presidents Franklin Delano Roosevelt as part of Social Security in 1935 and Harry Truman in 1945, who attempted to create a post-World War II system similar to the United Kingdom's newly formed National Health Service (NHS).[1-3] The most recent failed health care reform attempt was President William Clinton's Health Security Act in 1993.[4] Strong opposition from such groups as physicians, hospitals, the insurance industry, and the pharmaceutical industry were the primary reason for these failed attempts.

This is not to say that there have not been major triumphs along the way. It is important to remember that health policy changes in the United States have generally taken place very slowly over time and usually in small steps.[5] Very briefly, examples of this incremental approach to policy-making include major pieces of legislation such as the Social Security Amendment of 1965, which established the Medicare and Medicaid programs (providing coverage for the elderly, disabled, and the poor), the Health Insurance Portability and Accountability Act of 1996 (limiting exclusions for preexisting medical conditions when workers change or lose jobs and establishing health privacy standards), and the State Children's Health Insurance Program of 1997 (providing health insurance coverage for children who do not qualify for Medicaid, but cannot afford private insurance; reauthorized in 2009 as CHIP).[7-10] In addition, separate programs of care exist for active and retired military personnel and their families, veterans of foreign wars who have service-connected injuries or qualify for coverage based on a means test, and Native Americans.[11-13] For individuals in need of care, no simple roadmap exists for this fragmented system of entitlement programs and private insurance options to facilitate ease of understanding eligibility and coverage issues as well as navigation. Current estimates indicate that 49.4 million Americans of all ages (16.3%) are uninsured and 29 million (16% of adults 19 to 64 years old) are underinsured.[14,15]

However, on March 23, 2010, the quest for sweeping health care reform, to include an expansion of health care coverage to an increasing number of uninsured individuals, was finally successful with the signing into law of the Affordable Care Act (ACA) by President Barack Obama.[16] There were several challenges to the law with the Supreme Court finally agreeing to hear *Florida v HHS*.[17] However, on June 27, 2012, the constitutionality of ACA was upheld, although the Court ruling does not permit the federal government to withhold current Medicaid funds from states that choose not to participate in the Medicaid expansion.[18]

In the first half of the article, Virgo, Bromberek, and Brawley provide a brief overview of the major implications of ACA for the 13 million cancer survivors in the United States today.[19] More in-depth information regarding these and many other ACA provisions is available at www.acscan.org/healthcare/learn and www.healthcare.gov.[20,21] In the second half of the article, Glaser, Horgan, and Maher provide a review of European policy initiatives in general as well as those that directly affect cancer survivors.

CURRENT AFFORDABLE CARE ACT PROVISIONS

The following critical patient protections are already in place, if not fully at least in part, making insurance coverage more affordable for cancer survivors and increasing access to proven preventive services. Those provisions to be rolled out in future years will be discussed separately.

Coverage for Preexisting Conditions

In an American Cancer Society (ACS) Cancer Action Network poll conducted just after the ACA became law, 16% of households affected by cancer reported that a preexisting condition precluded enrollment in an insurance plan and was the reason for their uninsured status.[22] Separate provisions of ACA address this issue for children under age 19 years and adults. New health plans enrolling patients after September 23, 2010, and covering children can no longer exclude, limit, or deny coverage solely on the basis of health problems, such as cancer, or disabilities developed prior to applying for coverage.

For adults, the preexisting condition issue is addressed in 2 phases. Effective August 1, 2010, adults who had been uninsured for at least 6 months and denied coverage for a preexisting condition such as cancer became eligible for health insurance coverage through temporary high-risk health insurance pools funded entirely by the federal government. Access is generally provided to comprehensive major medical plans that include coverage for services such as prescription drugs, human immunodeficiency virus-related care, and mental health services. Total out-of-pocket costs cannot exceed 35% of the covered benefit cost, exclusive of premiums. Premiums cannot exceed 100% of the federal standard risk rate and cannot vary by age by a ratio of more than 4 to 1. For example, if the premium for a person aged 25 years is $400, then the premium for a person aged 62 years cannot exceed $1600.[21,23] These high-risk health insurance pools,

termed Preexisting Condition Insurance Plans (PCIPs), will be phased out on January 1, 2014, when state health exchanges become available. PCIPs can be run by either the state or federal government, and 23 states chose federal government-run PCIPs. Five billion dollars was set aside to support the program.[21,24]

Rescinding Coverage

Once an individual has enrolled in a health plan, that plan cannot cancel coverage except in cases of fraud. Thus, patients diagnosed with cancer after attaining health coverage will no longer be at risk of losing vital health coverage (effective with health plan years beginning September 23, 2010).

Lifetime and Annual Dollar Limits on Coverage

Cancer survivors also benefit from the new ban on lifetime dollar limits on essential benefits when enrolling in new health plans after September 23, 2010. Essential benefits, to be further defined by the Secretary of Health and Human Services, include ambulatory patient services, emergency services, hospitalization, maternity and newborn care, mental health and substance use services, prescription drug, rehabilitation services, laboratory services, preventive and wellness services, long-term disease management, and pediatric services (including oral and vision care).

In less than 2 years, cancer survivors will benefit from the total ban on annual dollar limits on coverage for essential services which takes effect in January 2014. In the interim, cancer survivors will benefit from provisions in ACA that regulate the value of these limits. The minimum coverage limit was originally set at $750,000 for new plan enrollment during September 23, 2010, through September 23, 2011. The current minimum coverage limit through September 23, 2012, is $1.25 million, after which it will increase to $2 million and remain there until the total ban on limits takes effect on January 1, 2014.[21]

Access to Proven Preventive Services

Access to proven preventive services is vitally important to ensuring early detection and treatment of disease and decreasing mortality. ACA reduces long-standing barriers to the use of preventive services by making such services more affordable. Under ACA, all proven preventive services such as mammograms, colonoscopies, Papanicolaou tests, and pelvic examinations must be offered at no cost (termed first-dollar coverage) to patients enrolled in new insurance plans (after September 23, 2010) seeing in-network providers and individuals enrolled in Medicare.

As of January 1, 2013, states have the option of including in their Medicaid programs an extension of first-dollar coverage for all preventive services with US Preventive Services Task Force (USPSTF) A or B recommendations.[25] (Preventive services recommended by the ACS differ in some circumstances from those recommended by the USPSTF. ACS guidelines are generally more comprehensive and address high-risk populations that the USPSTF often does not.) In return for providing these optional services without cost sharing, states will receive a 1% increase in the Federal Medical Assistance Percentage (the federal government's contribution to covering the costs of providing Medicaid services).[21,24]

The ACA includes $11 billion in increased funding over 5 years for Community Health Centers and the National Health Service Corps, a provision that will assist some of the nation's most vulnerable patients. In 2011, $250 million was made available to support the establishment of 250 new community health centers. These centers provide coordinated primary and preventive services and serve as a "medical home," promoting reductions in health disparities for underserved populations such as low-income individuals, racial and ethnic minorities, and rural communities.[26]

Extending Coverage for Dependent Children to Age 26

Prior to the passage of ACA, once a dependent child with cancer reached the age of 19 years, many insurance policies no longer permitted parents to retain these young adults on their insurance policies. Effective with health plan years beginning September 23, 2010, ACA now allows these young adults to remain on their parents' insurance policy up to age 26, regardless of school enrollment status, marital status, eligibility for coverage at work, level of financial dependence/independence, or whether residing with their parents or not. "Grandfathered" group plans are the only temporary exclusion to this rule, but this exclusion will expire in 2014. Young adults who remain on their parents' insurance policies are entitled to all the same benefit packages made available to similarly situated individuals who did not lose coverage because of cessation of dependent status and cannot be required to pay more for coverage.[27]

This is a vitally important provision for young adults, because they have the highest uninsured rate (31%) of any age group, almost 3 times higher than the uninsured rate for children and almost twice the rate for nonelderly adults aged 30 to 64 years. Young adults have higher uninsured rates than older adults in all work status categories because they tend to work in entry-level or part-time jobs that do not provide health insurance. Given

these high rates of uninsurance, it is not surprising that almost two-thirds of young adults have no usual source of care.[28] For young adult cancer survivors who choose to remain on their parents' insurance policies, ACA thus reduces the barriers to continued access to care for late and long-term effects of cancer as well as surveillance for new disease.

