EXPLORING THE ROLE OF CANCER CENTERS FOR INTEGRATING Aging and Cancer RESEARCH

Workshop Report

National Institute on Aging
National Cancer Institute

Lister Hill Center Auditorium and Natcher Cancer Conference Center
NIH Campus, Bethesda, MD
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MESSAGE FROM THE WORKSHOP ORGANIZERS

An excellent foundation for research planning was created in the multidisciplinary NIA/NCI Workshop, Exploring the Role of Cancer Centers for Integrating Aging and Cancer Research. We are pleased to present the results of a highly successful collaboration of individuals convened to identify high priority research at the complex interface of aging and cancer across a broad scientific spectrum. Workshop participants included senior scientific leaders from cancer centers, the medical practice community, health professionals, leaders in cancer patient advocacy groups, and NIA and NCI staff. This report presents a summary of their hard work and indicates their commitment to the workshop goal and objectives to increase the knowledge base on cancer in older persons. In breakout groups, research questions were generated to guide discussion. Participants also provided their perspectives on barriers to research progress and suggested mechanisms to facilitate integration of aging and cancer research.

The ever-increasing proportion and number of older persons in the American population present many scientific challenges and opportunities to integrate aging and cancer research and to translate the knowledge gained into interventions to improve cancer prevention in older persons and early detection, diagnosis, treatment, quality of care, and the quality of survival for cancer patients. The planning committee selected seven thematic areas for the workshop. Together, these themes provide a comprehensive framework for applying the expertise and unique research infrastructure of cancer centers on behalf of our nation's current and future older persons.

Research priorities proposed in the workshop provide direction and will contribute greatly to closing the considerable knowledge gap on cancer in older persons and the impact of aging and age-related health problems on the cancer course. Other components common to the seven individual reports, such as research questions, cancer center role, and research barriers, offer promising leads for translational research and critically essential interventions that could substantially reduce the magnitude of the high cancer incidence and mortality burden in the aging U.S. population. This report is intended to stimulate interest to design and propose aging/cancer research initiatives within a cancer center or in partnership with cancer centers and other research institutions.

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ACKNOWLEDGMENTS

As organizers of the NIA/NCI workshop, Exploring the Role of Cancer Centers for Integrating Aging and Cancer Research, we would like to extend special thanks to the following persons:

- Workshop participants—scientists and clinicians of established reputation in various disciplines and professions involved in aging and/or cancer research, health professionals, members of the advocacy community, and NIA and NCI staff—all of whom contributed to achieving the workshop goals and objectives by being vigorously involved in the plenary and breakout sessions.

- Dr. John H. Glick, Director, University of Pennsylvania Cancer Center, who served as chairperson for the NIA/NCI planning committee and cancer centers workshop. In the months preceding the workshop, Dr. Glick was an advisor and enthusiastic supporter. His commitment to the goals and objectives of the workshop was an essential element to its successful outcome.

- Members of the NIA/NCI workshop planning committee, many of whom were involved as consultants and participated in the workshop as co-chairpersons or speakers.

- Co-chairpersons and speakers, all of whom contributed to organizing the blend of rich ideas and insights incorporated in the seven workshop theme reports. Because of their efforts, information was organized so that research priorities could be stated in this report and conveyed to other researchers. We are grateful to them for serving in this capacity and for their subsequent input for the group reports.

- Directors of the sponsoring institutes, Dr. Richard J. Hodes, NIA, and Dr. Richard D. Klausner, NCI, who welcomed the workshop participants and whose remarks emphasized the importance of the workshop objectives and Dr. Robert E. Wittes, Director, Division of Cancer Treatment and Diagnosis, Deputy Director for Extramural Science, NCI, for his approval of the workshop concept and his consultation and support.

- Dr. Patricia McCormick, Cancer Centers Branch, NCI, whose leadership in the initiation of the workshop was vital to its success and Dr. Brian Kimes, Director, Office of Centers, Training, and Resources, NCI, for his expertise and guidance at the inception of the workshop and his consultation and support of its outcome.

- Palladian Partners staff members Fran Oscar and Bridgette Saunders, NIA staff members Clarissa Douglas and Wanda Solomon, and NCI staff member Stacy Gardner for their many and diverse contributions in planning workshop logistics and implementing all the necessary tasks that go into assuring a successful workshop.

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EXECUTIVE SUMMARY

Cancer Burden for Persons 65 Years and Older

The workshop, Exploring the Role of Cancer Centers for Integrating Aging and Cancer Research, was organized by the National Institute on Aging (NIA) and the National Cancer Institute (NCI) to provide a forum for leaders in cancer and aging research to express their views on pressing research needs. Representatives from the NCI-designated cancer centers were invited to formulate research priorities specifically focused on persons 65 years and older, the age group most vulnerable to cancer and in which the highest cancer incidence and mortality rates occur.

Advancing age is a high risk factor for cancer. Close to 60% of all newly diagnosed malignant tumors and 70% of all cancer deaths are in persons 65 years and older according to the NCI Surveillance, Epidemiology, and End Results (SEER) program data for 1994–1998. The age-adjusted cancer incidence rate for persons 65 years and older (2151.2 per 100,000 population) is ten times greater than the rate for persons under 65 years (208.8 per 100,000 population). The age-adjusted cancer mortality rate (1068.3 per 100,000 population) for persons 65 years and older is over 15 times greater than the rate for persons under 65 (67.3 per 100,000 population). Pancreas, stomach, rectum, lung, leukemia, non-Hodgkin's lymphoma, liver, kidney, and ovarian cancers account for two-thirds to three-quarters of cancer deaths in persons age 65 years and older. Over 75% of cancer deaths are due to urinary bladder, colon, and corpus uterine cancers. Breast cancer accounts for 59% of deaths in women in this age group. Ninety-two percent of prostate cancer mortality occurs in men 65 years and older.

Aging America

The cancer statistics showing the disproportionately high burden of cancer for older Americans take on even greater significance when cast against the changing demographics of the aging population in the United States. The number of older persons diagnosed with cancer is expected to increase because of the overall aging of the U.S. population and an unprecedented expansion of the 65 years and older age group in the next three decades.

Three factors contribute to our nation's changing age structure: changing mortality patterns, decreased fertility, and the aging of the baby boom cohort born between 1946 and 1964 (75 million persons). These factors, in particular the aging of the baby boom generation, will have far-reaching effects on the future overall health status and cancer burden of Americans. This phenomenon must be factored into our cancer research efforts. By 2030, 20% of the U.S. population will be 65 years and older. Age shifts within the 65 years and older segment of the population will increase the proportion of persons 85 years and older from our current 4.3 million to 8.9 million individuals over the next decades.

Workshop Objectives

Participants in the NIA/NCI workshop were asked to identify a concise set of priorities to address the aging/cancer research interface that were consistent with the research themes developed by the workshop planning committee for each of the seven participating working groups. They were to:

1. Identify promising scientific areas at the aging/cancer interface that could be pursued in the cancer centers given their unique resources and expertise.

2. Recommend opportunities in aging and cancer research that will advance medical progress at the aging/cancer research interface. Each working group was asked to select the top three research priorities.

3. Suggest various strategies and approaches for integrating aging and cancer research on behalf of older persons.

The focus designated by the workshop planning committee was on human cancer. Participants were encouraged to make recommendations for research implementation and research barriers as well.

Workshop Design and Participants

The NIA/NCI workshop was convened on the NIH Campus, Bethesda, MD, June 13–15, 2001. Two plenary sessions (held in the Lister Hill Center Auditorium) and the seven breakout groups (convened in the Natcher Conference Center) provided the forum and setting for brainstorming and the exchange of ideas and insights from participants. Each breakout group was Co-Chaired by two representatives from the cancer centers who were selected at the NIA/NCI workshop planning meeting. Seven scientific presentations were incorporated into the first plenary session to orient participants for their breakout group sessions. Breakout group reports were presented in the second plenary session.

Approximately 120 individuals—medical oncologists, geriatricians, health professionals, basic scientists, social scientists, epidemiologists, patient advocates, NIA and NCI staff, and others from relevant disciplines and professions participated in the NIA/NCI workshop. One or more participants, including 17 cancer center directors and senior program leaders, represented 44 of the 50 NCI comprehensive and clinical centers. Two of the ten basic science centers were represented. Dr. Richard J. Hodes, Director, NIA, and Dr. Richard D. Klausner, Director, NCI, welcomed workshop participants. Dr. John H. Glick, Director, University of Pennsylvania Cancer Center, chaired the workshop.

Research Themes and Priorities Identified

Many valuable suggestions were derived from the plenary and breakout group discussions. The full report identifies the domain of research issues and concerns that cut across institute, disciplinary, and professional boundaries and call for the integration of aging and cancer research. The Working Group Co-Chairpersons, speakers, and themes are identified and abbreviated versions of the research priorities are indicated below.

Group 1. Patterns of Care [studies with a focus on older patients using both prospective and retrospective data that could include community-based studies, patient management, cancer site-specific studies, and maximizing existing data (e.g., SEER special studies, HCFA linkage, tissue banks, family network studies)]

Co-Chairs:	Paul F. Engstrom, M.D., Fox Chase Cancer Center
	Jerome W. Yates, M.D., M.P.H., Roswell Park Cancer Institute
Speaker:	Vincent Mor, Ph.D., Brown University

Research Priorities:

1. Develop a key data matrix of content area items from relevant databases in the public domain that are pertinent to conducting patterns of quality cancer care research on the treatment of older patients. Some suggested databases include NCI SEER, Medicare, Managed Care, Insurance Encounter data, American College of Surgeons National Cancer Data Base, Veterans Administration studies, and Minimal Data Set reports in skilled nursing facilities.

2. Develop a dictionary of data elements (i.e., a compendium of items and their intended use) as a resource for investigators. While crafting geriatric assessments anew is not desirable, instruments are available that may be applicable to older cancer patients. Whether some instruments already exist that could be applied at the aging/cancer research interface should be determined.

3. Incorporate the clinical expertise from NCI projects, particularly the NCI SEER projects, that is available in cancer centers to improve the quality of care of the medically underserved, aging population. The cancer surveillance efforts should be enhanced to improve the clinical information base on cancer in older persons in SEER. NCI-designated cancer centers and NCI SEER registries that facilitate special studies on cancer in the elderly should be identified in strategic geographic locations.

Group 2. Treatment Efficacy and Tolerance [clinical trials, pharmacology of anticancer drugs, radiation therapy, surgery, available technology, other modalities, characterization of inadmissible older patients to clinical trials]

Co-Chairs: Richard L. Schilsky, M.D., University of Chicago
Joel E. Tepper, M.D., University of North Carolina School of Medicine
Speaker: Richard L. Schilsky, M.D., University of Chicago

Research Priorities:

1. Develop predictive models for tolerance to therapy. Hypothesis-generating work should be done in focused trials with older cancer patients and coordinated by an interdisciplinary team of cancer and aging research specialists in the cancer center research environment.

2. Study tumor-host interactions as a predictor of outcome. This is complementary to, but distinct from, changes in tumor biology in older patients.

3. Develop clinical trials that are specifically designed for older cancer patients. Trials based in cancer centers could address issues that would not likely be addressed in NCI cooperative group clinical trials and would be more appropriate for the cancer center environment.

Group 3. Effects of Comorbidity on Cancer [studies could include problems of diagnosis and treatment, disability, functional limitations, assessment, recurrence, detection of second primaries]

Co-Chairs: Hyman B. Muss, M.D., University of Vermont
Kathy Albain, M.D., Loyola University
Speaker: William A. Satariano, Ph.D., M.P.H., University of California, Berkeley

Research Priorities:

1. Develop a validated comorbidity assessment instrument that is user friendly, efficient, culturally sensitive, and reasonable in cost. Comorbidity assessment is a newly emerging area of opportunity to apply cancer center leadership, expertise, and coordination to the issue of comorbidities in elderly cancer patients.

2 . Ascertain the impact of comorbidity on patient care and outcome. Cancer centers are intended to enhance the potential of institutions for discovery and its application to patients and the population at risk.

3. Develop predictive models to allow individual treatment decision making, with a focus on prevention and adjuvant therapy.

Group 4. Prevention, Risk Assessment, and Screening [impediments for older-aged persons asymptomatic or with symptoms precluding their entrance to the preventive and health care system (e.g., delay behavior, insufficient knowledge of cancer risk), changes that occur in cancer risk as a function of aging]

Co-Chairs and
Speakers: Jeanne Mandelblatt, M.D., M.P.H., Lombardi Cancer Center
Lodovico Balducci, M.D., H. Lee Moffit Cancer Center

Research Priorities:

1. Develop and test interventions to decrease screening barriers. Colon and rectum cancers should receive high priority because of their associated morbidity and mortality in the elderly and the lack of prior research in this area.

2. Conduct chemoprevention and lifestyle change trials to decrease dependency, deterioration in quality of life, and mortality. The effects of chemoprevention should be studied, beginning at different ages, to identify the optimal age to start enrolling cohorts and determine the agents that should be promoted.

3. Develop models for decision making at the individual and clinical levels, including population forecasting for specific tumors. Develop models of academic research and community networks.

Group 5. Psychological, Social, and Medical Issues [quality of life, quality of cancer survival, family and caregiver resources, early and late effects of treatment, quality cancer care, tumor recurrence, multiple primary tumors]

Co-Chairs and
Speakers: Patricia A. Ganz, M.D., Jonsson Comprehensive Cancer Center,
University of California, Los Angeles
Alice B. Kornblith, Ph.D., Dana-Farber Cancer Institute

Research Priorities:

1. Develop a core set of instruments to assess the quality of life of older cancer patients. An individualized evaluation that includes functional status, activities of daily living, cognitive and emotional functioning, and socioeconomic status would standardize the assessment of older patients across cancer centers.

2. Examine the cancer caregiver's own functioning and quality of life and their impact on the older cancer patient's care and treatment trajectory. Caregiver strain is likely to be associated with the new primary responsibility for providing cancer care in the home setting.

3. Develop interventions to prevent or reduce the medical and psychological effects of cancer treatment in older adults. The prevalence of long-term medical and psychosocial effects should be determined.

Group 6. Palliative Care, End of Life Care, and Pain Relief [studies focused on patients with advanced cancer and associated issues in palliative care including caregiver and family support]

Co-Chairs: Nora Janjan, M.D., University of Texas, M.D. Anderson Cancer Center
Ruth McCorkle, R.N., Ph.D., F.A.A.N., Yale University
Speaker: Kathleen M. Foley, M.D., Memorial Sloan-Kettering Cancer Center

Research Priorities:

1. Organize descriptive work that is relevant to older cancer patients in a well thought out manner.

2. Develop and test service delivery models of care to provide palliative care to the elderly in a variety of contexts that include acute care, home care, and nursing homes.

3. Test and facilitate the use of evidence-based guidelines for pain relief and symptom control. Examine drug selection, pharmacokinetics, effects of drugs on surgery, and drug-drug interactions as they relate to agents for comorbidities, chemotherapy, and palliative care medications.

Group 7. Biology of Aging and Cancer [genetics, molecular signatures, bench to bedside application, translational research, age-related changes as they contribute to mortality, a focus on older persons who are vulnerable to cancer as contrasted with those who are not (e.g., sibship studies)]

Co-Chairs: Harvey Jay Cohen, M.D., Duke University Medical Center
Derek Raghavan, M.D., Ph.D., University of Southern California School of Medicine, Norris Comprehensive Cancer Center
Speaker: William B. Ershler, M.D., Institute for Advanced Studies in Aging and Geriatric Medicine, Washington, D.C.

Research Priorities:

1. Identify the processes and parameters of carcinogenesis in aging cells. Determine what to look for in cancer progression as it relates to aging.

2. Characterize cancers and cancer cells of the major tumors that are common in older persons. Determine whether the same types of cancer manifest themselves differently in older and younger hosts.

3. Explore elderly populations at low risk for cancer (i.e., with an age-resistant phenotype). Identify the genetic or epigenetic changes associated with this protective phenomenon. Conversely, develop insights into older cancer patients who are at high risk for multiple primary tumors. Identify the key shared predisposing or protective factors for development of multiple primary tumors.

Conclusion

The NIA/NCI workshop goal and outcome in research priority specification is an important step forward in the research planning and program development for the aging/cancer research interface. Creative ideas stemming from this workshop, which included scientists from diverse disciplines and professions, have the potential to produce groundbreaking research programs that facilitate collaborative studies to integrate aging and cancer research. The NCI-designated cancer centers are crucial in expanding the knowledge base on cancer in older persons. The cancer center workshop priorities encourage scientific productivity in critical areas on behalf of our nation's older citizens.

Organization of the NIA/NCI Workshop Report

A combination of expertise and rich ideas has produced the foundation for a research agenda directed at the complex interface of aging and cancer. The full report of the NIA/NCI workshop is organized into five sections:

I. Introduction
II. Goal and Objectives
III. Working Group Reports
IV. Participant Roster
V. Appendices
    A. Agenda
    B. Speaker Abstracts
    C. Planning Committee Roster
    D. Cross-Cutting Issues in Working Group Reports

INTRODUCTION

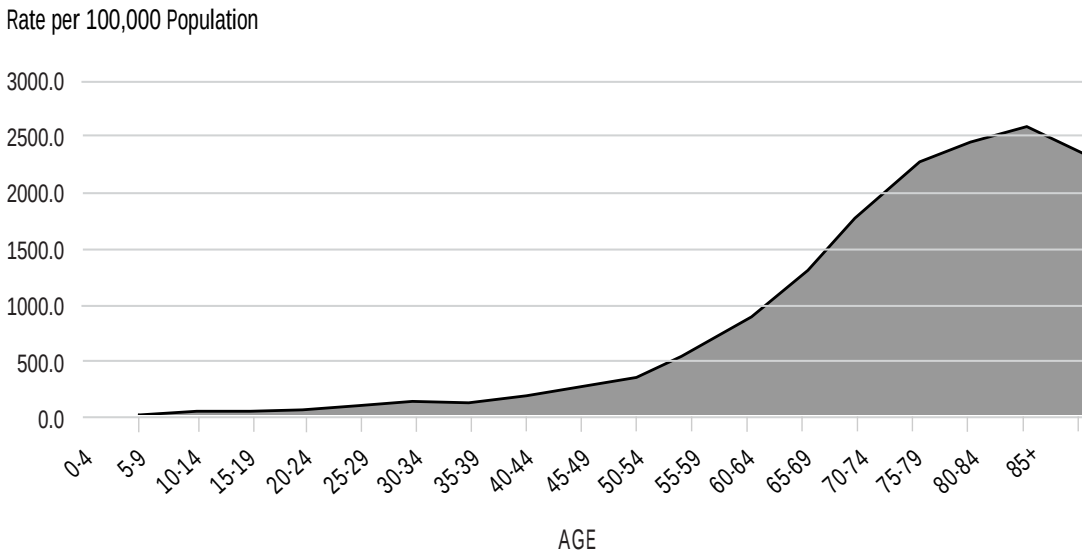
The National Cancer Institute (NCI) cancer centers have the potential to play a prominent role in integrating aging and cancer research. The NCI-designated cancer centers represent a network of institutions that can be mobilized to advance the knowledge base on cancer in older persons across the research spectrum of prevention, early detection, diagnosis, treatment, and the biology of cancer. On August 10, 2000, National Institute on Aging (NIA) and NCI staff presented the idea of focusing on aging/cancer research to senior representatives from several cancer centers. Scientific areas of research and ways to marshal the broad expertise and talent that exist in the cancer centers were also discussed. After deciding that it would be productive to hold a workshop so that research ideas could be generated by a broader-base group of individuals, the participants in the August 10 meeting evolved into the NIA/NCI workshop planning group.

The NIA/NCI workshop was convened to invite input from representatives of the cancer centers on the topic of human cancer. The rationale for the workshop is based on the need to address the critical gap in knowledge on cancer in older persons, cancer incidence and mortality data, aging-related health issues, and the expanding aging population in the United States.

Cancer Statistics

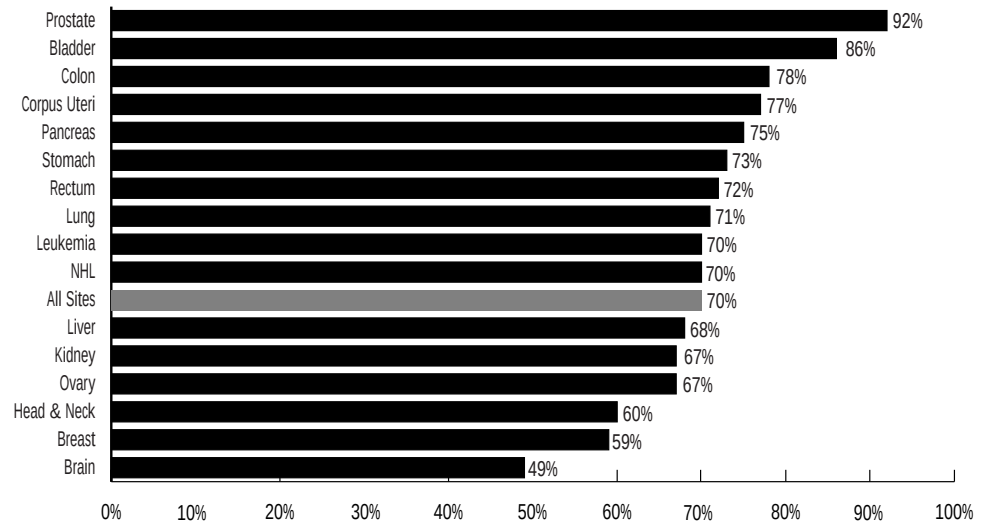
Aging is a high risk factor for cancer. NCI Surveillance Epidemiology, and End Results (SEER) Program data, 1994–1998, reveal that nearly 60% of all incident tumors occur in persons aged 65 years and older. The age-adjusted incidence rate for persons aged 65 and older (2151.2 per 100,000 population) is ten times greater than the rate for persons aged under 65 (208.8 per 100,000 population).[1] The rapid escalation of incidence rates is shown in

Figure 1. Cancer Incidence by Age Group, All Sites Combined, Both Sexes



Source: NCI SEER Program Data, 1994–98

Figure 2. Proportion (%) U.S. Cancer Mortality in 65+ Age Group



Source: NCI SEER Program Data, 1994-1998

Figure 1. Peak rates (ranging from 2233.5 to 2525.1 per 100,000 population) occur in persons aged 70 and older.

The age-adjusted cancer mortality rate (1068.3 per 100,000 population) for persons aged 65 and older is over 15 times greater than the rate for persons aged under 65 (67.3 per 100,000 population). The disproportionate burden of specific cancers in older Americans is shown in percentage proportions in Figure 2. Overall, 70% of all cancer deaths occur in persons aged 65 and over.[1]

Pancreas, stomach, rectum, lung, leukemia, non-Hodgkin's lymphoma, liver, kidney, and ovarian cancers account for two-thirds to three-quarters of cancer deaths in persons aged 65 and older. Over 75% of cancer deaths are due to urinary bladder, colon, and corpus uterine cancers. Breast cancer, often thought to be a disease more prominent in premenopausal women, accounts for 59% of the mortality in women aged 65 and older. Prostate cancer mortality is in a class by itself with 92% of the deaths occurring in men aged 65 and older. Nearly 50% of brain cancer mortality and 60% of head and neck cancer deaths occur in persons aged 65 and older.

Comorbidity Burden and Cancer

A diagnosis of cancer in older persons is likely to be made in the context of preexisting health conditions (i.e., comorbidity). Investigators have indicated that four out of five persons aged 65 and older have one or more chronic conditions. Comorbidity and age-related disabilities add to the complexity of cancer treatment and care in the elderly.[2]

In a population-based colon cancer patient sample of males (N=799) and females (N=811) in three age groups, 55–64, 65–74, and 75 and older, NIA/NCI SEER Collaborative Study investigators found that the number of preexisting health conditions in cancer patients ranged from none to 14 and were a combination of extremely serious conditions, possible precursors to major illnesses, and nonfatal conditions.[3] The number of conditions increased with advancing age. The prevalence of certain comorbidities increased with age for both women and men with 40% of each gender having five or more comorbidities. High prominence of hypertension, anemia (possibly tumor related), high impact heart problems, gastrointestinal (GI) problems, and arthritis were observed for both genders.[3]

A study on breast cancer by the same investigators illustrated the prevalence and age trends for selected comorbidities in postmenopausal women (aged 55–101 years, N=1800).[4] The number of comorbidities ranged from none to 13. Among the comorbid conditions documented, which were similar to those indicated in the colon cancer study, a high number of previous primary cancers were seen in the patient sample (N=268). The proportion of previous primary cancers increased according to age group: 11% for patients aged 55–64, 14% for patients aged 65–74, and 20% for patients aged 75 and older.[4]

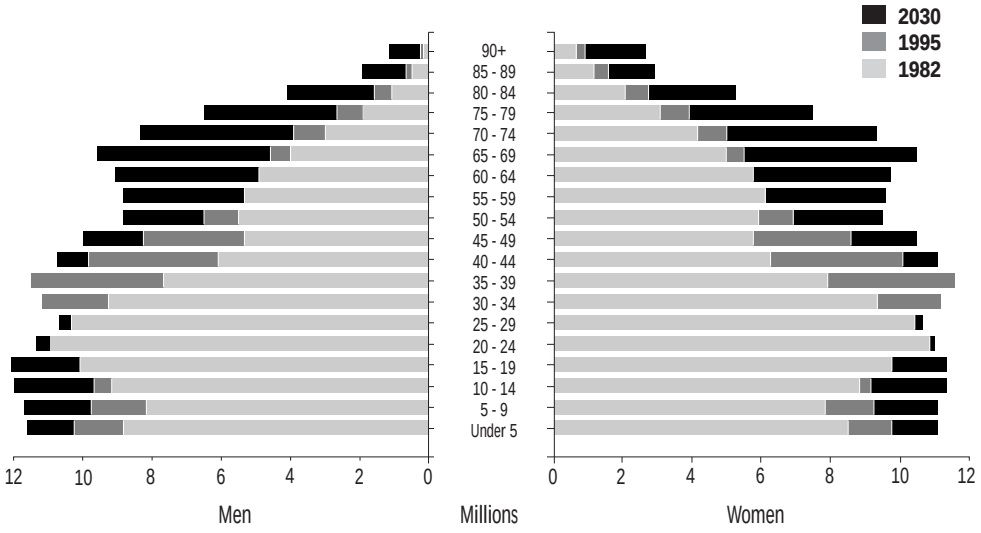
Data that indicate what happens when cancer is superimposed on the preexisting health problems of older patients are few. The varying health status and the physical and physiological substrates of the older individual needs to be incorporated into mainstream clinical research.

Aging of America

Our nation is aging. There is a growing recognition that the predicted expansion of the aging population in the United States will have far-reaching effects on the health status of our nation's citizens. There has been, and will continue to be, a substantial increase in the numbers and the proportion of Americans in the age group most vulnerable to cancer. Life expectancy at birth has increased from 48 years to 79.4 years for women and from 46 years to 73.6 years for men.[5] Life expectancy at 65 years and 85 years has also increased. Persons who live to age 65 can expect to live an average of another 18 years, while persons who survive to age 85 years can expect to live an average of approximately 6 or more years.[6]

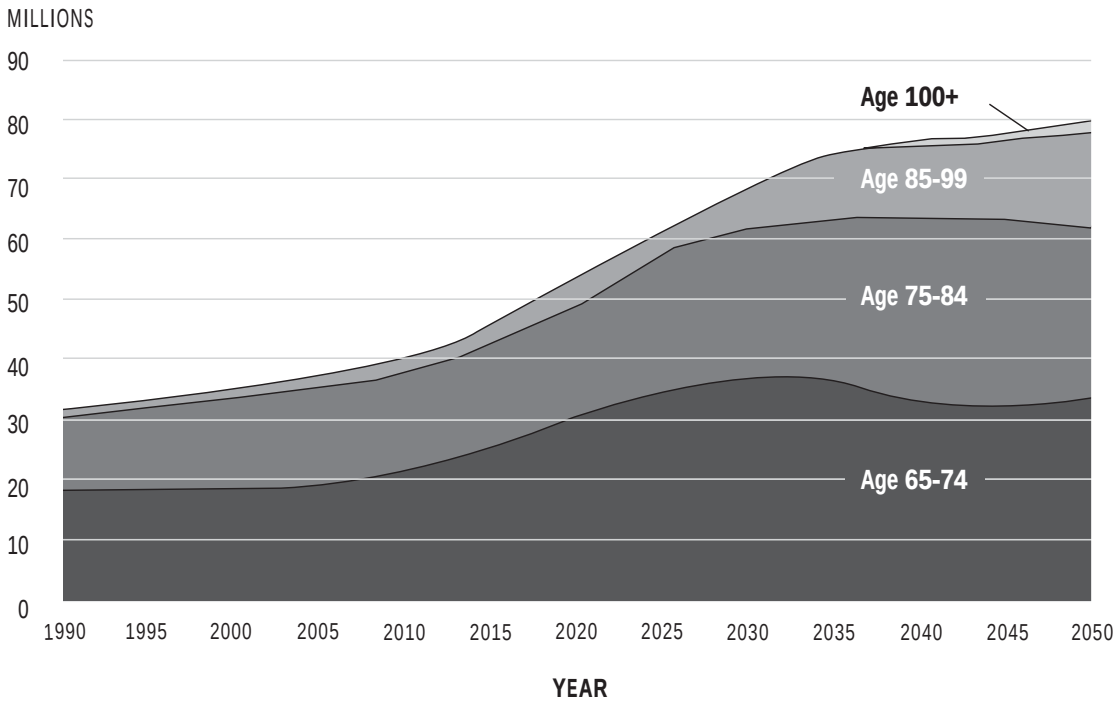
The first of the postwar baby boom cohort, born 1946–1964, will turn 55 years in 2001. In just three decades, an extraordinary change in the age structure of the United States is anticipated. By 2030, one in five persons (20% of the U.S. population) will be aged 65 or older, increasing from the present ratio of one in nine persons (12.8%).[7] The number of persons in the 65 and older age group will more than double, increasing from the current 34 million persons to 70 million persons. Moreover, within the older segment of the population, because of longer life expectancy and additional persons reaching older ages, there will be age shifts resulting in the 85 and older popula-