Prescription Drug Coverage for Medicare Beneficiaries

Prescription drug costs continue to be a major issue facing Medicare beneficiaries, even with the availability of Medicare Part D coverage beginning on January 1, 2006, which improved prescription drug accessibility and affordability for seniors. Prior to ACA, annual out-of-pocket costs included $310 in coinsurance as well as a deductible of 25% on up to $2830 in total drug costs. Beneficiaries then entered a coverage gap known as the "donut hole" where beneficiaries incurred 100% of the costs of all drugs up to $6448 in total drug costs. Only after incurring total out-of-pocket costs of approximately $4538 were Medicare beneficiaries eligible for catastrophic coverage, with the government covering all remaining costs in that year. Under ACA, seniors in the donut hole received a $250 rebate in 2010 and a 50% discount on covered brand-name drugs in 2011 and 2012. In 2011, seniors received a 7% discount on generics and a 14% discount on generics in 2012. For 2013 and 2014, seniors will receive a 52.5% discount each year on brand-name drugs and 21% and 28% discounts on generics, respectively.[21,29] The goal for 2020 is that 75% of noncatastrophic prescription drug expenses will be covered for Medicare beneficiaries in the donut hole. In dollar terms, the savings may seem relatively small to some. However, for elderly cancer survivors who are on limited incomes and have high prescription drug expenses, the thousands of dollars per year in out-of-pocket costs saved is critically important.[30]

FUTURE ACA PROVISIONS

All ACA provisions discussed below are scheduled to take effect on January 1, 2014. As with the earlier discussion of provisions that are already under way, highlighted below are those provisions with the greatest impact for patients with cancer.

Clinical Trials Participation

Prior to ACA, few cancer survivors had full coverage for the costs of both routine care and complications arising from participating in a clinical trial beyond those costs already covered by the clinical trial sponsors. A Medicare Coverage Determination in 2001[31] in response to an Institute of Medicine report[32] provided coverage for Medicare beneficiaries. Mandates in 26 states provided varying levels of coverage for individuals enrolled in health plans. Specifically, these mandates did not cover all clinical trials, and employer-sponsored self-insurance plans in these states were exempt from the mandates.[33,34]

Under ACA, all commercial health insurance plans offering group or individual coverage, health plans offered through the Federal Employee Health Benefit Program (FEHBP), employer-sponsored self-insured plans operating under the Employee Retirement Income Security Act (ERISA), and state self-insured plans will be required to pay for routine patient care costs associated with participation in phase 1 to phase 4 clinical trials for life-threatening diseases such as cancer, including those trials conducted out of state.[20] All beneficiaries referred for participation in the trial by an in-network health care professional or who have themselves provided medical information demonstrating that they meet trial eligibility requirements for a life-threatening disease will be eligible for this coverage.[35]

Insurance Exchanges

As described in the introduction, identifying a source of affordable health insurance in the United States can be challenging, particularly if a cancer survivor's employer does not offer insurance and the individual does not qualify for an entitlement program such as Medicare or Medicaid. Under ACA, patients without access to qualified insurance through one of these programs or their employer will have the option of purchasing coverage through state- or region-specific American Health Benefit Exchanges operated by either the state or the federal government. The federal government will operate the exchange if a state chooses not to. The exchanges will provide seamless one-stop shopping with a single application form for coverage determinations. Applicants will be notified whether they qualify for a premium subsidy or are eligible for Medicaid. Plan options will be available online in a standardized format and permit estimation of plan costs.[21,24]

Plans participating in the exchange must cover the essential health benefits package, as discussed previously. Each exchange must offer at least a silver- and gold-level health insurance plan. Silver-level plans cover 70% of the health costs for a standard population covered by the plan (actuarial value), whereas gold-level plans cover 80% of costs. Bronze- and platinum-level plans may also be

offered, covering 60% and 90% of costs, respectively. Premiums increase with actuarial value, and plans with low actuarial values tend to have higher deductible and copayment requirements.[21,24]

As of March 21, 2013, 17 states (California, Washington, Oregon, Nevada, Utah, Idaho, New Mexico, Montana, Colorado, Hawaii, New York, Vermont, Kentucky, Massachusetts, Rhode Island, Connecticut, Maryland) and the District of Columbia had declared intent to establish an exchange.[36] Seven states (New Hampshire, West Virginia, Delaware, Michigan, Iowa, Illinois, and Arkansas) have announced decisions to partner with the federal government to establish an exchange. The remaining 26 states have defaulted to a federally run exchange. Exchange enrollment begins October 1, 2013 with coverage to begin January 1, 2014. It is estimated that 28 million individuals will enroll in the exchanges.[37]

Effective January 1, 2014, each state must also establish a Small Business Health Options Program (SHOP) Exchange for small employers with up to 100 employees. (Until 2016, states can choose to limit participation to employers with 50 or fewer employees.) Typically, many small employers simply cannot afford to offer employee health benefits. The SHOP Exchanges are designed to assist small businesses in enrolling their employees in qualified health insurance plans within the state. After 2017, the SHOP can be expanded to permit participation of businesses with more than 100 employees. The states have the option of operating a single exchange to meet both the American Health Benefit Exchange requirement and the SHOP requirement.[21]

Tax Credits and Reductions in Out-of-Pocket Caps

Although the health exchanges will provide a wider range of plan options for cancer survivors who do not currently qualify for access to an entitlement program, there is still the issue of out-of-pocket costs, such as premiums and deductibles. Under ACA, tax credits will be made available to those with incomes between 100% and 400% of the federal poverty level (FPL), ie, $23,050 to $92,200 for a family of 4,[38] who are not eligible for affordable health insurance coverage. In order for individuals with employer-sponsored coverage to qualify for the tax credits, the annual plan premium must exceed 9.5% of annual income or employer coverage of the premium must be less than 60%. The tax credits will be on a sliding scale ranging from 2% of income for those at 100% FPL to 9.5% of income for those at 300% to 400% FPL.[21] Tax credits equaling up to 50% of total premium cost (35% through 2013) will also be available for small businesses with fewer than 25 full-time equivalent employees, average annual wages of less than $50,000, and coverage of at least 50% of employee health insurance premiums. These credits are meant to encourage the provision of health insurance as a benefit of employment.[21]

To further assist low-income individuals with affording health insurance, the usual out-of-pocket maximums ($5950 for individuals and $11,900 for families in 2011, to be indexed in following years) are reduced by 66% for those with household incomes below 200% of FPL, 50% for those with incomes between 200% and 300% of FPL, and 33% for those with incomes between 300% and 400% of FPL. The usual out-of-pocket maximums pertain to the sum of the annual deductible and other annual out-of-pocket expenses for covered benefits, other than payments for premiums.[21]

Insurance Mandate

Under ACA, cancer survivors who can afford it will be required to buy health insurance or pay a fee to offset the cost of caring for uninsured Americans. Individuals can apply for an exemption based on religious beliefs or low income and the absence of affordable insurance. In addition to the Medicaid expansion to be discussed next, this component of ACA was one of the most fiercely debated and was one of the reasons the Supreme Court was called upon to rule on the constitutionality of the legislation.