Figure 3. Expanding Aging U.S. Population



Source: U.S. Census Bureau, Population Projections of the United States by Age, Race, and Hispanic Origin: 1993–2050, P25-1104, 1993

Figure 4. U.S. Population Aging 65 Years and Older: 1990 to 2050



Source: U.S. Census Bureau, Population Projections of the United States by Age, Race, and Hispanic Origin: 1993–2050, P25-1104, 1993

tion more than doubling in size from 4.3 million persons to approximately 8.9 million persons.[7] The age pyramid depicted in Figure 3 presents the estimated and projected age structure for selected years.[8]

The U.S. Bureau of Census has depicted the U.S. population as a roller coaster to show the effects of aging on the baby boom population over time.[8] Seventy-five million persons were born in that period. This phenomenon should be factored into our cancer research efforts. As the total population continues to age and expand, so does the aging of the elderly. Age shifts within the segment of the population aged 65 and older are projected to increase the proportion of persons aged 85 and older from 4.3 million in 2000 to 8.8 million individuals in 2030.[5]

In this forum, participants had an opportunity to assist the NCI and the NIA in organizing research to advance the state of knowledge specific to cancer prevention, early detection, diagnosis, treatment and prognosis, biology, and enhancement of cancer survival. The vulnerability of older persons to cancer is unmistakable. As the nation ages, clinicians will be treating more older patients.

Information from a variety of disciplines and professions must converge, and new knowledge must be developed and applied at the aging/cancer research interface. In the workshop, a concise set of research priorities were identified to facilitate the integration of aging and cancer research that will establish a pathway to reduce the cancer burden for current and future older Americans.

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GOAL AND OBJECTIVES

In this workshop senior cancer center representatives (i.e., center directors, individual researchers, science administrators, scientific program directors) explored the expertise and resources of the cancer centers that can be organized to generate research on the aging/cancer interface. The NCI Cancer Centers Program supports major academic and research institutions throughout the United States to sustain broad-based, coordinated, interdisciplinary programs in cancer research, and also promotes inter-institute studies and collaborations among investigators in oncology and geriatric medicine and investigators of the biology of aging and cancer. The workshop setting was meant to provide a forum for constructive brainstorming and to obtain a productive exchange of ideas among participants from varying disciplines and professions who were invited to share their perspectives.

The goal of the workshop was to identify a concise set of research priorities to facilitate the interface of aging and cancer research so that scientific pathways can be established to reduce the magnitude of the cancer burden for older Americans.

The objectives of the NIA/NCI cosponsored workshop were to:

1. Identify promising scientific areas at the aging/cancer research interface that could be pursued in the cancer centers, given their unique resources and expertise.

2. Recommend research opportunities in aging and cancer research (considering each working group's theme) that will advance medical progress at the aging/cancer research inter face. In each working group, the top three research priorities were selected.

3. Suggest various strategies and approaches for integrating aging and cancer research on behalf of older persons (i.e., a research plan of action).

Charge to the Working Groups

- Each working group was charged with nominating the **three highest research priorities** out of all opportunities and needs discussed.

- Group deliberations on the research themes also addressed the following factors in their report during the plenary session:

  – **Barriers to research progress** (e.g., lack of sufficiently trained researchers and clinicians, insufficient technology, organizational infrastructure, inadequate funding, complexity of the older patient's situation, research problem definition, lack of leadership or expertise)

  – **Mechanisms to facilitate research progress** (e.g., evaluation tools to assist in the assessment of prognosis and treatment of older cancer patients, development and standardization of alterations or modifications of cancer treatment modalities in older patients because of comorbidity, ways to enhance participation of older persons in clinical studies, novel funding mechanisms as incentives for conducting research on cancer in the elderly)

Research Topics

Many excellent ideas emanated from the August 10, 2000, workshop planning meeting and are incorporated within the seven themes for the breakout sessions. Other ideas were introduced by individuals in the breakout

group discussions. Among the suggestions for themes that emerged within the planning group were:

- patterns of care studies;
- pharmacology of anti-cancer agents in older patients;
- prospective studies of surgical and radiation treatment in individuals with varying age-related functional limitations;
- activities of new drug and biologic anti-cancer agents in older patients;
- follow-up studies on adverse effects of treatment in older and younger patients;
- single institution and/or multicenter clinical trials;
- Phase IV trials (standard therapy outcome) to improve management of older cancer patients;
- characterization of older patients ineligible for treatment protocols;
- correlative research studies;
- cancer-site specific studies (e.g., refinement of current characterization of different tumors in relation to aging);
- effective management of older cancer patients with preexisting chronic conditions and concurrent diseases (i.e., comorbidity);
- studies of mechanisms of carcinogenesis and senescence and their overlap;
- coping with psychosocial, social, and medical effects of cancer and its treatment; and
- palliative care, pain management, and end of life issues.

The cancer centers also have many existing databases that could be examined for insights into generate hypotheses (tissue bank data) and treatment patterns (e.g., in-house tumor registries).

Research Themes Selected

Patterns of Care

[studies with a focus on older patients using both prospective and retrospective data that could include community-based studies, patient management, and cancer site-specific studies as well as maximizing existing data (e.g., SEER special studies, HCFA linkage, tissue banks, family network studies)]

Speaker: Vincent Mor, Ph.D., Brown University

Group Co-Chairs: Paul F. Engstrom, M.D., Fox Chase Cancer Center and Jerome W. Yates, M.D., M.P.H., Roswell Park Cancer Institute

Treatment Efficacy and Tolerance

[e.g., clinical trials, pharmacology of anticancer drugs, radiation therapy, surgery, available technology, other modalities, characterization of older patients ineligible for clinical trials]

Speaker: Richard L. Schilsky, M.D., University of Chicago

Group Co-Chairs: Richard L. Schilsky, M.D., University of Chicago and Joel E. Tepper, M.D., University of North Carolina School of Medicine

Effects of Comorbidity on Cancer

[e.g., studies could include problems of diagnosis and treatment, disability, functional limitations, assessment, recurrence, detection of second primaries]

Speaker: William A. Satariano, Ph.D., M.P.H., University of California, Berkeley

Group Co-Chairs: Hyman B. Muss, M.D., University of Vermont and Kathy Albain, M.D., Loyola University

Prevention, Risk Assessment, and Screening

[impediments for older-aged persons (asymptomatic or symptomatic precluding their entrance into the preventive and health care system (e.g., delay behavior, insufficient knowledge of cancer risk), changes that occur in cancer risk as a function of aging]

Speakers: Jeanne Mandelblatt, M.D., M.P.H., and Lodovico Balducci, M.D., H. Lee Moffit Cancer Center

Group Co-Chairs: Jeanne Mandelblatt, M.D., M.P.H., Lombardi Cancer Center and Lodovico Balducci, M.D., H. Lee Moffit Cancer Center

Psychological, Social, and Medical Issues

[e.g., quality of life, quality of cancer survival, family and caregiver resources, early and late effects of treatment, quality cancer care, tumor recurrence, multiple primary tumors]

Speaker: Alice B. Kornblith, Ph.D., Dana-Farber Cancer Institute

Group Co-Chairs: Patricia A. Ganz, M.D. (Keynote Speaker) Jonsson Comprehensive Cancer Center, University of California, Los Angeles and Alice B. Kornblith, Ph.D., Dana-Farber Cancer Institute

Palliative Care, End of Life Care, and Pain Relief

[e.g., studies focused on patients with advanced cancer and associated issues in palliative care including caregiver and family support]

Speaker: Kathleen M. Foley, M.D., Memorial Sloan-Kettering Cancer Center

Group Co-Chairs: Nora Janjan, M.D., University of Texas, M.D. Anderson Cancer Center and Ruth McCorkle, Ph.D., F.A.A.N., Yale University

Biology of Aging and Cancer

[e.g., genetics, molecular signatures, bench to bedside application, translational research, age-related changes as they contribute to mortality, a focus on older persons who are vulnerable to cancer as contrasted with those who are not (i.e., sibship studies)]

Speaker:	William B. Ershler, M.D., Institute for Advanced Studies in Aging and Geriatric Medicine
Group Co-Chairs:	Harvey Jay Cohen, M.D.(Keynote Speaker), Duke University Medical Center and Derek Raghavan, M.D., Ph.D., University of Southern California, Norris Comprehensive Cancer Center

WORKING GROUP REPORTS

Working Group 1:
Patterns of Care

Speaker:
Vincent Mor, Ph.D., Brown University

Co-Chairs:
Paul F. Engstrom, M.D., Fox Chase Cancer Center
Jerome W. Yates, M.D., M.P.H., Roswell Park Cancer Institute

Introduction

Cancer is an age-related disease with peak incidence and mortality rates in the segment of the population 65 years and older. Thus, it is surprising that so little descriptive information is available about cancer treatment in older persons. Not only is limited information available on the kinds of cancer care older patients receive in NCI-designated cancer centers, but few data are collected in a systematic manner prospectively or retrospectively in community cancer treatment settings, in population-based studies, and in case-control studies.

There is a dearth of information on cancer care in older patients. No evidence-based or clinically-based consensus exists on how older patients who are newly diagnosed with a malignancy should be treated. Moreover, no recommended or standardized scientific approaches are available to specify the appropriate treatment for patients with age-related health problems *concurrent* with their cancer (i.e., comorbidity). The critical knowledge gap in this area needs urgent attention.

Working Group 1 addressed the need for information on how to identify older persons who are likely to benefit from treatment that is known to be effective in younger populations. Such information must be communicated to the research and practice communities.

In his introductory presentation, Dr. Vincent Mor gave an overview of the cancer treatment of older patients from the small number of studies conducted in the 1990s on breast, prostate, colorectal, and lung cancers. Articles that did not examine age as a predictor of care received were not included. Dr. Mor's review provided the following insights on age differences:

- Across tumors, diagnostic intensity (e.g., the probability of receiving a referral to a "chest physician") declines with advancing age.
- Older cancer patients tend to receive less aggressive treatment (e.g., they are less likely to receive radiation therapy with or without chemotherapy after surgery for colon cancer).
- When appropriate treatment has been identified for a particular tumor, older patients are less likely to receive that standard of care (e.g., breast cancer surgery plus radiation).
- Variations identified in treatment for older patients may stem from differences in physician training, geographic location, academic versus community hospital care and treatment, and rural and urban settings.
- Physician bias is evident in these studies, which suggests that treatment differences and exclusion are not based only on risk assessment and/or patient/family preferences.

Dr. Mor indicated that, in the studies examined in this review, the extent to which the preexisting health status of the newly diagnosed cancer patient (i.e., comorbidity) contributes to diagnostic and treatment variations and the higher observed rates of cancer mortality among aged cancer patients is not known. Unfortunately, obtaining detailed information on the physiological condition and the presence of comorbidities in older patients is extremely difficult. Participants in Working Group 1 agreed that any prospective study developed and supported by the NCI and NIA on cancer in older persons must include some reasonable medical measures of cancer patient comorbidities.

Research Questions

1. Can patterns-of-care studies assess the effects of comorbidity as it relates to treatment and care decisions?
2. Is multidisciplinary care more likely to address age factors in older patients?
3. Does treatment for older patients differ in cancer centers and the community setting?
4. Can comorbidity profiles be devised to characterize elderly patients who are more likely to benefit from those therapies known to be effective in younger populations?
5. At what age and stage is effective treatment less beneficial for aged patients (i.e., benefits of treatment are remote)?

Cancer Center Role

In the NIA/NCI planning meeting for the cancer centers workshop in which working group themes were selected, it was acknowledged that information on older patients treated in cancer centers might not be generalizable to all older persons. Therefore, to facilitate population-based patterns-of-care studies, cancer center leaders and experts could collaborate with the NCI Surveillance, Epidemiology, and End Results (SEER) Program leaders, as almost all NCI SEER registries are located in states or regions in which NCI-designated cancer centers are located.

In addition, the NCI and other federal agencies have increased their efforts to improve the quality of cancer care by enhancing their data collection systems and linkages among systems. Although these efforts do not focus directly on older patients, their descriptive and analytical research targets certain tumors (e.g., colorectal and lung cancers) that are among the major malignancies that affect the elderly disproportionately and will yield useful data on the elderly. For example, the NCI recently announced awards for the Cancer Care Outcomes Research and Surveillance (CanCORS) Program (October 2001). Awards totaling approximately $34 million within a 5-year period will be made through cooperative agreements with the NCI Division of Cancer Control and Populations Sciences. These projects will assess community practice patterns and disparities in care for population subgroups with colorectal and lung cancers. A research infrastructure will support six teams of scientific investigators and a coordinating center to collect common data elements describing the processes and outcomes of care for all enrolled patients through medical record abstracts, surveys, and administrative data. The data-coordinating center and one of the six research groups are cancer centers. Given the large number of older persons afflicted by colorectal and lung cancers, these new studies are likely to focus on older patients, at least to some extent.

Research Priorities

The priorities of Working Group 1 address the infrastructure for conducting retrospective and prospective patterns-of-care studies to elucidate what is occurring in the cancer treatment arena for older patients. The recommendations do not identify major research areas or malignancies that deserve in-depth pursuit in patterns-of-care studies or suggest study designs. But the priorities do call for groundwork to support potential investigations that could be conducted in partnership with cancer centers.

1. Develop a key data matrix of content area items from relevant databases in the public domain that are pertinent to conducting patterns of quality cancer care research on the treatment of older patients. *Some suggested databases include NCI SEER, Medicare Managed Care, Insurance Encounter data, American College of Surgeons National Cancer Data Base, Veterans Administration studies, and Minimal Data Set reports in skilled nursing facilities.*
   - This effort should begin with existing studies to ascertain what might be applied to a cancer center study effort.
   - The complexity and expense of conducting patterns-of-care studies were discussed. A major obstacle is that available data on treatment effectiveness do not include specific information on older

cancer patients, and large prospective studies on the aged include few, if any, details on cancer.
- Supplemental data are required to make the existing data collection efforts useful and applicable to older patients. Related issues include sociodemographic and ethnic disparities, continuity of care, and the best models for delivery of care.
- Networking with the community is essential for patterns-of-care studies. Few collaborations of this nature have occurred, but compelling reasons exist for cancer center oncologists and community cancer care physicians to work together.

2. Develop a dictionary of data elements (i.e., a compendium of items and their intended use) as a resource for investigators. *Although crafting geriatric assessments anew is not desirable, instruments are available that may be applicable to older cancer patients. Whether some instruments already exist that could be applied at the aging/cancer research interface should be determined.*
   - To facilitate future compilations of information on older patients, a computer-accessible data set should be developed that indicates which items are in which set of survey study information.
   - Development of a progressive database requiring inclusion of certain items should be considered.
   - Potential should be built for aggregation of patterns-of-care data across selected cancer centers.
3. Incorporate the clinical expertise from NCI projects, particularly the NCI SEER projects, that is available in cancer centers to improve the quality of care of the medically underserved, aging population. *Cancer surveillance efforts should be enhanced to improve the clinical information base on cancer in older persons in SEER. NCI-designated cancer centers and NCI SEER registries that facilitate special studies on cancer in the elderly should be identified in strategic geographic locations.*
   - Whether patterns of care for older patients treated in cancer centers are different from patterns of care for other older patients with the same types of cancer who are treated in the community should be ascertained.
   - Cancer center consortia should be developed to address treatment efficacy and tolerance for selected tumors that primarily affect older patients.

Research Barriers

- Heterogeneity of cancer centers is a significant barrier—treatment environments vary greatly among cancer centers.
- More uncommon malignancies are seen in cancer centers than in other settings; common cancers tend to be managed in the community.
- Patients treated in cancer centers tend to be younger.
- Cooperation with local physicians in the community is required, so cancer centers must facilitate networking. Although this is not an unachievable goal, it requires a strategic collaborative planning effort on the part of both center and community sectors.

Mechanisms

- Encourage geographically compatible Community Clinical Oncology Programs (CCOPs) and NCI-designated cancer centers to conduct consortium studies.
- Organize demonstration projects within cancer centers and community settings to enhance comorbidity assessment and measurement of older patients' health problems concurrent with their malignancies.
- Consider conducting patterns-of-care studies in certain cancer centers (e.g., possibly those in New Hampshire, New Mexico, Iowa, Wisconsin, North Carolina, and Colorado) that serve reasonably well-defined catchment areas, if certain study criteria can be met.

- Consider supplemental funding for a task force to implement some patterns-of-care activities, such as funding a short-term, centralized cancer center patient data system.
- Develop incentives to facilitate study teams of geriatricians and oncologists to create model protocols for testing efficient geriatric assessments of cancer patients. These instruments may later be used in large-scale patterns-of-care studies.

Working Group 2: **Treatment Efficacy and Tolerance**

Speaker:
Richard L. Schilsky, M.D., University of Chicago

Co-Chairs:
Richard L. Schilsky, M.D., University of Chicago
Joel E. Tepper, M.D., University of North Carolina School of Medicine

Introduction

Clinical research on cancer is often conducted in individuals who are younger than those in whom the targeted malignancy predominates, and older patients in the NCI Cooperative Group clinical trials represent only a narrow subset of older cancer patients undergoing treatment in the United States. Although information on treatment tolerance and efficacy is very much needed for persons in the age groups in which the cancer primarily occurs (the median age range for most major tumors is 70–74 years at initial diagnosis), the unfortunate reality is that older patients tend not to meet clinical trial eligibility criteria and therefore are not referred to such trials. Other health problems and lack of social support (e.g., transportation, caregiver assistance) also preclude the entry of many elderly patients into these studies.

Because so few older patients are enrolled in clinical trials, data from existing trials cannot be generalized to the older population as a whole. As one discussant said, "You have to enter older patients on trial to get data on them; if they do not get on trials, you do not get the data, and therefore, we [i.e., the cooperative groups] undoubtedly do have a very biased subset of elderly patients in clinical trials."

Working Group 2 discussed these issues in the context of promoting collaborative and innovative research and clinical and community applications via the NCI-designated cancer centers on behalf of older persons. With their flexible infrastructure for interdisciplinary research, the cancer centers are an ideal setting for integrating aging and cancer research.

Efforts to obtain information on patient tolerance of cancer therapy can be facilitated through the clinical studies of NCI-designated cancer centers. Some cancer centers have a circumscribed catchment area, virtually all have cancer registries, and all comprehensive cancer centers have an integrated research environment that fosters complex interactions to address the "big picture" problem and specific cancer treatment needs of the elderly.

Research Questions

1. Where, on the spectrum of limited homeostatic mechanisms in older patients, is a particular patient located? How well might a particular patient tolerate the stress induced by prescribed chemotherapy, surgery, or radiation therapy? Are performance status measurement tools available to detect what needs to be known?
2. Are physicians successfully identifying older patients who are more likely to experience toxicity and not entering them in trials? Are older patients treated appropriately with state-of-the-art therapy? Does an age bias exist in the cancer treatment of older patients (i.e., are they medically underserved)?
3. Do ways exist to obtain population-based data on the treatment of older patients? Alternatively, can study parameters be implemented so that patients who are not defined through the trial eligibility criteria are also

described? Can the reasons why these patients did not or could not participate in the study (e.g., comorbidity, frailty, lack of functional reserve, doctor and/or patient family decision) be indicated?

Older patients represent a disproportionately large number of those treated for malignancies. Oncologists need to know how therapies will affect older cancer patients with less than ideal health as well as those with good to excellent health. Most older patients have some type of age-related health condition that could affect the cancer course or cancer treatment trajectories. The time course of absorption, distribution, metabolism, and excretion of drugs from the aged host (i.e., pharmacokinetics); the response of the aged host to the anticancer drug (pharmacodynamics); the course of radiation treatment; the surgery recommended; and the tolerance of these treatments could be affected by the following:

- The general health status of older patients at the time of cancer diagnosis;
- The presence of moderate to severe comorbid conditions in aged patients; and
- Pathophysiological changes that occur with aging, particularly the decline in functional reserve.

Cancer Center Role

An infrastructure is needed to allow appropriate studies to be conducted in the older population. An organized research structure should incorporate the combined professional skills and experience of gerontologists and oncologists, nurses, social support personnel, and other health professionals. Without this infrastructure, conventional centers are unlikely to be able to perform these studies and the studies' applicability to the population as a whole is likely to be unclear. This effort should also provide the educational programs necessary for a successful research program. Many barriers could be overcome by an organized effort involving the cancer centers.

Research Priorities

1. Develop predictive models for tolerance to therapy. *Hypothesis-generating work should be done in focused trials with older cancer patients and should be coordinated by an interdisciplinary team of cancer and aging research specialists in the cancer center research environment.*
   - Incremental studies should be organized to focus intensively on issues that are age relevant to toxicities of individual drugs, individual treatment regimens, local therapies, and combinations of therapies to build a knowledge base on functional outcomes of aged patients.
   - Predictive models should incorporate the multiple factors that influence a patient's tolerance for therapy—performance status, preexisting comorbid medical conditions, decreased functional reserve, polypharmacy (i.e., drug-drug interaction), and the social situation (e.g., whether capable caregivers are available).
   - Predictive models should be developed to anticipate adverse effects, such as neurotoxicity from taxanes, renal toxicity, hepatic toxicity, radiation recall, and diarrhea. Better algorithms are needed for prospective dose adjustment for antineoplastic agents in the presence of comorbid conditions and/or age-related physiologic changes.
   - Radiation therapeutic complications associated with dose volume, field size, and scheduling of treatment should be minimized. Predictive methods should be developed to estimate tolerance in older cancer patients based on body composition, size, age, concurrent health problems, kidney function, and other physiologic parameters.
   - Research should be conducted on dose-limiting parameters to predict and avoid risk and severity of short-term and long-term side effects of radiotherapy in older cancer patients.

- Research on exposure to multiple modalities is needed to assess whether modalities interact to induce increased toxicity.

2. Study tumor-host interactions as a predictor of patient response to therapy. *This is complementary to, but distinct from, changes in tumor biology in older patients.*
   - What is significant in the older patient's disease and treatment trajectory—such as tumor behavior, treatment-related issues, or unrelated age-associated health problems—needs to be identified. Who should not receive certain types of treatment needs to be determined.
   - Research is needed on how the host reaction to the tumor and/or treatment becomes modified in older patients.
   - Research should address how the tumor reacts to the aged host environment.
   - Key shared predisposing factors to multiple primary tumors should be identified.
   - Phenotypic or genotypic alterations that correlate with therapy resistance or intolerance in older patients should be identified.
3. Develop clinical trials that are specifically designed for older cancer patients. *Trials based in cancer centers could address issues that would not (or could not) be addressed in NCI cooperative group randomized clinical trials.*
   - A first step is to accept into studies that are solely observational (and, ideally, population based) all patients with certain diseases who are willing, in order to define the issues and acquire valuable baseline data. Investigations could then be broadened to treatment studies that would collect tolerance data and define more precisely the limitations of the present systems. Although certain issues would not be easy to address in the research context of the NCI's large randomized clinical trials, they could be accommodated in the cancer centers environment. Examples include the following:
     - Examine the considerable variations in prostate cancer therapies according to age: younger patients are more likely to receive surgery than older patients, who are more likely to receive radiation treatment. The oldest patients are most likely to receive hormone therapy alone. Data supporting such practices are limited.
     - Ascertain why older glioma patients have poorer outcomes than younger patients.
     - Apply the combined expertise of cancer pharmacology and the physiology of aging to assess the age-dependent differences that influence drug efficacy in selected tumors that primarily affect the elderly.
     - Explore differences in the pharmacokinetics and pharmacodynamics of chemotherapeutic and biologic antitumor agents in older and younger patients. Identify the mechanisms for these differences.

Research Barriers

- Insufficient knowledge and bias of medical professionals about proper management of older patients is a barrier to research. Age alone is not a contraindication to standard cancer therapy in most clinical situations.
- Recruiting older patients to clinical trials is difficult.
- Collaboration among gerontologists, geriatricians, and oncologists is limited.
- Research on older patients in clinical practice is time-consuming.
- Social support systems for older cancer patients are inadequate.

Working Group 3:
Effects of Comorbidity on Cancer

Speakers:
William A. Satariano, Ph.D., M.P.H., University of California, Berkeley
Hyman B. Muss, M.D., University of Vermont, Fletcher Allen Health Care Center

Co-Chairs:
Hyman B. Muss, M.D., University of Vermont, Fletcher Allen Health Care Center
Kathy S. Albain, M.D., Loyola University Medical Center

Introduction

Aging-related health problems are common in newly diagnosed older cancer patients given that the median age range for most tumors is 70–74 years. To ensure high-quality cancer care, the health status of the aged host prior to the diagnosis of cancer must be considered. Participants in Working Group 3 considered the need to assess the influence of concurrent and previous illnesses on the course of cancer treatment in older patients and approaches to evaluating them.

In his introductory presentation, Dr. William Satariano summarized the potential impact of comorbidity (i.e., the presence of one or more health problems) on the cancer trajectory by noting that:

- Comorbidity elevates the risk of disability and death among cancer patients,
- Comorbidity is associated with the receipt of less definitive cancer therapy, and
- Less definitive therapy is associated with poorer outcomes after adjustment for comorbidity.

Many newly diagnosed older cancer patients have experienced age-related, chronic health problems of various types—such as heart disease, pulmonary disease, diabetes, osteoporosis, arthritis, and hypertension—and degrees of severity before a diagnosis of cancer. Older persons may also have preexisting abnormalities of peripheral nerves, mental status, and cardiac function; geriatric syndromes, such as frailty, urinary incontinence, and balance disorders; other age-related limitations, such as physical disabilities; and restricted functional reserve capacity in certain organ systems, such as decreased renal excretion.

Yet, chronological age should not serve as a proxy for comorbidity. Given the heterogeneity of the aging processes, a particular older patient may have numerous, some, or no age-related health problems and/or disabilities.

Fundamental mechanisms of the body decline progressively at different rates with age, giving way to a gradual incapacity for maintenance and repair. A specific age threshold cannot serve as a guide to treatment decisions.

The health status of older persons diagnosed with cancer and the severity of their concurrent problem conditions need to be assessed in conjunction with therapeutic decision making, which will result in better care for older patients. Comorbidity assessment can be applied in the public health domain (e.g., in oncology practice, in primary prevention, screening, and promotion of quality of life) as well as in research investigations (e.g., in clinical trials, epidemiologic studies, cancer control studies).

Methods of producing reliable information to enhance the diagnostic acumen of oncologists in the management and evaluation of older cancer patients are urgently needed. Assessment of the impact of preexisting health problems and conditions on the cancer treatment course of older patients is crucial to providing high-quality care to older individuals who are newly diagnosed with cancer. However, little information exists on the interaction between the older cancer patient's prediagnostic health status and the malignancy.

Research Questions

1. How do older patients' comorbidities affect their tolerance of the additional stress of cancer treatment and survival?
2. How are the atypical presentations of disease, fluctuating health problems, wavering nutritional status, and multiple medication usage that often characterize older persons addressed in cancer therapeutic planning?
3. What is the impact on cancer treatment and recovery of the preexisting diseases and conditions that older persons are likely to experience?
4. How are concomitant diseases and conditions managed in the course of cancer treatment?

5. What is the impact on the therapeutic regimens prescribed for patients' preexisting illnesses and conditions, given the urgency for cancer treatment, and how might these regimens interact with cancer therapies?
6. Do specific tumors require special comorbidity research questions due to their anatomic location, biologic behavior, disease stage, and effect on patients?

Learning the extent to which comorbidity increases risk of adverse treatment effects is essential. The severity of tumor stage and morbidity, together with the treatment modalities, must be carefully considered in relation to the age-associated comorbidities of older persons with cancer. The research goal is to develop optimum ways to characterize before cancer treatment the nature, severity, and likely effects of comorbidities in order to offset and reduce any deleterious impact of the patient's other health problems on the cancer course. *The more the individual's comorbid health status is understood, the greater the chance of optimum treatment of the malignant tumor and of optimum recovery.*

Cancer Center Role

The unique cancer center infrastructure and its critical mass of multidisciplinary expertise provides an ideal research setting for meeting the challenges inherent in characterizing the comorbidity burden of older cancer patients and its impact on cancer care and treatment. The disproportionate burden of cancer in the elderly is poorly understood and needs attention from a focused research community, which the cancer center research environment can provide. This will ensure creative development of comorbidity assessment technology.