The government mandate impacts multiple stakeholder groups in the health care arena (not just the currently uninsured) and was viewed as crucial to the success of the health exchanges. Health exchange plans cannot hope to break even or achieve slim profit margins if only the very sick enroll (adverse selection), particularly within the cost-sharing limits under which they must operate. A balance of healthy and sick individuals is required for the exchange plans to remain viable. The exchange plans must attract employers as well as individuals if they are to succeed. Employers represent large groups of exactly those basically healthy individuals that the exchange plans seek.[24,39] A novel component of the exchanges is the use of risk adjusters to incentivize health plans to enroll higher risk populations. Plans would receive higher levels of reimbursement for enrolling more, versus fewer, high-risk individuals.

Medicaid Expansion

January 1, 2014, will be a momentous date for the uninsured in those states that elect to participate in the expansion. In those states, Medicaid will finally become a

program for all of the poor who are younger than 65 years with incomes below a particular threshold. Specifically, all individuals in participating states who are younger than 65 years, including children, parents, and nonpregnant childless adults, with family incomes up to 138% of the FPL (including 5% asset disregard) will become eligible for Medicaid.[21] Participating states will receive 100% federal funding for 2014 through 2016, decreasing to 90% by 2020.

Prior to the Supreme Court ruling, it was predicted that 10.8 million uninsured individuals would transition to Medicaid.[37] It is unclear now how these estimates will change because it is not yet known which states will participate in the expansion and there is no deadline by which a state must decide whether to undertake expansion. However, it is estimated that most individuals with incomes between 100% and 138% of the FPL in states that decline to expand Medicaid or defer expansion will be eligible for subsidized coverage in the health exchanges.[40] States that choose not to participate in the expansion may still maintain existing federal Medicaid funding, but will receive no new funding intended solely for expansion. The enticement of federal funding has traditionally motivated states to expand Medicaid eligibility in previous years. At least in some states, decisions were on hold for a time while awaiting the results of the fall 2012 elections.[41] Though governors in eight states that were previously opposed to Medicaid expansion have now agreed to expand Medicaid, states such as Ohio, Louisiana, Florida, and Arkansas are attempting to build a case that the federal government should permit the use of federal funds to purchase private insurance for newly eligible Medicaid recipients.

A recent survey of state budget directors was conducted by the US Government Accountability Office[42] to determine which aspects of Medicaid expansion would contribute most to costs. The survey revealed concerns regarding administrative capacity for managing new enrollment, acquisition or modification of information technology systems to support expansion, and enrolling previously eligible but not enrolled individuals in Medicaid.

AMERICAN OPPORTUNITIES

The health care system that cancer survivors must negotiate in the United States has traditionally been a blend of private insurance and entitlement programs, leaving many survivors with little or no access to care. The United States has never had national health insurance to ensure that all citizens have a minimum level of coverage. Such insurance is common in the EU, but is country-specific, and private insurance remains an option for access to newer technologies. Both the EU and the United States recognize that unprecedented health care workforce shortages loom near and have taken steps to begin to address the issue.[43,44]

The availability of a single data source to permit assessment of the impact of health policy changes is also problematic. Each payer (eg, Medicare, Medicaid, the Department of Veterans Affairs, the Department of Defense, private insurance companies) maintains its own database, and linking the various databases together is highly problematic due to the lack of common identifiers. Similar issues impact the various cancer registry databases (Surveillance, Epidemiology, and End Results [SEER]-Medicare linked data, North American Association of Central Cancer Registries, National Cancer Data Base) in addition to a primary focus on the period of initial treatment only. National surveys of the United States population (eg, National Health Interview Survey, Medical Expenditure Panel Survey, National Hospital Discharge Survey) are each very useful for tracking changes in the general population over time, but have been less useful for data on cancer survivors due to the small number of cancer survivors accrued for such surveys and the recurring problem of lack of common identifiers to permit matching across survey databases.[45,46]

Prior to the enactment of ACA in the United States, standard general health indicators seemed to suggest better outcomes at lower cost in the EU compared with the United States,[2] although comparisons of cancer-specific outcomes are less decisive. With major health reform currently underway in the United States, the eventual impact on costs and outcomes of care is difficult to predict, although affordability, access to care, and continuity in access seem destined to improve. The Congressional Budget Office and Joint Committee on Taxation currently suggest that ACA has the potential to reduce the number of nonelderly people without health insurance coverage by 26 million to 30 million in 2016 and subsequent years, leaving 29 million to 30 million nonelderly residents uninsured in those years. The price tag is currently estimated at $1.17 trillion over the period 2012 to 2022.[40]

Because of improvements in early detection and treatment and the aging of the population, the number of cancer survivors in the United States is predicted to increase to 18 million by 2022.[19] It is important that cancer survivors have access to necessary treatment, follow-up, and psychosocial support services at the point in time when the services are needed, not 6 months later when an

insurance plan finally provides approval for care or the survivor's name eventually rises to the top of a waiting list. As the United States moves toward a system where fewer individuals are uninsured, there is the potential to learn from European models of national health insurance in which care is generally provided free of charge, with the exception of newer, more expensive technologies.

EUROPEAN HEALTH POLICY

In Europe, health care is increasingly seen as a key component of social welfare, contributing to social cohesion and social justice. Although the EU has no formal jurisdiction in relation to the delivery of health care, health has been mentioned in every treaty from the EU foundation (where Article 15 of the original EU treaty included "a high level of human health protection shall be ensured in the definition and implementation of all community policies and activities").[47]

The Maastricht treaty of 1991[48] began to define policies in relation to public health and prevention, with more scope for interstate cooperation in relation to health promotion and information systems. The Lisbon treaty of 2009[49] reinforced the importance of health and the need for interstate cooperation for the prevention of illness, food safety and nutrition, population aging, threats to health, new technology, and reduction of inequalities. It emphasized the fundamental right of citizens to be able to access preventive health care and their right to benefit from medical treatments within the context of national legal frameworks.

At the European policy level, the challenge is to agree on pan-European initiatives which add value in addressing the range of multilevel and complex social factors contributing to health across 27 countries with more than 700 million inhabitants, while still respecting the overarching principle of subsidiary that is the primary authority of individual member states. Hence, there are only indirect possibilities for EU policy to influence cancer survivor care.

CANCER, SURVIVORSHIP, AND CHRONIC ILLNESS

The EU estimates a doubling of those over age 65 in the next 50 years, with a cost of 15% to 40% on top of current expenditures just to maintain existing health services.[50] Two in 3 Europeans of retirement age currently have at least 2 chronic conditions, including at least 1 in 3 with a cancer diagnosis. By 2050, it is estimated that the expected increase in spending as a share of GDP could be halved if people lived healthier lives.

Since 2005, there has been more emphasis on quality, rather than length, of life. Healthy Life Years was proposed in 2009 as a key structural indicator.[51] This shift has "direct" relevance for the survivorship agenda and may provide the most appropriate lever to influence EU policy with respect to cancer after-care. Recent cross-sectional studies looking at health indicators in cancer survivors have suggested higher than expected levels of disability, comparable to having a recognized chronic illness. For example, a UK study demonstrated that survivors without either active cancer or any other known long-term condition had the same health and well-being profile as individuals with one known chronic illness, whereas cancer survivors with 1 or 2 other chronic illnesses had the same profile as those with 2 or 3 chronic illnesses, respectively.[52] Treatment related morbidity is increasingly recognized as contributing to reduced "healthy life years," particularly for those treated as children or young people.[53,54] Therefore, early intervention, with rehabilitation and lifestyle change, and appropriate follow-up programs after curative cancer treatment have the potential to increase healthy life years.