Research Priorities

Participants in Working Group 3 identified three interdependent research priorities. Priority 1 is fundamental to the research proposed in priorities 2 and 3. The objective of all three priorities is to develop *reliable and valid clinical assessment methods* for physicians in oncology practice and clinical research.

1. Develop a validated comorbidity assessment instrument that is user-friendly, efficient, culturally sensitive, and reasonable in cost. *Comorbidity assessment is a newly emerging area of opportunity to apply cancer center leadership, expertise, and coordination to the issue of comorbidities in elderly cancer patients.*
   - The technology of assessment development requires a solid conceptual and clinical base.
   - Scientific development of assessment technology within a network of cancer centers facilitates collaboration among experts from a wide range of relevant professional and disciplinary fields.
   - Highly motivated multidisciplinary professional teamwork can lay the groundwork for a new level of technology for application to older cancer patients.
   - The cancer center network provides the continuity needed to launch different levels of investigations, including instrument pretesting, feasibility assessment of administration in the clinical setting, and pilot demonstration studies. The design and testing recommended in priority 1 would be implemented in the applications suggested in priorities 2 and 3.
2. Ascertain the impact of comorbidity on patient care and outcome. *Cancer centers are intended to enhance the potential of institutions for discovery and its application to patients and the population at risk.* Whether the impact of comorbidity should be assessed in the population base versus cancer center catchment areas needs to be determined. How comorbidity affects overall patterns of care in older patients and the differences in cancer treatment should be assessed.
   - From a provider-driven perspective, the hypothesis is that systematic differences

exist between treatment patterns, depending on whether the care is delivered from within a cancer center or from the community. Differences are largely attributed to comorbidity, frailty, and antiaging bias among cancer center providers or to the referral of patients to (or acceptance of patients by) cancer centers.
- The concerns of patients compared with those of professional cancer providers are complementary to the systematic differences between treatment patterns. The effect of patients' perceptions of their comorbidities on physicians' decisions about diagnostic evaluation, treatment, and outcomes needs to be identified. How these issues differ in medically underserved and minority populations must also be determined. Data-driven models are needed that incorporate severity and type of comorbid conditions, number and interaction of comorbidities, tumor stage and other disease parameters, previous malignant primary tumors, active (i.e., functional) life expectancy, and overall life expectancy.
- Who will benefit needs to be addressed. Specifically, research is needed on the age, stage, and other parameters at which treatment is of less value for older patients (e.g., conditional profiles) and how to discern whether short-term and long-term effects of toxicity diminish the benefits of treatment.

The impact of comorbidity on the selection of optimal care, as discussed in this priority, is congruent with the research priorities recommended by other working groups (e.g., the Patterns of Care and Efficacy of Treatment and Tolerance working groups).

3. Develop predictive models to allow individual treatment decision making, with a focus on prevention and adjuvant therapy.
   - Predictive models are intended to provide first for individual treatment decision making in the clinical setting.
   - Models with a focus on adjuvant therapy and prevention are also important and will build on the predictive primary therapeutic models.
   - The models should be constructed so as to be clinician friendly and enhance interactive communications among oncologists, primary care practitioners, and geriatricians for optimum decision making. The aim is to incorporate comorbidity assessment into initial cancer patient evaluations.

Research Barriers

- No gold standard or universally accepted assessment tool exists for comorbidity measurement. There are various means of collecting data on patient comorbidity from patients (i.e., self-reports), patient medical records, and administrative databases (e.g., hospital-based discharge data).
- Developers of the assessment tools used for various purposes are invested in and loyal to their methods. The tools used for clinical geriatric assessment tend to be excessive in length (requiring several hours or more) and not suitable for clinical oncology assessment.
- Comorbidity assessment in clinical research is complex. Research methods need to be consolidated, and a research infrastructure must be created to develop methods for incorporation into cancer treatment and care research. This is difficult to achieve, given the perception that comorbidity assessment is an unfunded mandate.
- An antiaging bias may exist in many cancer centers, expressed in the assumption that older patients have comorbid conditions or other factors related to aging that make them unable to withstand treatment or likely to respond poorly to treatment.
- Personnel, an appropriate infrastructure for comorbidity assessment development, and encouragement and support for multidisciplinary interaction are needed. The priority level of comorbidity assessment research needs to be raised.
- Even though comorbidity assessment of older cancer patients has evoked more interest in recent years, technology and

methods development lag far behind the growing clinical- and population-based research needs.

Working Group 4: **Prevention, Risk Assessment, and Screening**

Speakers:
Jeanne Mandelblatt, M.D., M.P.H., Lombardi Cancer Center
Lodovico Balducci, M.D., H. Lee Moffitt Cancer Center and Research Institute

Co-Chairs:
Jeanne Mandelblatt, M.D., M.P.H., Lombardi Cancer Center
Lodovico Balducci, M.D., H. Lee Moffitt Cancer Center and Research Institute

Introduction

Older persons have the highest incidence rates of almost all cancers but the lowest rates of receiving early detection tests of proven efficacy. Whether this is a paradox depends on one's perspective about whether older persons should be screened. Conflicting recommendations exist about upper age limits for screening because of a lack of randomized clinical trials data, enormous heterogeneity among older individuals, and uncertain biology of tumors in aged patients.

In their introductory presentations, Drs. Jeanne Mandelblatt and Lodovico Balducci discussed the demography and biology of aging and cancer and presented evidence on the effectiveness of primary prevention and early detection. Working Group 4 discussed the efficacy and cost-effectiveness of screening, screening research, barriers to screening, the goal of cancer prevention, and the use of chemoprevention techniques in older persons. In the final plenary session of the workshop, several participants cautioned that cancer centers do not offer the best infrastructures for conducting large-scale, population-based studies (e.g., on chemoprevention and lifestyle) that require considerable statistical power. Other research infrastructures, with the participation and leadership of cancer centers, would provide more suitable environments for such studies. This is discussed further in the section entitled Cancer Center Role.

Research Questions

1. Do age biases in the health care system interfere with the delivery of effective, optimal prevention and early detection services?
2. Should upper age or physiologic health limits be established for screening?
3. What are the most appropriate endpoints for primary and secondary prevention in older individuals?
4. What is the efficacy of screening in different age groups?
5. Should screening be done for precursor lesions?
6. Might aging-related changes, gene expression, and other factors, such as molecular markers, in young to middle-aged populations be predictive for malignancies whose progress could be prevented by noninvasive procedures?
7. What system changes would serve as an incentive for physicians to routinely conduct cancer screening and risk assessment in older patients?

Cancer Center Role

Cancer centers can play a prominent role in conducting new screening, prevention, and risk assessment studies of cancer in the elderly. The expansion of knowledge emanating from the cancer centers in basic and clinical sciences should be extended to public health policy and community application in advocacy for access to cancer care and quality cancer care.

Although developing and organizing research networks across cancer center programs, other research institutions, community groups, and providers of care present a considerable challenge, efforts should be undertaken to promote public health goals in cancer screening, prevention, and chemoprevention in older persons. Cancer centers can serve an institutional leadership role by developing clinical oncology/geriatric service teams.

The research priorities of Working Group 4 provoked much discussion among participants in the final plenary session. Several workshop participants who were associated with cancer centers indicated that the large-scale screening and chemoprevention trials suggested in the priorities are not within the purview of cancer centers. Not only are these population-based trials lengthy, but they also require large samples and considerable funding. As one individual said, "These trials are done in people, not patients." Another participant added that, even if unlimited resources were available, cancer centers are unlikely to offer the numbers of research subjects needed to acquire sufficient power for the small effect differences likely to be noted.

Possibly, the cancer centers could conduct pilot studies to address issues such as adherence and recruitment. Cancer center linkage with the community should be encouraged but not necessarily for large-scale screening and chemoprevention trials. A few participants expressed support for the working group's research priorities, however, and gave examples of cancer centers that could achieve these goals, perhaps in certain parts of the country.

Research Priorities

Working Group 4 identified colorectal cancer as a malignant tumor on which little screening research has been done in older persons, who are at high risk for this particular malignancy.

1. Develop and test interventions to decrease screening barriers. *Colon and rectum cancers should receive high priority because of their associated morbidity and mortality in the elderly and the lack of prior research in this area.*
   - Colon cancer ranks third in cancer mortality, after lung and prostate tumors for males, and after lung and breast tumors for females. Over 75 percent of colon cancer deaths and 72 percent of rectum cancer deaths are in individuals aged 65 years and older.
   - When a person is too old to benefit from screening is not clear, although the average 65-year-old has a life expectancy of about 18 years. Progression of a polyp to cancer takes 5–10 years. The highest age-specific incidence and mortality rates per 100,000 population for both males and females are in the age groups 80–84 years and 85 years and older.
2. Conduct chemoprevention and lifestyle change trials to decrease dependency, deterioration in quality of life, and mortality. *The effects of chemoprevention should be studied, beginning at different ages, to identify the optimal age to start enrolling cohorts and determine the agents that should be promoted.*
   - If starting a chemoprevention agent at age 60 years is as effective as it is at age 40, patients could save years of the lifestyle changes involved.
   - Older persons should be oversampled in ongoing, randomized, clinical trials.
   - Enrollment strategies should be developed for older patients.
   - Biorepositories of tissue samples from older patients should be established.
   - For both screening and prevention studies, sufficient statistical power is needed to study race and cultural group differences as well as to stratify by age and gender.
   - Intermediate endpoints, such as functional ability, should be included.
3. Develop models for decision making at the individual and clinical levels, including population forecasting for specific tumors. *Develop models of academic research as well as community networks.* Models can be used to:
   - Synthesize available data to extend the time horizon of observation to answer new questions;
   - Assist clinical decisions by weighing the risks and benefits of a given action;
   - Evaluate upper age limits for prevention and screening decisions;
   - Determine the role of individual preferences in prevention or screening decisions; and
   - Assess the risks, benefits, and costs of new prevention or early detection technologies.

Research Barriers

- Research infrastructure for prevention and screening activities is lacking within

cancer centers, across cancer centers, and in cancer center partnerships with communities.
- Few investigators study both aging and cancer, and no common language exists to evaluate older individuals.
- Collaboration between and among centers should be encouraged.

Caveats

In the final plenary session, Dr. Mandelblatt offered three caveats:
- The research priorities were the opinion of one group,
- The reliability and validity of the priority-setting process have not been validated, and
- The working group had no input from older consumers in its discussion.

Working Group 5: **Psychosocial Issues and Medical Effects**

Speakers:
Patricia A. Ganz, M.D., Jonsson Comprehensive Cancer Center, University of California, Los Angeles
Alice B. Kornblith, Ph.D., Dana-Farber Cancer Institute

Co-Chairs:
Patricia A. Ganz, M.D, Jonsson Comprehensive Cancer Center, University of California, Los Angeles
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Introduction

Psychosocial research in cancer treatment and care is burgeoning, primarily in white, upper-middle-class cancer patients, including within the NCI cooperative group studies. However, older cancer patients are underrepresented in most investigations. The discussions of Working Group 5 focused on disparities in research on quality of life and quality of survival.

Research Questions

1. What are the psychosocial needs of older cancer patients and their caregivers? Who are the most vulnerable?
2. What are the short- and long-term medical effects of treatment that affect older patients and survivors? Who are the most vulnerable?
3. How are the needs and concerns of older patients expressed in diverse communities?
4. What new technologies and culturally relevant strategies can be developed for them?

The prevalence of acute and late medical effects of treatment in older patients and older survivors is, as one participant expressed it, "largely a question mark." Few data are available on the short- and long-term medical effects of cancer treatment in older patients.

Lack of information on the psychosocial and physical health status of the caregivers of older patients prompted their inclusion in Working Group 5's research priorities. A comprehensive database is required in these research areas, with a systematic focus on the older patient and the caregiver, particularly because many caregivers are older, and caregivers are providing more health care because of the increasingly shorter hospital stays of cancer patients.

Cancer Center Role

Research on the fear of cancer recurrence or of a second primary cancer; emotional, psychological, and/or social strain; multiple coexisting and emergent medical problems; and the interaction of comorbid conditions with any or all of these circumstances requires the research expertise and multidisciplinary enrichment offered by a cancer center or cancer center consortium.

Research Priorities

Some issues discussed in Working Group 5 were also addressed by the Patterns of Care and Effects of Comorbidity on Cancer working groups. Working Group 5, however, focused on the psychological and social issues and the medical effects of treatment.

1. Develop a core set of instruments to assess the quality of life of older cancer patients. *An individualized evaluation that includes functional*

status, activities of daily living, cognitive and emotional functioning, and socioeconomic status would standardize the assessment of older patients across cancer centers.

- Instrument development requires 2–3 years, and subsequent testing in selected cancer centers requires an additional 2–3 years.
- Multidisciplinary collaboration among geriatricians, oncologists, psychologists, and oncology nurses is required for instrument development. This could occur in academic settings that include both cancer centers and geriatric centers.
- Existing self-report and objective measures as well as measures that were developed primarily in cancer patients or elderly populations need to be reexamined for their applicability to older cancer patients.
- Instruments need to be developed in diverse populations so that they are representative of a range of minority groups and cultures.

2. Examine the cancer caregiver's functioning and quality of life and impact on the older cancer patient's care and treatment trajectory. *Caregiver strain is likely to be associated with the new primary responsibility for providing cancer care in the home setting.*
   - Cancer care research has focused primarily on the needs of patients. The caregiver role, usually taken on by a spouse, adult child, or sibling, is rarely studied, even though caregivers are responsible for direct and indirect delivery of high-quality cancer care.[1]
   - Family members and friends must take on a new role in providing cancer care that includes a wide range of important responsibilities, such as monitoring symptoms, providing emotional support, administering medications, relieving pain, arranging health care services, and discussing advance directives. The level and length of care required by the patient, as well as the caregiver's health, can compound caregiver strain.
   - Longitudinal studies are needed on the impact of caring for the older cancer patient on the caregiver's quality of life and its reciprocal influence on the patient.
   - Studies should be conducted on the adequacy and quality of caregiving and its impact on the patient's access to and receipt of high-quality cancer care.
3. Develop interventions to prevent or reduce the medical and psychological effects of cancer treatment in older adults.
   - The prevalence of long-term medical and psychosocial effects should be determined.
   - How medical effects of treatment may contribute to additional comorbidity (e.g., second primary tumors, exacerbation of preexisting and/or concomitant age-related comorbid conditions) beyond the normal physical changes associated with aging needs to be examined.
   - Cancer survivor clinics should be established for the follow-up of, and research on, psychosocial issues, late medical effects, early detection of recurrence, and new malignancies.
   - For long-term survivors, normal and cancer- or treatment-induced physical changes should be identified. For example, age-associated factors may induce acute and late treatment effects in normal tissue tolerance and vital organs after radiation treatment of older cancer patients.[2]
   - Clinical studies are needed to develop optimum treatment parameters that will help improve tumor response in older patients with concurrent diseases and conditions. These might include poor

[1] When caregivers provider indirect care, they assume the usual family responsibilities of the sick person before illness. Direct care involves administering medications, checking proper dosage, providing pain relief, monitoring treatment interventions, etc.