HEALTH CARE SYSTEMS

European Union member states broadly agree on underpinning principles of health care (ie, universal access for all citizens, effective care for better outcomes, efficient use of resources, high-quality services, and responsiveness to patient concerns).[55] The institutional arrangements for funding and delivering services differ depending on history, culture, and political experience. In most European countries, treatment is free of charge for the individual patient, with access to novel drugs and new technologies varying. Increasingly, the private insurance market is seen as a gateway for novel, diagnostic, and therapeutic products to enter the health arena earlier.[56] In addition, private providers are developing more sophisticated rehabilitation and home service programs including for cancer survivorship.

European health care delivery systems are broadly divided into those funded through taxation and those operating with some form of universal social health insurance (SHI) where insurance funds are independent of government. Within these frameworks, the balance of state, employer, and private sector involvement in financing, providing, and regulating health services, and providing access to new drugs and technologies varies between countries. By the early 1980s, more than 90% of the EU population had access to health care either through a tax-based scheme (for example, United Kingdom, Denmark, Portugal, Sweden, and Spain) or a social insurance scheme (Belgium, France, Germany, and the Netherlands). However,

most countries also had some form of cost sharing with copayments for some medicines and services.

A SHIFT TOWARD CHRONIC ILLNESS MANAGEMENT?

The majority of health systems are still focused on providing specific interventions to treat acute episodes of single illnesses rather than the prevention and management of today's more intractable chronic illness and multiple comorbidities. Acute sector usage is recognized as too high, and a potential solution is more focus on prevention and management by primary care with more ambulatory care services replacing inpatient care. However, the potential disadvantages of a strong primary care gate-keeping service have also been highlighted in the EuroCare studies, suggesting low 1-year survival rates (a surrogate for late diagnosis) in 2 countries with particularly well-developed primary care gatekeeper services (England and Denmark). Nevertheless, there has been a clear shift to primary care-led health care and more robust commissioning of services (eg, in England). After 10 years of single condition-based frameworks, there is now a push for more focus on chronic illness and multiple-morbidity management and a move toward more integration of state funding of health and social care.[57]

THE CHALLENGES OF PAN-EUROPEAN DATA COLLECTION

A shared approach to data collection is recognized as key to making meaningful links between cancer outcomes and policy initiatives. Collection of pan-European data remains a particular challenge, amplified by the requirements to preserve the privacy of personal medical records and the lack of electronic health records in many European countries. The establishment of the European Cancer Registry Network in 1989[58] set an important precedent, enabling explicit "benchmarking" in relation to survival after a cancer diagnosis. Benchmarking has been a stimulus to policy in several countries despite the acknowledged differences in coverage. For example, in the United Kingdom and Norway, coverage is nearly 100%, with unique identifiers allowing follow-up for many years, whereas in other European countries coverage may be significantly less with no option for long-term follow-up. By 2008, 24 of 30 European countries reviewed had registries with 100% coverage (Table 1).[59] The exceptions were Greece and Luxembourg with no population registry, France, Italy, and Spain (less than 50% coverage), and Switzerland (62% coverage). The relatively poor UK cancer survival results in the first EuroCare report[60] were a major driver for the UK National Cancer Plan in 2000, which led to the Cancer Reform Strategy in 2007 and eventually to the National Cancer Survivorship Initiative in 2010,[54,61,62] as thinking about cancer outcomes became more sophisticated.

TABLE 1. Coverage of European Cancer Registries

Country	National Coverage (% Population Covered)	No. of Registries	Population (Inhabitants)
Austria	Yes	5	8,298,923
Belgium	Yes	1	10,584,534
Bulgaria	Yes	1	7,679,290
Cyprus	Yes	1	778,700
Czech Republic	Yes	1	10,287,189
Denmark	Yes	1	5,447,084
Estonia	Yes	1	1,342,409
Finland	Yes	1	5,276,955
France	No (13.7)	11	64,057,790
Germany	Yes	16	82,314,906
Greece	No (0.0)	-	-
Hungary	Yes	1	10,076,581
Ireland	Yes	1	4,239,848
Italy	No (36.4)	26	20,722,341
Latvia	Yes	1	2,281,305
Lithuania	Yes	1	3,384,879
Luxembourg	No (0.0)	-	-
Malta	Yes	1	404,039
Netherlands	Yes	9	16,357,992
Poland	Yes	1	38,115,967
Portugal	Yes	4	10,599,095
Romania	Yes	8	22,408,364
Slovakia	Yes	1	5,391,194
Slovenia	Yes	1	2,019,406
Spain	No (26.5)	14	11,847,964
Sweden	Yes	1	9,113,257
United Kingdom	Yes	11	60,209,500
Iceland	Yes	1	312,872
Norway	Yes	1	4,681,411
Switzerland	No (6.7)	10	4,633,666

Source: Bastos et al.[59]

The European Partnership for Action against Cancer (EPAAC) in 2009[63] supported the recognized need to develop a common platform to unify cancer burden indicators (incidence, mortality, survival, and prevalence) collected by different countries. Funding from the EU 7th Framework Program (FP7) has enabled extension of registry coverage, establishment of a receipt portal and considerable work on harmonizing the legal and ethical framework in which the registries operate.[64] The European Registry Network remains without substantial permanent funding or existence as a legal entity. Several registries are concerned about the impact of EU privacy legislation which could require informed consent or anonymity, reducing the ability to follow individuals over time using unique identifiers, which is the bedrock of early intervention linkages (eg, effective rehabilitation for cancer recurrence or therapy-related illness in the years following treatment).

THE ROLE OF THE PRIVATE SECTOR IN EUROPE

Since the peak of public financing in the late 1970s, there has been a trend for a higher involvement of the private sector in a number of European countries, particularly for inpatient care. Between 1970 and 1979, public financing as a percentage of the total health budget grew across Europe. After 1979, private sector involvement in insurance rose, particularly in the Southern European countries where there had not been such an expansion of state funding in the 1970s. Numbers of publicly funded beds began to fall across the EU while the number of privately funded beds remained stable. Different countries have taken different approaches to the issue of cost containment in recent years: Germany and the United Kingdom have increased the gate-keeping primary care model, introduced health-related groups, and applied rigorous health technology assessment. Approximately 8% (84 million citizens) have private health insurance replacing, or in addition to, publicly funded insurance, with a wide range across member states from 12% in the United Kingdom to 90% in France.

EUROPEAN INITIATIVES AND CANCER PLANS

A range of strategies for cancer control were discussed in Lisbon in 2003 during the Portuguese presidency, including cancer plans, population-based registries and screening programs for breast, cervical and colorectal cancer.[65] A major European policy landmark was the publication of "Communication on Action against Cancer: European Partnership" by the European Commission in 2009, which highlighted the need for stronger European collaboration to improve outcomes and reduce inequalities.[66] Similarly, the EPAAC in 2009 had the aim of developing a common platform to unify cancer burden indicators (incidence, mortality, survival, and prevalence) collected by different sources.

Importantly, the European Commission urged member states to publish individual cancer plans by 2013 (www.epaac.eu/national-cancer-plans). Although most of these plans deal largely with prevention, diagnosis, and treatment of cancer, some have an explicit focus on survivorship and/or palliative care including rehabilitation (5 plans), care plans (3 plans) or follow-up care reform (4 plans). Atun et al[67] identified 19 European cancer control programs in 2008 and reviewed them in terms of priorities, aims and objectives, actions, resourcing, quality control, time frames, and institutional support. They found that in general situational analysis, objectives and actions were well articulated but resourcing and governance less so. Only 4 countries had both identified resources and stipulated how they were was to be used.