[2] Acute effects are problems developed during the standard 6- to 7-week treatment period or shortly thereafter in, for example, the skin or mucosa. Late effects develop months or even years after treatment and may include anemia, alteration of connective tissue, chronic endocarditis, progressive fibrosis of the lung, colonic perforation or obstruction, bladder contraction, vasculature injuries, or a second primary tumor.

physical performance status and morbidity or the special problems sometimes associated with the aging process, including poor repair mechanisms, functional loss, and functional reserve limitations in renal, pulmonary, and cardiovascular organ systems that may contribute to greater susceptibility to treatment toxicity.

These initial descriptive studies will make it possible to develop and test interventions that will improve the medical and psychosocial status of older cancer patients.

Research Barriers

- Measures of quality of life and quality of survivorship that were not developed in older cancer patients may not be sensitive to the psychological and social issues of this population.
- In conjunction with a comprehensive measure of older patients' functional and psychosocial status, *medical databases* must be developed that systematically collect information about selected laboratory tests and patient functioning, as rated by oncologists. This information could be used to complement that obtained by self-report from the patient.
- Without state-of-the-art computer technology, establishing combined databases of older cancer patients' medical and psychosocial data will be more difficult. The newer technologies (e.g., touch screens, handheld tablets or Palm pilots, video telephones) might facilitate the collection of quality-of-life data from older cancer patients.
- The situation of the older cancer patient is very complex and may include health conditions other than cancer, multiple drug regimens, inadequate income, disabilities, lack of support services, and absent or insufficient caregiving. Any of these may impose research barriers.
- More research staff are likely to be needed for studies on older than on younger patients, so *protocol-specific research support for dedicated personnel* is suggested.
- Resources to foster collaboration among geriatricians, gerontologists, and cancer center researchers are urgently needed through *fellowships for geriatric oncologists and multi-institutional support for research collaborations* focusing on older cancer patients.

Working Group 6: **Palliative Care, End-of-Life Care, and Pain Relief**

Speaker:
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Co-Chairs:
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Introduction

Research on treatment- or cancer-related distress has not targeted older cancer patients as a group, even though persons aged 65 years and older experience most of the cancer burden. As a result, knowledge about measures of pain and other types of symptom control and palliative care in older cancer patients is limited. Moreover, palliative care in most adult age groups in the United States has not reached its full potential; attention to this issue is critically important, as 20 percent of the American population will be aged 65 years and older in less than three decades (by 2030). Accelerated strides in cancer therapy have tended to blur the distinction between hope for a cure and recognition that cancer is a terminal illness. In fact, cancer is often considered a chronic disease. However, recent advances in cancer treatment still require aggressive symptom management as well as psychological, social, and spiritual support throughout all phases of cancer diagnosis and treatment in all age groups. Supportive and

palliative care is essential for managing the complications of cancer and its treatment at any stage of the disease. In addition, the psychosocial care of patients and families and care of the dying must be addressed.

Two key national studies have evaluated these issues. The first, a National Cancer Policy Board (NCPB) study, responded to the 1997 Institute of Medicine (IOM) report, Approaching Death: Improving Care at the End of Life, which discussed a range of end-of-life issues. This report received national attention and is now regarded as a milestone in palliative care. Opportunely, the NCPB report Improving Palliative Care for Cancer: Summary and Recommendations was issued by the IOM the week after the NIA/NCI cancer centers workshop. Two cancer center workshop participants, Dr. Kathleen M. Foley, the speaker for Working Group 6, and Dr. Charles S. Cleeland, a participant in Working Group 6, contributed to the NCPB report, which is an excellent resource for all initiatives generated from the priorities of Working Group 6.

Following the lead of the NCPB, Working Group 6 adopted the World Health Organization definition of palliative care as "the active total care of patients whose disease is not responsive to curative treatment." Control of pain; other symptoms; and psychological, social, and spiritual problems are of paramount importance in palliative care, whose goal is to achieve the best quality of life for patients and their families.

In her introductory remarks at the NIA/NCI cancer centers workshop, Dr. Foley indicated that the term palliative care was formerly associated with patients who were clearly near the end of life. In Dr. Foley's view, more comprehensive definitions of palliative care should address the multidimensional aspects—interpersonal, physical, psychological, social, and spiritual—of patients and their families. The primary objective of palliative care is to enhance the quality and meaning of life and death.

Research Questions

1. How can quality cancer care and treatment, including pain management, that provides comfort and reflects patient and family preferences be ensured for older individuals with cancer?
2. What are the available resources/difficulties in the current system for the specific needs of older patients and their caregivers during cancer care?

The lessons learned from palliative care in the older population can apply to all patients. The research priorities of Working Group 6 represent broad-based, epidemiologic studies and translational health services research. The outcomes of the proposed research may improve tolerance of therapy and supportive care and increase participation of the elderly in clinical trials.

Cancer Center Role

The NCPB report's summary and recommendations include a special focus on the contribution that cancer centers, in particular, could make to palliative care research. According to the NCPB, "NCI-designated cancer centers should play a central role as agents of national policy in advancing palliative care research and clinical practice, with initiatives that address many of the barriers identified in this report."

The activities recommended for cancer centers in palliative research include the following examples:

- Formally testing and evaluating new and existing practice guidelines for palliative and end-of-life care, such as pain relief and control of other symptoms;
- Incorporating the best palliative care, pain relief, and depression and fatigue management into NCI-sponsored clinical trials;
- Pilot testing quality indicators for end-of-life care at the patient and institutional level; and
- Developing innovations in the delivery of palliative and end-of-life care, including collaborating with local hospice organizations.

Research Priorities

1. Organize descriptive work that is relevant to older cancer patients in a well-thought-out manner.
   - Outcomes should be correlated with the application of guidelines to comorbidity, treatment-related toxicities, and survival outcomes.
   - Available methodologies for such evaluations need to be identified.
2. Develop and test service delivery models to provide palliative care to the elderly in a variety of contexts that include acute care, home care, and nursing homes.
   - Prospective evaluations of older cancer patients should be implemented in these different settings.
   - Parameters to be examined are cost of care, including the amount of cost shifted to the family (such as time off from work and the resulting loss in wages), and ways to make the models of care cost-effective.
   - Prospective evaluations should address symptom control and end-of-life care over the continuum of care, as opposed to the traditional "cure versus care" approach.
   - Caregivers and their activities should be evaluated to determine who they are, their locations with respect to the elderly patients for whom they care, their availability to provide care, and their own well-being.
   - Special needs and resources, such as mental health, dental health, nutrition, cataracts, and hearing aids, should be addressed in these models.
   - Principles of care that have research support should be applied to all age groups.
3. Test and facilitate the use of evidence-based guidelines for pain relief and symptom control. *Examine drug selection, pharmacokinetics, effects of drugs on surgery, and drug-drug interactions as they relate to agents for comorbidities, chemotherapy, and palliative care medications.*
   - The focus should be on factors that influence decision making and outcomes, such as the ability of patients with comorbidities to understand and tolerate therapies. Physical symptoms need to be distinguished from overlapping psychological problems, such as confusion and depression.
   - Access to care needs to be improved for underserved groups, including minority patients, patients whose primary language is not English, patients with limited financial resources, and patients who live far away from physicians or centers.
   - Best practices for symptom control in the elderly must be determined.
   - Generic guidelines for problems specific to the elderly (e.g., age-related comorbid conditions; limited functional reserve) should be examined.

Research Barriers

- Research in some areas requires descriptive studies before testing interventions. Although descriptive information is greatly needed, it is not usually highly regarded in the academic community.
- Few researchers are trained in geriatrics and palliative care.
- More health care providers in palliative care for the elderly are needed, including medical residents, hospice staff, nurse practitioners, physician assistants, and social workers. Working Group 6 also strongly recommended developing and implementing health professional training programs in palliative care for the elderly.
- The reimbursement and duration of hospice care is limited by current payment systems, which also severely limit options for palliative care, such as radiation therapy, in hospice settings.

Mechanisms

- More experts in palliative care need to participate in research, and this should be encouraged by developing incentives for investigators to design new protocols. This would demonstrate the importance of care for elderly cancer patients and of investigators' participation in research on such care.

- A Specialized Program of Research Excellence (SPORE) in symptom management and palliative care should be implemented.
- Professional education should be provided in cooperative groups and cancer center settings.
- Palliative care should be included in core grant shared resources.
- Existing Web-based resources should be used to disseminate information and assess existing data from Surveillance, Epidemiology, and End Results (SEER).
- Collaborations are needed within geriatric medicine and other pertinent specialties.
- Multidisciplinary approaches to treating elderly patients with cancer are needed to compare the new approaches with traditional models, such as Project Enable (Educate, Nurture, Advise, Before Life Ends).
- A network should be formed with the academic community to conduct research on aging and create links among NIH institutes—such as NIA; the National Heart, Lung, and Blood Institute; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute of Nursing Research—to focus on Alzheimer's disease, heart and lung disease, neurology, arthritis and pain, cancer, and nursing.
- A network should be formed among government agencies, such as the Centers for Medicare and Medicaid Services and the Health Resources and Services Administration, academic/regional cancer centers, and the NIH institutes to implement research findings more rapidly in cancer patients.
- Mechanisms are needed to ease navigation through the system by older cancer patients who require the support of nurses, social workers, and nutritionists. The relative costs of navigating this complex system should be assessed, and a more simple and cost-effective system of health care should be designed.
- A network should be formed with legislative bodies to inform them of findings that can be acted upon rapidly.

Working Group 7:
The Biology of Aging and Cancer

Speaker:
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Co-Chairs:
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Introduction

Recent advances in the scientific understanding of the associations between aging and the development of cancer have facilitated the convergence of research perspectives to identify the molecular alterations in carcinogenesis that are related to the aging process. Common scientific perspectives of biological gerontology and oncology include the following:

1. Regulation of cellular proliferation and expression of oncogenes and tumor suppressor genes;
2. Telomere length and telomerase;
3. Free radical-induced protein and nucleic acid damage, and regulation of apoptosis; and
4. Immune function and response, such as senescence, surveillance, and enhancement.

Refined technologies and key research achievements in the biology of both aging and cancer in these and other areas hold promise for enhancing the knowledge base on the relationship between aging and the natural history of the major tumors—colon, rectum, prostate, pancreas, lung, bladder, stomach, and breast—for which peak incidence and mortality rates occur in the older population. The aging/cancer relationship is well recognized but not well characterized.

Research on the biology of aging and cancer is clinically important. Stratification of the biological characteristics of tumors with age may reveal which aspects of tumor biology and tumor growth vary in different age groups. The age-related factors that contribute to tumor

growth could provide insights that could lead to tailored therapeutic approaches.

The physiologic and other disease conditions of the aged host need to be determined individually to optimize treatment selection. For example, older breast cancer patients are more likely to have estrogen/progesterone-receptor-positive tumors and less abnormal p53 expression than younger patients.

The working group noted that older patients with acute myelogenous leukemia are more likely than younger patients to present with myelodysplasia, have unfavorable cytogenetic profiles, and exhibit inherent drug resistance; they are also less likely to achieve remission. The cytogenetic and molecular genetic subtypes of acute leukemia differ in younger and older persons, and differences in epithelial tumors produce a range of biochemical and molecular changes in older persons, resulting in the vastly different clinical behaviors of these tumors in older and younger patients.

Research Questions

In his introductory remarks, Dr. William B. Ershler posed three questions that were later used to guide discussion in the working group. Dr. Tony Murgo of NCI introduced a fourth, related question in the plenary discussion.

1. Why is cancer more prominent in older persons?
2. Is cancer different in younger and older hosts?
3. Should cancer be treated differently in younger and older hosts?

These questions prompted consideration of the seed versus soil hypotheses. According to the seed hypothesis, tumor cells from older individuals are different from those of younger individuals; according to the soil hypothesis, the fundamental features of senescent hosts favor (restrained or increased) tumor growth.

4. What can we learn about the biology of cancer in the elderly that can be applied to cancer research and cancer treatment in general?

Few data exist to substantiate definitive responses to these questions, but among the theories to explain increased cancer with age are the following:

- Increased time required for cancer development (mutational load),
- Increased susceptibility of cells to carcinogens,
- Decreased ability to repair DNA,
- Dysregulated cellular proliferation, and
- Decline in immune surveillance.

Cancer Center Role

The NCI-designated cancer centers are in a position to create a critical mass of multidisciplinary professionals with expertise in the biology of aging and of cancer. An interactive network of investigators with appropriate resources and technology could catalyze research efforts to elucidate the relationship between aging and cancer in biology. An infrastructure to increase progress in assessment and intervention in regards to cancer in older persons through detection of premalignant disease, early diagnosis of malignant disease, and optimal treatment is developing (e.g., NIA is supporting studies directed at the aging/cancer interface in the Cancer and Leukemia Group B and Southwest Oncology Group).

A consortium of cancer centers could be developed for successful grant applications to:

1. Target cancer centers (those with specific laboratory/clinical expertise and/or access to population bases) and the NIA Claude Pepper and Nathan Shock centers to develop alliances for age-relevant cancer research on specific tumors, and define the minimum requirements for these consortia;
2. Target cooperative groups to conduct Phase III studies and follow-up of completed trials to address cancer survivors' late effects of treatment and conduct translational studies on older persons/patients;
3. Support infrastructure through enhancement grants or supplements for biostatistical support and data management, accrual, and

labor in clinical trials, including core supplements to support specific techniques, such as polymerase chain reaction (PCR), proteomics, informatics, and imaging that require specific types of experts (e.g., statisticians, computer specialists, epidemiologists, gerontologists, and basic scientists);
4. Develop incentives that will attract both junior and senior faculty to aging/cancer research efforts;
5. Encourage junior faculty with career development grants; and
6. Encourage affiliations among cancer centers, cooperative groups, and communities, and create translational supplement awards for these partnerships to support studies on aging and cancer.

Research Priorities

1. Identify the processes and parameters of carcinogenesis in aging cells. *Determine what to look for in cancer progression as it relates to aging.*
   - The current cancer research focus on molecular targets should include secondary genetic changes, environmental (carcinogenic) factors, and microenvironmental (host) factors that may modulate the effects of these targets as a function of aging.
   - The overlap between cancer progression and aging should be addressed by defining the steps involved in tumor initiation, progression, and maintenance.
   - The connection between aging and microenvironments—such as the neovascularization of tumors, immune function, and hormonal control—should be examined, and processes such as oxidant stress and cell death should be considered.
   - Epigenetic mechanisms, such as methylation and multiprotein complex modulation of gene expression, should also be examined.
2. Characterize cancers and cancer cells of the major tumors that are common in older persons. *Determine whether the same types of cancer manifest themselves differently in older and younger hosts.*
   - How cancers of the same subtype differ between older and younger hosts should be determined. Models exist of differences in cancer in older and younger persons. For example, the cytogenetics, molecular genetics, and subtypes of leukemia differ by age, and breast cancer and sarcomas differ in histology, cytogenetics, and tumor sites. Mesenchymal-derived tumors (melanoma, sarcoma, germ cell, hematologic malignancies) behave differently than epithelial-derived tumors in older patients.The constitutive factors that are altered with age (soil hypothesis) and the factors that make tumors different in older persons (seed hypothesis) should be assessed.
   - Human studies that include appropriate controls should be conducted in association with the NCI clinical trials cooperative groups. Differences in the treatment of older cancer patients and their low participation rates in clinical trials currently make it difficult to assess their treatment response. Studying biological issues in the context of standardized treatment would be very useful.
   - The sequence of events in tumorigenesis and cancer progression needs to be explored. Younger and older persons may exhibit the same initiation event, but the sequence of events between that event and the malignancy may differ.
   - The epigenetic differences in older and younger hosts, such as methylation patterns that alter the regulation of tumor suppressors and oncogenes, should be investigated. Recent studies suggest that age-related changes in methylation may explain the differences in cancer.
   - Age-related treatment and outcome differences need to be explained.
   - The effects of cancer on young and old “normal” cells and tissues should be compared.
   - A comparative set of biomarkers needs to be defined. Molecular profiling of malignant and nonmalignant cells may be a useful

approach. Profiles must be created to examine host and tumor factors in relation to aging and cancer progression. Issues for molecular profiling include methylation and epigenetic changes, telomere biology, whole exon sequencing, single nucleotide polymorphism identification, proteomics and genomics, gene expression microarrays, and molecular therapeutic response parameters.
- Tumors should be characterized to examine age-related expression of molecular targets, such as tyrosine kinases. Leukemias may be easier to characterize because of tissue accessibility. Solid tumors are more difficult to characterize, but they have a higher level of heterogeneity.

3. Explore elderly populations at low risk for cancer (i.e., with an age-resistant phenotype). *Identify the genetic or epigenetic changes associated with this protective phenomenon.* Conversely, develop insights about why certain older cancer patients are at high risk for multiple primary tumors. *Identify the key shared predisposing or protective factors for developing multiple primary tumors.*
   - The efficacy of radiotherapy in elderly patients should be explored. Radiobiologic and genetic studies could contribute to the development of information on older patients, because they probably constitute the largest subset of individuals with a greater susceptibility to treatment toxicity due to (1) the inherent cellular radiosensitivity of their tumor cells or normal cells; (2) differences in cellular repair and cell kinetics, including repopulation of normal and malignant cells; and (3) differences in recruitment of normal cells into active proliferation.
   - New technologies should be used to explore old models. Mice mutagenized for other studies might be classified by age; this would make it possible to examine the ability of genes that affect the predisposition for cancer to influence aging rates.
   - New preclinical models should be examined. Animal models with long life spans should be used to generate hypotheses, taking advantage of their extensive characterization and adequate controls to facilitate translation to clinical research.
   - Tissue acquisition programs and tissue banks focused on aging/cancer studies should be developed.

Research Barriers

- Maintaining long-living animal systems is costly.
- Aging research is lengthy. Funding cycles need to be appropriate to the research endeavor.
- Solid tumors are often heterogeneous.
- Quality of clinical data varies, which is also a problem of quantity. Because of the low participation rates of older patients in clinical trials, sufficient statistically valid data are not available.
- Annotation systems differ for mice and humans.
- Translation of data from animal studies to the clinic is problematic because no transfer mechanism exists to allow the free flow of information.
- Ethnic heterogeneity is a significant barrier. For example, Latino populations have different drug resistance gene expression than non-Latino whites. Other racial variations exist in tumor growth, susceptibility, and treatment response of the elderly.

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APPENDICES

AGENDA

Wednesday, June 13, 2001 OPENING EVENING SESSION
Natcher Conference Center, 6:30 p.m.–9:00 p.m.

6:30 p.m. **Registration/Informal Reception**

7:15 p.m. **Welcome and Opening Remarks**
John H. Glick, M.D., Workshop Chairman, Director, University of Pennsylvania Cancer Center

Rosemary Yancik, Ph.D., National Institute on Aging
Margaret E. Holmes, Ph.D., National Cancer Institute

7:30 p.m. **Keynote Presentations**
Geriatric Perspectives on Cancer Care and Treatment
Harvey Jay Cohen, M.D., Duke University Medical Center

Medical Effects of Cancer Care and Treatment
Patricia A. Ganz, M.D., Jonsson Comprehensive Cancer Center, University of California, Los Angeles

8:30 p.m. **Discussion**

9:00 p.m. **Evening Session Adjournment**
Post-Session Briefing for Workshop Chairpersons

Thursday, June 14, 2001 PLENARY SESSION I
Lister Hill Center Auditorium, 7:30 a.m.–1:00 p.m.

7:30 a.m. **Registration/Continental Breakfast**

8:00 a.m. **Director's Welcome**
Richard J. Hodes, M.D., Director, National Institute on Aging
Richard D. Klausner, M.D., Director, National Cancer Institute

Welcome/Workshop Aims/Meeting Format
John H. Glick, M.D., Workshop Chairman, Director, University of Pennsylvania Cancer Center

Rosemary Yancik, Ph.D., National Institute on Aging
Margaret E. Holmes, Ph.D., National Cancer Institute

SCIENTIFIC ORIENTATION PRESENTATIONS

8:15 a.m. **Patterns of Care**
Working Group 1
Co-Chairs: Paul F. Engstrom, M.D., Fox Chase Cancer Center
Jerome W. Yates, M.D., M.P.H., Roswell Park Cancer Institute
Speaker: Vincent Mor, Ph.D., Brown University

8:45 a.m. **Treatment Efficacy and Tolerance**
Working Group 2
Co-Chairs: Richard L. Schilsky, M.D., University of Chicago
Joel E. Tepper, M.D., University of North Carolina School of Medicine
Speaker: Richard L. Schilsky, M.D., University of Chicago

9:15 a.m. **Effects of Comorbidity on Cancer**
Working Group 3
Co-Chairs: Hyman B. Muss, M.D., University of Vermont
Kathy Albain, M.D., Loyola University Medical Center
Speakers: William A. Satariano, Ph.D., M.P.H., University of California, Berkeley
Hyman B. Muss, M.D., Fletcher Allen Health Care Center, University of Vermont

9:45 a.m. **Prevention, Risk Assessment, and Screening**
Working Group 4
Co-Chairs and Speakers:
Jeanne Mandelblatt, M.D., M.P.H., Lombardi Cancer Center
Lodovico Balducci, M.D., H. Lee Moffitt Cancer Center

10:15 a.m. **Discussion/Speaker Panel**
Patterns of Care
Treatment Efficacy and Tolerance
Effects of Comorbidity on Cancer
Prevention, Risk Assessment, and Screening

10:30 a.m. **Break**

11:00 a.m. **Psychosocial Issues and Medical Effects**
Working Group 5
Co-Chairs: Patricia A. Ganz, M.D., University of California, Los Angeles
Alice B. Kornblith, Ph.D., Dana-Farber Cancer Institute
Speaker: Alice B. Kornblith, Ph.D., Dana-Farber Cancer Institute

11:30 a.m. **Palliative Care, End of Life Care, and Pain Relief**

Working Group 6

Co-Chairs: Nora Janjan, M.D., University of Texas, M.D. Anderson Cancer Center

Ruth McCorkle, R.N., Ph.D., F.A.A.N., Yale University School of Nursing

Speaker: Kathleen M. Foley, M.D., Memorial Sloan-Kettering Cancer Center

12:00 p.m. **The Biology of Aging and Cancer**

Working Group 7

Co-Chairs: Harvey Jay Cohen, M.D., Duke University Medical Center

Derek Raghavan, M.D., Ph.D., Norris Comprehensive Cancer Center, University of Southern California School of Medicine

Speaker: William B. Ershler, M.D., Institute for Advanced Studies in Aging and Geriatric Medicine, Washington, D.C.

12:30 p.m. **Discussion/Speaker Panel**

Psychosocial Issues and Medical Effects
Palliative Care, End of Life Care, and Pain Relief
The Biology of Aging and Cancer

1:00 p.m. **Box Lunch**

Natcher Conference Center

1:45 p.m. **Afternoon Breakout Groups**

Natcher Conference Center Meeting Rooms
Please See Room Assignment Sheet in Program Book

3:30 p.m. **Break**

3:45 p.m. **Breakout Groups Resume**

5:30 p.m. **Day One Adjournment**

Working Group Report Preparation by Co-Chairs and Collaborators

Friday, June 15, 2001 PLENARY SESSION II. WORKING GROUP REPORTS *
Lister Hill Center Auditorium, 8:30 a.m.–1:00 p.m.

8:30 a.m. **Patterns of Care**
Working Group 1, Co-Chairs – Paul F. Engstrom, M.D.; Jerome W. Yates, M.D., M.P.H.

9:00 a.m. **Treatment Efficacy and Tolerance**
Working Group 2, Co-Chairs – Richard L. Schilsky, M.D.; Joel E. Tepper, M.D.

9:30 a.m. **Effects of Comorbidity on Cancer**
Working Group 3, Co-Chairs – Hyman B. Muss, M.D.; Kathy Albain, M.D.

10:00 a.m. **Prevention, Risk Assessment, and Screening**
Working Group 4, Co-Chairs – Jeanne Mandelblatt, M.D., M.P.H.; Lodovico Balducci, M.D.

10:30 a.m. **Break**

11:00 a.m. **Psychosocial Issues and Medical Effects**
Working Group 5, Co-Chairs – Patricia A. Ganz, M.D.; Alice B. Kornblith, Ph.D.

11:30 a.m. **Palliative Care, End of Life Care, and Pain Relief**
Working Group 6, Co-Chairs – Nora Janjan, M.D.; Ruth McCorkle, R.N., Ph.D., F.A.A.N.

12:00 noon **The Biology of Aging and Cancer**
Working Group 7, Co-Chairs – Harvey Jay Cohen, M.D.; Derek Raghavan, M.D., Ph.D.

12:30 p.m. **General Discussion**

1:00 p.m. **Workshop Adjournment**

***Participant discussion follows each working group report.**

Geriatric Perspectives on Cancer Care and Treatment

Harvey Jay Cohen, M.D., Duke University Medical Center, Durham, North Carolina

Cancer is the second leading cause of death for the growing number of individuals over the age of 65. Geriatrics and oncology share the approach of considering the whole patient. In that respect, many principles of care are similar. In the geriatric approach, however, particular attention is directed toward the situation in which aging-related changes affect the clinical expression, course, and treatment of disease. Applying geriatric principles to the care of elderly cancer patients may be one approach to enhancing care. These principles include recognizing that aging per se is not a disease but a process. It occurs at different rates in different organ systems and in different individuals. It reduces physiologic reserve and makes the elderly more susceptible to many diseases and also increases risks during diagnostic and therapeutic interventions. Improving and maintaining functional capacity is a major goal, as is recognizing the appropriateness of cure vs. care and the importance of comfort care when appropriate. In older individuals, cancer frequently occurs in persons who have other chronic comorbid conditions. They may be multiple in nature and present atypically and sometimes involve both physical and cognitive alterations. Diagnosis and planning for treatment should involve geriatric assessment to evaluate the biological, psychological, socioeconomic, and functional aspects of a patient's condition. Planning for care may incorporate all aspects of the evaluation including age-related alterations in physiologic status, altered functional status, altered pharmacokinetics, comorbidities, cognitive status, quality of life, and caregiver and family issues. All specific cancer-related therapeutic modalities (i.e., surgery, radiation therapy, and chemotherapy) may be affected by age-related changes. However, changes in drug metabolism and excretion demand particular attention. Hopefully, by incorporating these geriatric principles into the care of the elderly patient with malignancies, improved outcomes can be achieved.

Late Effects of Cancer Treatment

Patricia A. Ganz, M.D., University of California at Los Angeles School of Medicine and Public Health, Jonsson Comprehensive Cancer Center, Los Angeles, California

With the growing number of cancer survivors, there is increased interest in the late effects of cancer treatment. As cancer is primarily a disease of older persons, there is an urgent need to address the interaction of the physiologic late effects of cancer treatment in the aging population as well as in association with various comorbid conditions. This presentation uses a quality-of-life perspective to review what is known about the late effects of various cancer treatments (e.g., surgery, radiation, chemotherapy) and their interaction in multimodal therapies. The tables below describe the content areas to be reviewed:

Table 1. Common Physical and Medical Late Effects of Cancer Treatment

Body changes: scars, disfigurement, amputation
Cardiorespiratory symptoms
Cognitive dysfunction
Fatigue or decreased energy
Immune dysfunction
Infertility
Lymphedema
Osteoporosis/fractures
Pain
Premature menopause
Second cancers
Sexual dysfunction
Skin sensitivity to UV radiation
Urinary incontinence

Table 2. Psychological Late Effects of Cancer

Concerns about the future, death
Depression, sadness
Feelings of gratitude and good fortune
Health worries, hypervigilance
Inability to make plans
Self-esteem, mastery
Uncertainty and vulnerability

Table 3. Social Late Effects of Cancer

Affinity and altruism
Alienation and isolation
Comparison with peers
Social relationship changes
Socioeconomic concerns: health insurance, job, return to school, financial impact

Table 4. Existential and Spiritual Late Effects of Cancer

Appreciation of life
Changed or new orientation to time and future
Changed values and goals
Concerns about death and dying
Sense of purpose

Example cases are discussed to illustrate the issues cancer survivors face and the strategies that might be used to increase systematic information gathering on this topic.

Age Differences in Patterns of Cancer Treatment: A Summary and Review of Issues

Vincent Mor, Ph.D., Brown University, Providence, Rhode Island

Cancer is an age-related disease. Most cancers increase progressively with age and some do not peak until after age 85. Over the past 20 years there have been treatment advances in breast, colon, and even lung cancer along with other solid and hematological tumors, making it possible that overall cancer survival might increase. In spite of these advances, however, the proportion of the population with cancer who are receiving treatments that have been shown to be effective varies dramatically according to demographic characteristics of the patients as well as by region of the country. Thus, older persons, people of color, and the poor and uninsured, regardless of color, are less likely to receive "standard" and effective cancer treatment. Although treatment differences associated with race, poverty, and insurance status are attributable to the fact that these groups of individuals have less access to high-quality medical care, there is considerable argument about the legitimacy of the observed age-related differences. The purpose of this talk is to summarize the literature documenting age differences in cancer treatment and to highlight several factors that some suggest "explain" and justify these differences: comorbidity, patient and family preferences, and quality of life versus quantity of survival. Finally, I end by speculating that transmitting the message about the need to treat older cancer patients is difficult because it is conditional not on age but on pre-existing health state and changing perspectives on the likelihood of survival.