Bastos et al[59] reviewed cancer control programs in Europe in 2008 in 27 European countries plus Iceland, Norway, and Switzerland in 2008. Nine and 7 countries, respectively, had 100% population coverage of breast and cervical cancer screening with participation ranging from 26% to 87%. Notably, 8 countries had no screening programs for either cancer, whereas 6 countries had colorectal cancer screening programs. By 2008, 5 countries had complete bans on smoking in public places and further progress has been made in all these areas since 2008.

There has been steady improvement in survival for several cancers across the EU, but wide variation between countries remains. Some early aims to cut smoking from 28% to 20% in 5 years (eg, in the Netherlands) have proved overambitious, but a number of individual countries have seen cancer plan successes. For example in the United Kingdom, there have been significant reductions in waiting times, reviews by multidisciplinary teams, and improved patient experience.[68]

Which European Health System Delivers the Best Outcomes?

Views regarding which European system delivers the best outcome depend on the perspective of those asking the question. The European Consumer Index 2012,[69] looking through the lens of the consumer, distinguishes "Bismarckian systems" based on social insurance involving a multitude of insurance providers organizationally independent of health care providers (eg, the Netherlands) from "Beveridge systems" where financing and provision is provided by one organization (for example, the UK NHS or the Nordic countries). Countries are judged from the perspective of the consumer in 5 key areas (patient rights and information, accessibility, health outcomes, range and reach of health prevention, and access to pharmaceuticals). Using this scoring system, the Netherlands tops the league table. This is attributed to service provision through a multitude of health insurance providers acting in competition, but separated from health care providers, together with the best and most structured arrangements for patient organization and participation in health care policy-making (Table 2). However, in relation to health outcomes alone (myocardial infarction fatalities, infant deaths, cancer deaths, preventable years of lives lost, methicillin-resistant S. aureus infection, Caesarian section rates, undiagnosed diabetes, and depression), Sweden and Norway come out top across all outcome

TABLE 2. Outcomes for European Countries (European Consumer Index Score)

Country	Issue						
	Patient Rights and Information	Accessibility	Outcomes	Prevention/Range and Reach of Services Provided	Pharmaceuticals	Total Score	Rank
Albania	101	217	113	70	33	535	29
Austria	141	217	188	111	81	737	11
Belgium	117	233	213	140	81	783	5
Bulgaria	88	133	138	64	33	456	33
Croatia	146	133	200	128	48	655	17
Cyprus	112	183	188	88	57	627	20
Czech Republic	107	183	225	117	62	694	15
Denmark	175	167	250	140	90	822	2
Estonia	141	167	175	123	48	653	18
Finland	131	133	250	152	86	752	10
France	136	167	238	140	86	766	8
FYR Macedonia	112	183	113	82	38	527	30
Germany	117	200	200	111	76	704	14
Greece	88	200	175	88	67	617	22
Hungary	122	167	138	99	52	577	28
Iceland	146	183	263	146	62	799	3
Ireland	107	150	238	134	86	714	13
Italy	131	133	213	93	52	623	21
Latvia	107	117	138	88	43	491	31
Lithuania	131	183	138	99	33	585	26
Luxembourg	112	233	250	134	62	791	4
Malta	88	183	163	128	48	609	26
Netherlands	170	200	263	163	76	872	1
Norway	160	83	300	146	67	756	9
Poland	126	117	188	99	48	577	27
Portugal	126	117	163	117	67	589	25
Romania	88	167	100	88	48	489	32
Serbia	102	117	113	82	38	451	32
Slovakia	122	200	118	99	67	675	16
Slovenia	112	133	213	99	81	638	19
Spain	102	100	213	117	71	606	24
Sweden	141	100	300	158	76	775	6
Switzerland	126	233	213	111	86	769	7
United Kingdom	160	133	200	146	81	721	12

Source: European Consumer Index Report 2012.[69]

indicators and these are *Beveridge* health economies. Similarly, when the *Commonwealth Fund Report* looked at slightly different outcomes (quality of care, access, efficiency, length of productive life, health expenditure per capita) for 7 countries (Australia, Canada, Germany, the Netherlands, New Zealand, United Kingdom, and United States), the Netherlands came out on top, followed closely by the United Kingdom and Australia.[70] There was no clear trade-off between spending and outcomes. The most expensive service (United States) had poor outcomes in relation to a number of domains.

EUROPEAN OPPORTUNITIES

Within the EU, the notion of meeting the needs of an increasing number of cancer survivors is usually framed in terms of the added demands and pressures which result from an aging population with increased unmet health needs. Within this context, there are real opportunities to promote a cancer survivorship agenda. Important pan-European initiatives included in the Innovation Union,[71] such as the European Innovation Partnership on Active and Healthy Ageing[72] have the potential to be coordinated with the cancer survivorship agenda, with a reorientation of existing prevention activities around a survivorship population. European Year 2012 on Ageing and Solidarity between Generations[73] aims to add 2 years of life in good health by 2020 with increasing focus on the importance of chronic illness, integrated care, patient empowerment, distance monitoring, and e-health. As with all such European initiatives, less importance is placed on whether particular targets are reached. More emphasis is placed on the commitment of countries to work together to identify common problems related to a range of solutions based on good practice, without changing the primary responsibility of member states, which is to provide for the health of their citizens.

Cancer survivorship has not been prominent in the chronic illness discourse; yet the financial implications of cancer diagnosis, treatment, recovery, and monitoring are beginning to appear in European health discussions. The exciting and genuine opportunity is that transformed cancer aftercare pathways may support a reduction in subsequent chronic illness and number of disabled years before death (with an increase in quality adjusted life years). This may be the lever to influence European nations to invest and support integrated holistic support for the increasingly prevalent population living with and beyond cancer.

DISCUSSION

The cost of caring for an increasing number of aging cancer survivors is an area of concern for both the United States and the EU. Particularly in the United States where rising health care costs are outpacing real wages, many question whether the money is well spent. Cancer represents the leading cause of death for developed countries.[74] One recent study suggests that, in the case of cancer, higher health spending is worth it. Philipson et al[75] estimated in the aggregate that US survival gains have a value of $61,000 per cancer survivor on average, with the largest gains seen for prostate and breast cancer where new technologies were more rapidly approved for use in the United States than in the EU. Although such results are promising, the study did not specifically focus on the cost-effectiveness of specific tests or treatments; thus, it is unclear which tests or treatments were primarily responsible for the gains in survival. Much additional research remains to be done. In the interim, devoting more than 16% of GDP to health care spending while almost 50 million Americans are uninsured and almost 30 million are underinsured is not sustainable in the United States. Although ACA represents a major step for the United States, much more work is needed to bring health care spending under control. Because both the European Union and the United States struggle with looming health care workforce shortages and increasing demands for care, learning from history and from each other will be critical.

FUNDING SOURCES

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center and Health Services Research Program.

CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

REFERENCES

1. Hoffman C. National health insurance—A brief history of reform efforts in the U.S. Kaiser Family Foundation publication #7871. March 2009. http://www.kff.org/healthreform/upload/7871.pdf. Accessed June 30, 2012.
2. Central Intelligence Agency. World Factbook. Country Comparison: Health Expenditures. https://www.cia.gov/library/publications/the-world-factbook/rankorder/2225rank.html. Accessed June 30, 2012.
3. Califano JA Jr. America's Health Care Revolution: Who Lives? Who Dies? Who Pays? New York, NY: Random House; 1986:36-57.
4. Starr P. What happened to health care reform? *The American Prospect*. Winter 1995;(20):20-31. http://www.princeton.edu/~starr/20starr.html. Accessed June 30, 2012.
5. Brawley OW, Virgo KS. From the guest editors: introduction for the impact of health care reform on cancer patients. *Cancer J*. 2010;16:551-553.
6. Social Security Amendments of 1965, Public Law 89-97, (79 US Statute 286). Transitional Provision on Eligibility of Presently Uninsured Individuals for Hospital Insurance Benefits. Approved July 30, 1965. http://www.socialsecurity.gov/OP_Home/comp2/F089-097.html. Accessed June 30, 2012.
7. Klees BS, Wolfe CJ, Curtis CA. Brief summaries of Medicare and Medicaid: Title XVIII and Title XIX of the Social Security Act as of November 1, 2011. http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareProgramRatesStats/Downloads/MedicareMedicaidSummaries2011.pdf. Accessed June 30, 2012.
8. Health Insurance Portability and Accountability Act of 1996, Public Law 104-191 (110 US Statute 1936). Approved August 21, 1996. http://www.gpo.gov/fdsys/pkg/PLAW-104publ191/html/PLAW-104publ191.htm. Accessed June 30, 2012.
9. US Department of Labor. Fact Sheet: Health Insurance Accountability and Portability Act of 1996. http://www.dol.gov/ebsa/newsroom/fshipaa.html. Accessed June 30, 2012.
10. Lambrew JM. The State Children's Health Insurance Program: Past, Present, and Future. The Commonwealth Commission on a High Performance Health System. January 2007. http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/2007/Feb/The%20State%20Childrens%20Health%20Insurance%20Program%20%20Past%20%20Present%20%20and%20Future/991_Lambrew_SCHIP_past_present_future%20pdf.pdf. Accessed June 30, 2012.
11. Department of Veterans Affairs. VA history in brief. http://www.va.gov/opa/publications/archives/docs/history_in_brief.pdf. Accessed June 30, 2012.
12. Department of Defense. Military Health System History. http://www.health.mil/About_MHS/History.aspx. Accessed June 30, 2012.
13. Indian Health Service. Fact sheets: Basis for health services. January 2012. http://www.ihs.gov/PublicAffairs/IHSBrochure/BasisHlthSvcs.asp. Accessed June 30, 2012.
14. DeNavas-Walt C, Proctor BD, Smith JC. U.S. Census Bureau Current Population Reports, P60-239, Income, Poverty, and Health Insurance Coverage in the United States: 2010. Washington, DC: US Government Printing Office; 2011. http://www.census.gov/prod/2011pubs/p60-239.pdf. Accessed June 30, 2012.
15. Schoen C, Doty MM, Robertson RH, Collins SR. Affordable Care Act reforms could reduce the number of underinsured U.S. adults by 70 percent. *Health Aff (Millwood)*. 2011;30:1762-1771.
16. Compilation of Patient Protection and Affordable Care Act of 2010 (Public Law 111-148) as amended through May 1, 2010 including health-related portions of the Health Care and Education Reconciliation Act of 2010 (Public Law 111-152). Prepared by the Office of the Legislative Counsel for the use of the U.S. House of Representatives. http://housedocs.house.gov/energycommerce/ppacacon.pdf. Accessed June 30, 2012.
17. Goldman TR. Health reform gets its day in court—the Supreme one. *Health Aff (Millwood)*. 2012;31:8-11.

18. The White House, Office of the Press Secretary. Remarks by the President on Supreme Court Ruling on the Affordable Care Act, June 28, 2012. http://www.whitehouse.gov/the-press-office/2012/06/28/remarks-president-supreme-court-ruling-affordable-care-act. Accessed June 30, 2012.
19. American Cancer Society. Cancer Treatment and Survivorship Facts & Figures 2012-2013. Atlanta, GA: American Cancer Society; 2012.
20. American Cancer Society Cancer Action Network. Affordable Care Act—Background Information, Policy Documents, Factsheets & Reports. http://www.acscan.org/healthcare/learn/. Accessed June 30, 2012.
21. US Department of Health and Human Services. Key features of the Affordable Care Act by year. http://www.healthcare.gov/law/timeline/full.html. Accessed June 30, 2012.
22. American Cancer Society Cancer Action Network. A National Poll: Facing Cancer in the Health Care System. Atlanta, GA: American Cancer Society; 2010.
23. Newsom M. Temporary federal high risk health insurance pool program. Congressional Research Service, July 28, 2010. http://www.nahu.org/legislative/resources/Temporary%20Federal%20High.pdf. Accessed June 30, 2012.
24. Virgo KS, Burkhardt EA, Cokkinides VE, Ward EM. Impact of health care reform legislation on uninsured and Medicaid-insured cancer patients. *Cancer J*. 2010;16:577-583.
25. US Preventive Services Task Force. USPSTF A and B Recommendations. Published July 2010. http://www.uspreventiveservicestaskforce.org/uspstf/uspsabrecs.htm. Accessed June 30, 2012.
26. Collins LG, Wender R, Altshuler M. An opportunity for coordinated cancer care: Intersection of health care reform, primary care providers, and cancer patients. *Cancer J*. 2010;16:593-599.
27. Bleyer WA. Potential favorable impact of the Affordable Care Act of 2010 on cancer in young adults in the United States. *Cancer J*. 2010;16:563-571.
28. Schwartz K, Schwartz T. Uninsured young adults: A profile and overview of coverage options. Kaiser Commission on Medicaid and the Uninsured. http://www.kff.org/uninsured/7785.cfm. June 2008.
29. Hoadley J, Summer L, Hargrave E, Cubanski J, Newman T. Medicare Part D 2011: The coverage gap. Kaiser Family Foundation. September 2011. http://www.kff.org/medicare/upload/8222.pdf. Accessed June 30, 2012.
30. Thorpe KE, Philyaw M. Impact of health care reform on Medicare and dual Medicare-Medicaid beneficiaries. *Cancer J*. 2010;16:584-587.
31. US Department of Health and Human Services. Medicare coverage database. http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=310.1&ncd_version=1&basket=ncd%3A310%2E1%3A1%3ARoutine+Costs+in+Clinical+Trials\. Accessed June 30, 2012.
32. Gelband H; prepared for the National Cancer Policy Board. A Report on the Sponsors of Cancer Treatment Clinical Trials and Their Approval and Monitoring Mechanisms. Washington, DC: Institute of Medicine, National Research Council; 1999. http://www.nap.edu/readingroom/books/sponcan/. Accessed June 30, 2012
33. Taylor PL. State payer mandates to cover care in US oncology trials: do science and ethics matter? *J Natl Cancer Inst*. 2010;102:376-399.
34. Edge SB, Zwelling LA, Hohn DC. The anticipated and unintended consequences of the Patient Protection and Affordable Care Act on cancer research. *Cancer J*. 2010;16:606-613.
35. Schwartz K, Claxton G. The Patient Protection and Affordable Care Act: how will it affect private health insurance for cancer patients? *Cancer J*. 2010;16:572-576.
36. Kaiser Family Foundation. State action toward creating health exchanges as of March 21, 2013. http://www.statehealthfacts.org/comparemaptable.jsp?ind=962&cat=17. Accessed March 24, 2013.
37. Eibner C, Price CC. The effect of the Affordable Care Act on enrollment and premiums, with and without the individual mandate. Rand Health Technical Report #TR-1221-CMF. http://www.rand.org/pubs/technical_reports/TR1221.html. Accessed June 30, 2012.
38. US Department of Health and Human Services. 2012 HHS poverty guidelines. http://aspe.hhs.gov/poverty/12poverty.shtml. Accessed June 30, 2012.
39. Jost TS. Health insurance exchanges and the Affordable Care Act: eight difficult issues. The Commonwealth Fund, September 2010. http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/2010/Sep/1444_Jost_hlt_ins_exchanges_ACA_eight_difficult_issues_v2.pdf. Accessed June 30, 2012.
40. Congressional Budget Office. Estimates for the insurance coverage provisions of the Affordable Care Act updated for the recent Supreme Court decision. July 2012. http://cbo.gov/sites/default/files/cbofiles/attachments/43472-07-24-2012-CoverageEstimates.pdf. Accessed July 25, 2012.
41. Pear R, Cooper M. Reluctance in some states over Medicaid expansion. New York Times. June 29, 2012:A1.
42. Czerwinski SJ, Yocom CL. United States Government Accountability Office Report to the Ranking Member, Committee on the Judiciary, U.S. Senate. Medicaid Expansion: States' Implementation of the Patient Protection and Affordable Care Act, August 2012, GAO-12-821.
43. Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract*. 2007;3:79-86.
44. Villanueva T. Europe develops action plan to address health workforce shortfall. *CMAJ*. 2010;182:E825-E826.
45. Wingo PA, Howe HL, Thun MJ, et al. A national framework for cancer surveillance in the United States. *Cancer Causes Control* 2005;16:151-170.
46. Lerro CC, Stein KD, Smith T, Virgo KS. A systematic review of large-scale surveys of cancer survivors conducted in North America 2000-2011. *J Cancer Surviv* 2012;6:115-145.
47. Treaty establishing the European Community (Nice consolidated version). Part Three: Community policies, Title XIII: Public health, Article 152, Article 129-EC Treaty (Maastricht consolidated version), Article 129-EEC Treaty; 2002. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12002E152:EN:NOT
48. The history of the European Union: The European citizenship. The Treaty of Maastricht (1992). http://www.historiasiglo20.org/europe/maastricht.htm. Accessed July 12, 2012.
49. Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community, 2007. http://europa.eu/lisbon_treaty/full_text/index_en.htm. Accessed July 12, 2012.
50. European Commission Directorate-General for Economic and Financial Affairs. The 2012 Ageing Report: Economic and budgetary projections for the EU27 Member States (2010-2060). Brussels, Belgium: European Commission. May 2, 2012. http://ec.europa.eu/economy_finance/publications/european_economy/2012/pdf/ee-2012-2_en.pdf. Accessed July 12, 2012.
51. Robine JM, Jagger C. The rationale for healthy life years as a structural indicator for the European Commission. Brussels, Belgium: European Commission; 2005. http://ec.europa.eu/health/ph_information/implement/wp/indicators/docs/ev_20050125_rd01_en.pdf. Accessed July 12, 2012.
52. Elliott J, Fallows A, Staetsky L, Smith PWF, Foster CL, Maher EJ, et al. The health and well-being of cancer survivors in the UK: findings from a population-based survey. *Br J Cancer*. 2011;105(suppl 1):S11-S20.
53. NHS Improvement. Children and young people living with and beyond cancer. Designing and implementing pathways to benefit patient aftercare: continuing to build the evidence. London, UK: NHS; 2011.
54. Macmillan Cancer Support DoH. The National Cancer Survivorship Initiative Vision. London, UK: NHS; 2010.
55. Organisation for Economic Co-operation and Development. Health at a glance 2011: OECD indicators. Paris, France: OECD; 2011.
56. The Economist. Squeezing out the doctor: the role of physicians at the centre of health care is under pressure. *The Economist*. June 2, 2012. http://www.economist.com/node/21556227
57. United Kingdom. Health and Social Care Act 2012. Chapter 7. London, UK: 2012.
58. Registries ENoC. European Network of Cancer Registries 2012. http://www.encr.com.fr/. Accessed July 11, 2012.
59. Bastos J, Peleteiro B, Gouveia J, Coleman MP, Lunet N. The state of the art of cancer control in 30 European countries in 2008. *Int J Cancer*. 2010;126:2700-2715.
60. Berrino F, Sant M, Verdecchia V, Capocaccia R, Hakulinen T, Estéve J. Survival of cancer patients in Europe: the EUROCARE Study. Lyon, France: IARC; 1995.

61. UK Department of Health. The NHS Cancer Plan: a plan for investment, a plan for reform. London, UK: 2000. http://www.thh.nhs.uk/documents/_Departments/Cancer/NHSCancerPlan.pdf. Accessed July 12, 2012.
62. UK Department of Health. Cancer Reform Strategy. London, UK: NHS; 2007.
63. Cancer EPfAA. European Partnership for Action Against Cancer 2012. http://www.epaac.eu/. Accessed July 12, 2012.
64. European Network of Cancer Registries. European Network of Cancer Registries. 2012. http://www.encr.com.fr/. Accessed July 12, 2012.
65. Gouveia J, Coleman MP, Haward R, et al. Improving cancer control in the European Union: conclusions from the Lisbon round-table discussion under the Portuguese presidency, 2007. *Eur J Cancer*. 2008;44:1457-1462.
66. European Commission. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions of 24 June 2009 on Action against Cancer: European Partnership. Brussels, Belgium: European Commission; 2009.
67. Atun R, Ogawa T, Martin-Moreno JM. Analysis of National Cancer Control Programmes in Europe. London, UK: Imperial College London Business School; 2008. https://spiral.imperial.ac.uk/bitstream/10044/1/4204/1/Cancer%20Control%20vf2.pdf. Accessed October 25, 2012.
68. Rosen R, Smith A, Harrison A. Future trends and challenges for cancer services in England: a review of literature and policy. Kings Fund, Cancer Research UK: 2006. http://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/future-trends-challenges-cancer-services-england-review-of-literature-policy-rebecca-rosen-alex-smith-tony-harrison-kings-fund-24-august-2006.pdf. Accessed October 25, 2012.
69. Björnberg A. Euro Health Consumer Index 2012 Report. Health Consumer Powerhouse, 2012. http://www.healthpowerhouse.com/files/Report-EHCI-2012.pdf. Accessed October 25, 2012.
70. Davis K, Schoen C, Stremikis K. Mirror, Mirror on the Wall: How the Performance of the U.S. Health Care System Compares Internationally, 2010 Update. Commonwealth Fund, June 2010. http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/2010/Jun/1400_Davis_Mirror_Mirror_on_the_wall_2010.pdf
71. European Commission. Innovation Union: A Europe 2020 Initiative. Brussels, Belgium: European Commission; 2012. http://ec.europa.eu/research/innovation-union/index_en.cfm. Accessed July 10, 2012.
72. European Commission. European Innovation Partnership on Active and Healthy Ageing. Brussels, Belgium: European Commission; 2012. http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing. Accessed July 10, 2012.
73. European Commission. European Year for Active Ageing and Solidarity between Generations. Brussels, Belgium: European Commission; 2012. http://europa.eu/ey2012/. Accessed July 10, 2012.
74. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva, Switzerland: WHO; 2008.
75. Philipson T, Eber M, Lakdawalla DN, Corral M, Conti R, Goldman DP. An analysis of whether higher health care spending in the United States versus Europe is 'worth it' in the case of cancer. *Health Aff (Millwood)*. 2012;31:667-675.

Afterword

The Role of Comprehensive Cancer Centers in Survivorship Care

Wim H. Van Harten, MD, PhD[1]; Angelo Paradiso, MD, PhD[2]; and Michelle M. Le Beau, PhD[3]

Considering that survival trends in most tumors are rapidly increasing and may nearly double by 2025,[1] establishing the needs of cancer survivors and survivor groups, including designing appropriate and effective programs and organizing them in an efficient and cost-effective way, is a vital goal. In this supplement, several aspects of survivorship care have been discussed by European and American experts, paying specific attention to medical and social problems such as the long-term toxic effects of cancer treatments, the education of stakeholders, rehabilitation programs, and employment challenges. These experts have shown the emergence of a complex scenario with multifaceted aspects, which will require an integrated and multidisciplinary approach to care and research.[2] Thus, there is a need to identify those services that are required by each survivor, and to determine when these services are most effective. Furthermore, as oncologists, we have to determine which survivors need our time and attention for extended periods, and which are best cared for by their primary care physicians.

These questions represent an open area for research in which new primary treatments, the biology of the tumor, and the characteristics of the host are each thoroughly investigated. Such studies, which hopefully will lead to personalized patient-centered approaches to care, require knowledge of a complex clinical or biological picture. In conclusion, both from the viewpoint of patient empowerment and cost-effectiveness, developing more appropriate care programs for cancer survivors on a case-by-case basis appears to be very fitting.

Although only a minority of cancer patients are treated at comprehensive cancer centers (CCCs), these centers can play a crucial role in this emerging field because of their strength in translational research, and because the full spectrum of treatments is available for patients throughout their clinical course, from the point of diagnosis through long-term survivorship. Furthermore, CCCs can play a key role in research and treatment development based on their strong tradition of providing curative and palliative oncology care and their insights into the various patient subsets and their respective problems; such specialized knowledge should be combined with expertise from the rehabilitation field.

CCCs represent a unique structure in which underestimated issues of cancer survivors could be evaluated and addressed. For example, specific programs focusing on fertility preservation and sexuality for cancer survivors have been initiated in several CCCs (eg, mskcc.org/cancer-care/survivorship and hopkinsmedicine.org/kimmel_ cancer_center/centers/cancer_survivorship).

From a policy perspective, both the Association of American Cancer Institutes (AACI),[3] with its cluster of 95 of the premier academic and free-standing cancer research centers in the United States, and its European counterpart, the

Corresponding author: Wim Van Harten, MD, PhD, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121 1066 CX Amsterdam, the Netherlands; Fax: (011) 31 20 5121944; w.v.harten@nki.nl

[1]Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands; President, Organization of European Cancer Institutes, Brussels, Belgium; [2]National Cancer Research Centre, Giovanni Paolo II Cancer Institute, Bari, Italy; Chairman of Education and Training, Organization of European Cancer Institutes, Brussels, Belgium; [3]Section of Hematology and Oncology and the Comprehensive Cancer Center, University of Chicago, Chicago, Illinois; President, Association of American Cancer Institutes, Pittsburgh, Pennsylvania.

European-American Dialogues on Cancer Survivorship: Current Perspectives and Emerging Issues

This supplement was guest edited by Vittorio Mattioli, MD (NCRC, Bari, Italy) and Kevin Stein, PhD (American Cancer Society, Atlanta, Georgia) and was produced with the authoritative contribution of 58 authors from the European Union and the United States. The primary aims are to highlight the potential differences between European and American approaches to cancer survivors' issues, increase coordination among oncologists and other primary care providers, and aid the development of a shared care model that can improve the quality of cancer care.

DOI: 10.1002/cncr.28054, **Received:** January 25, 2013; **Accepted:** January 31, 2013, **Published online** May 20, 2013 in Wiley Online Library (wileyonlinelibrary.com)

Organization of European Cancer Institutes (OECI),[4] which is composed of a network of more than 71 European cancer institutes, face challenges in which CCCs can play an important role. Establishing a treatment infrastructure in survivorship care and cancer rehabilitation would also provide a setting in which new treatment programs can be tested and proper research conducted.

But what is the actual need for rehabilitation per subgroup characteristics? How can we develop cost-effective treatments as part of the treatment pathway? What is the best design of services? How can we serve patients who live a long way from the treatment center? Can patients be empowered to assume the management of their own situation?

The organizations of CCCs in Europe (OECI) and the United States (AACI) have an opportunity to share expertise to address these issues. At the beginning of the third millennium, few cancer centers provided comprehensive services for survivors across all age groups. In some of these CCCs, the model of the survivorship clinic has now been explored, mainly aimed at addressing the long-lasting or late-onset effects of cancer therapy. Although several well-established programs for cancer survivors currently are available in CCCs, many are still evolving.

Is there room for the further improvement of CCCs in the cancer survivorship area? Without a doubt. Developing solutions for many of the remaining questions will require collaborative efforts, such as the promotion of large trials, clinicobiological studies, and longitudinal approaches. Clearly, these are expensive and time-consuming, and call for collaborative projects at the international level. In this regard, the European Research Framework Cooperation Work Programme for Health 2013 is specifically looking for collaborative, investigator-driven projects aimed at improving the quality of life of cancer survivors (cordis.europa.eu/fp7/health/). Similarly, the US National Institutes of Health recently announced funding opportunities for specific interventions among cancer survivors (grants.nih.gov/grants/guide/PAR-12-229). They represent compelling opportunities to plan and conduct multicenter trials with the potential to involve CCCs from both Europe and the United States. Another interesting aspect is represented by bioethics. Ethics committees supporting CCCs were previously concerned with end-of-life matters but, with the growth of survivorship initiatives, they are now expanding their purview to consider the totality of cancer care.

The priorities in research and development in this field, especially for CCCs, are:

- Understanding the biological mechanisms that lead to impairments in specific survivor or cancer patient subgroups. The strong interaction between various partners in translational research is essential for this.
- The identification of survivor subgroups most in need, and the design of appropriate general, disease-related, and symptom-specific care programs. Large patient groups are needed for this.
- Developing easily accessible case-by-case care approaches that fit into survivorship care planning and can be adapted for diffusion throughout the health care system. The geographical leadership role in developing cancer care by CCCs positions them well for this role.

The unique and multidisciplinary perspective of a CCC regarding the "survivorship problem" focuses on its complexity, and identifies key issues for further research. However, it remains an important social problem and there is a need to incentivize survivorship care planning. The ongoing attempt in the United States to reintroduce the Comprehensive Cancer Care Improvement Act of 2012, which will provide Medicare reimbursement for complete survivorship care plans,[5] is an example of how this goal is being pursued.

FUNDING SUPPORT

This supplement was sponsored by the National Cancer Research Centre Istituto Tumori "Giovanni Paolo II" Bari (Italy) through the Italian Ministry of Health-funded research project "Multidimensional assessment of long-term cancer survivors including discovery of genetic bases of susceptibility, depressive stage, prevention of affective disorders," and through intramural funding of the American Cancer Society's Behavioral Research Center.

Co-sponsored by Organization of European Cancer Institutes (OECI) and the Association of American Cancer Institutes (AACI).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1996-2005.
2. Elena JW, Travis LB, Simonds NI, et al. Leveraging epidemiology and clinical studies of cancer outcomes: recommendations and opportunities for translational research. *J Natl Cancer Inst*. 2013;105:85-94.
3. Association of American Cancer Institutes. aaci-cancer.org.
4. Organization of European Cancer Institutes. European Economic Interest Grouping. oeci-eeig.org. Accessed March 12, 2013.
5. GovTrack.us. S. 2097 (112th): Comprehensive Cancer Care Improvement Act of 2012. http://www.govtrack.us/congress/bills/112/s2097. Accessed March 12, 2013.