Despite worldwide evidence about the effectiveness of treatments for early stage breast cancer, age differences persist in the receipt of appropriate therapy (Mor et al., 1985; Silliman et al., 1989; Bergman et al., 1991). Women older than 80 years of age (and younger than 40) have poorer survival rates than others (Chung et al., 1996). A recent analysis of the survival consequences of incomplete breast cancer treatment among older women revealed an adjusted relative risk of 5-year mortality of 1.7 (Lash et al., 2001). In the case of lung cancer, advanced age is consistently associated with receiving less aggressive care. Surgery is potentially curative for patients with stages I, II, and IIIa/b non-small cell lung cancer, where preoperative assessment suggests that the patient would not be a respiratory cripple and would be able to undergo surgery. Although there is a slightly

increased risk of mortality with age, more than 90% of people aged 80 and older who undergo surgery for lung cancer survive surgery. Yet, research clearly demonstrates that most elderly persons are not offered that treatment option (Greenberg et al., 1983; Mor et al., 1987). Indeed, a multivariate logistic regression model with SEER data found that age was inversely associated with receipt of chemotherapy (AOR 0.46 for each incremental decade of life). Similar findings obtain in the case of colon cancer (Chu, 1986; Mor et al., 1987; Samet et al., 1985). Interventions to reduce these differences in treatment have not been successful in changing physicians' referral patterns (Mor et al., 2001).

Critics of this research suggest that age-related comorbidity accounts for the differences, although many of the studies controlled for it. Others note that patients and their families are unwilling to undergo aggressive treatment, but there is little evidence to support this contention. However, because very old and sick patients are less likely to benefit from treatment in terms of survival, treatment recommendations for the aged are necessarily conditional, which complicates the message and, as we know, reduces its effectiveness. What is needed is research to understand how to best deliver such conditional messages in a manner that will overcome prejudice on the one hand without leading to excessive and unnecessary treatment on the other.

Treatment Tolerance and Efficacy in the Elderly

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Cancer is largely a disease of the elderly and as the percentage of the U.S. population over the age of 65 continues to increase, a rapid expansion in the number of cancer cases among elderly individuals will occur. Special considerations in older cancer patients include the impact of comorbidity, organ dysfunction, drug interactions, cognitive dysfunction, and social support on treatment tolerance and outcomes. Because of these issues, elderly cancer patients display a great deal more interindividual variability than do younger patients and therefore represent a difficult challenge in treatment optimization. Although changes in body composition and organ function occur with age, there is little evidence that these changes result in significant differences in chemotherapy tolerance among older patients. For example, paclitaxel clearance declines with age and results in increased neutropenia but no clinically significant change in infectious complications or hospitalization rates.

The larger number of drugs used by older individuals has the potential to increase the frequency of drug interactions with chemotherapy agents, particularly those metabolized by CYP3A4. Although the elderly are underrepresented in cancer clinical trials, it is possible to examine the effect of age on treatment outcomes in many studies. In a study of non-small cell lung cancer patients up to age 80 years, the CALGB found no differences by age in treatment discontinuation for toxicity, response rate, or survival after treatment with cisplatin-based chemotherapy. In a meta-analysis of adjuvant chemotherapy trials for stage B2-C colon cancer, the NCCTG found a similar benefit from treatment for all age groups examined with little difference in toxicity by age cohort.

Breast cancer in older women has been extensively studied and appears to have biological features associated with more indolent disease. The benefits of adjuvant hormone and chemotherapy are equivalent in older and younger women, and older women with metastatic disease achieve response rates, TTP, and survival similar to those of younger women following doxorubicin-based chemotherapy.

Women over age 70 years with early stage breast cancer are more likely to die from non-cancer-

related causes than from complications of breast cancer and should be treated conservatively. Older patients with non-Hodgkin's lymphoma appear to have worse survival than younger patients independent of stage and performance status, yet *a priori* attenuation of chemotherapy doses and death due to comorbid illness likely contribute to the apparently worse outcomes. Vigorous supportive care, including the use of hematopoietic growth factors, appears to permit maintenance of dose intensity with acceptable toxicity in patients up to age 70 years.

Important areas of future research include better defining and assessing functional status and "functional reserve," studying drug interactions between chemotherapy agents and other drugs commonly used by the elderly, and developing treatment regimens that are less toxic but retain the efficacy of established treatment programs.

The Effect of Comorbidity on Cancer

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Comorbidity (i.e., the presence of two or more concurrent health conditions in the same person) has a significant effect on cancer incidence and survival. Specific health conditions, such as diabetes, have been shown to increase the risk of particular cancers. Other conditions (e.g., cardiovascular disease) have an adverse effect on the quality and duration of life among cancer patients.

Cancer patients aged 65 and older are more likely than younger cancer patients to have comorbid conditions. For that reason, comorbidity may significantly complicate the treatment protocols for older patients.

The purpose of this presentation is (a) to critically review the current methods and sources of data for studies of comorbidity, and (b) to identify and evaluate new directions for research on the effects of comorbidity on cancer treatment and prognosis. Criteria for the selection of comorbid conditions include the overall prevalence of the conditions and the effect of those conditions on health outcomes, such as cost of care, disability, and mortality. Severity of comorbidity is typically assessed in terms of the independent risk of death associated with that condition. Personal interviews, medical records, computerized hospital discharge summaries, and death certificates have all served as sources of data on comorbidity. Additive, summary comorbidity indexes, commonly used in studies of cancer treatment and prognosis, are reviewed, and the effects of those scales on the conduct of clinical and epidemiologic research are assessed.

New directions for clinical and epidemiologic research include the following: (a) identifying new sources of data on comorbidity, especially for longitudinal studies that involve repeated assessments of the number and types of health conditions; (b) establishing new criteria for assessing severity, including physiologic markers such as serum albumin; and (c) developing and evaluating multiplicative comorbidity indexes. Finally, it is recommended that studies also be developed to assess the effects of newly diagnosed cancer on the course of preexisting comorbid conditions in older patients. Together, these studies should contribute to effective treatments for cancer in older populations.

Cancer Prevention in the Older Person: The Role of Comprehensive Cancer Centers (CCC)

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The incidence and prevalence of malignant diseases continue to increase in the older

population; the median age of cancer patients in the United States is 70 years. With the "graying of America," cancer prevention and early detection targeted to the growing older populations have the potential to lessen the morbidity and mortality related to cancer and cancer treatment. In this session, we examine (a) the biology of cancer and aging, which affect decisions about optimal prevention and early detection strategies; (b) current evidence about the effectiveness and cost-effectiveness of prevention and early detection; and (c) potential leadership roles of comprehensive cancer centers (CCC) in studying and promoting cancer prevention and early detection among the elderly.

Primary prevention of cancer through chemoprevention may have an appropriate role given the enhanced susceptibility of aging tissues to environmental carcinogens. However, these benefits need to be balanced by risks of susceptibility to therapeutic complications, such as deep vein thrombosis or cerebrovascular accidents caused by selective estrogen receptor modulators (SERMs) and reduced life expectancy due to comorbid conditions.

Secondary prevention of cancer through screening can be more effective in older than in younger populations because of the improved positive predictive value of screening tests as a result of the rising prevalence of cancer and the increased sensitivity of some screening techniques such as mammography. The value of early cancer detection may be lessened by reduced life expectancy from concomitant conditions. However, once prevalent disease is removed from the screening pool, true new disease rates may be lower. A number of sociocultural barriers may interfere with instituting effective cancer prevention in older individuals. Finally, the costs of continuing screening into the last decades of life may be high relative to the risks and benefits, although new screening technologies may hold greater promise as tools for older populations.

Given the concentration of resources devoted to cancer research, CCCs are in a privileged position to promote and study cancer prevention in this high-risk population. In addition to the development of new chemopreventive agents and new and more accurate screening techniques, CCCs could facilitate cancer prevention and early detection in the elderly through special initiatives that include the following: (a) research in molecular aging aimed at identifying the mechanisms of enhanced susceptibility to environmental carcinogens and at establishing which age-related changes favor the growth and the spread of cancer; (b) decision analysis aimed at selecting the older individuals who will most benefit from cancer primary and secondary prevention at the most reasonable costs; (c) research on patient preferences and shared decision making; and (d) establishing a network of institutions able to translate basic science insights, clinical trials, and observational research in cancer prevention/early detection into diverse communities. Such a network could share expertise, collaborate on research, build databases, and disseminate results.

CCCs are ideally positioned to take the lead in cancer control for older Americans. Such initiatives will readily translate into improvements in the quality of care delivered to older individuals at risk for and with cancer.

Quality of Life of the Older Cancer Patient

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Two large separate bodies of literature describe the quality of life and psychosocial functioning of the geriatric population and the cancer patient population. Few studies are devoted to assessing the overlapping characteristics of these two groups: the older cancer patient population. Although the prevalence of psychiatric

disorders is largely unknown in older cancer patients, studies have consistently found a modest, inverse relationship between age and adjustment, with better adjustment and less depression in older cancer patients than in their younger counterparts, a relationship that is independent of patients' physical status. Although possible reasons have been speculated to explain this phenomenon, none has been empirically determined. Greater psychological distress in older patients is significantly related to a worsening of their physical status, including issues such as metastatic disease, worsening physical functioning and symptom severity, and nonphysical factors such as inadequate social support. Those at greatest risk of poor social support were those aged 85 years and older, with lower income, and who had more recently moved to their current residence. Despite the shrinkage of older cancer patients' social support system with aging, due to deaths of family members and friends and to family and friends moving away, a number of studies document that most older cancer patients report high levels of social support. Goodwin et al.'s (1991) study documented that over 80% of newly diagnosed older cancer patients had weekly contact with friends and relatives in their area.

The impact of caring for older cancer patients on primary caregivers has also begun to be studied. As with older cancer patients, older caregivers report less depression, less disruption to their daily routines, and fewer financial problems than those who are younger. Yet, older caregivers report significant levels of depression, with 31.5% scoring at levels that suggest clinical depression and with 50% reporting disruption to their daily routines and socializing (Mor et al., 1994). Studies of mixed age groups of cancer patients indicate that caregivers' distress increases in relation to multiple factors, including patients' worsening physical condition, greater patient care needs, patients' increasing depression, increasing loss in caregivers' physical strength, a poor marital relationship, and a patient's nonempathic physician (Kurtz et al., 1995; Nijboer et al., 1999; Emanuel et al., 2000). The relative risk of mortality of older caregivers for cardiovascular patients was 1.63, representing a 63% increase in mortality over a 4-year period compared with spouses of nondisabled patients (Schulz and Beach, 1999). If this finding applies to older spouses of cancer patients, it underscores the serious consequences of the stresses of caregiving on the older family member.

The primary future research needs in quality of life of the older cancer patient include the longitudinal evaluation of the impact of cancer treatment on the quality of life of older patients and their family members, primarily through the use of randomized Phase III trials, to compare the effect of different cancer treatments. Through this research paradigm, the prevalence of psychiatric disorders and psychological strengths of older cancer patients could be studied along with the neuropsychological effects of cancer treatments as well as the role of the relationship of the oncologist to patients' and family members' adjustment. The vulnerability model (Kornblith, 1998) is proposed as a theoretical framework by which to understand older cancer patients' adaptation, taking into account a range of factors (e.g., cancer and its treatment, physical functioning, economic, personality, social, and medical management) that may exacerbate or ameliorate the stress of having been treated for cancer. With a better understanding of the issues that affect older cancer patients' lives, interventions can be developed and targeted to improve the quality of life of the most vulnerable older cancer patients and their family members. The most promising areas include interventions designed to improve psychosocial functioning, informational devices such as decision aids to better meet patients' informational needs, and techniques to improve doctor-patient/family communication. This research agenda needs to go hand in hand with instrument development and refinement to improve assessment of geriatric-specific quality-of-life issues along with a reexamination of the reliability and validity of existing measures to verify their adequacy for older cancer patients.

Palliative Care in the Elderly

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As we focus on enhancing the quality of life for our aging population, special attention should be given to the quality of living for elderly cancer patients and their caregivers. Every day 1800 cancer patients die in the United States and most are over the age of 65. Numerous studies have identified deficiencies in end-of-life care for cancer patients. The Institute of Medicine 1997 report "Approaching Death" summarized the significant gaps in scientific knowledge needing serious attention from biomedical, social science, and health service researchers. The report recognized significant organizational, economic, legal, and educational impediments to good care and indicated health care professionals' lack of education and knowledge about end-of-life care as one of the major barriers to improving care.

The World Health Organization, the President's Cancer Panel, and the National Cancer Policy Board have strongly endorsed the importance of palliative care as an integral aspect of cancer care. "Palliative care is the active total care of patients whose disease is not responsive to cancer treatment. Control of pain, other symptoms, psychological and spiritual distress is paramount. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with anticancer treatments." Elderly cancer patients with advanced disease experience eight major symptoms that interfere with their quality of life. Two recent nursing home studies reported that severe pain in elderly nursing home residents with cancer is prevalent, persistent, and poorly managed. Anxiety, depression, and suicide have an increased incidence in the elderly with cancer. Both underdiagnosis and undertreatment are well documented in national surveys.

Economic issues have focused attention on the fact that one of eight Medicare dollars is spent in the last 3 weeks of life and the cost of care for cancer patients is 20% higher than the cost of caring for other patients. An increasing shortage of nurses, a shortage of caregivers, and a high caregiver burden add complexity and urgency to the need to shape a better system of care appropriate for our aging population. Palliative care should be fully integrated into a geriatric cancer program to facilitate patients' ability to receive quality cancer care from diagnosis to death. Palliative care research must address the special needs of the aging population to facilitate the evidence-based guidelines for pain relief, symptom control, and service delivery models for the care of the frail elderly.

Aging and Cancer: Biologic Interface

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Oncologists and gerontologists have long been examining common biological processes. Thus, the genetic, molecular, and biochemical regulators of cellular proliferation, transformation, and death are fertile investigational domains in both disciplines. Central to the aging/cancer nexus are two basic questions:

- How does aging predispose to cancer?
- Do tumors in older animals have different malignant properties?

Explanations for increased cancers in old animals include an increased susceptibility to carcinogenic exposure, impaired DNA repair, altered regulation of cellular proliferation, and impaired immune surveillance. Perhaps as significant as these factors, the most important explanation relates to the time required to progress from normal tissue to invasive cancer, which is estimated to be decades for most human epithelial cancers.

Clinicians are well aware that histologically identical tumors have different patterns of growth and spread in older patients. This may not be a consequence of aging as much as it is that older patients are more likely to have

Figure 1

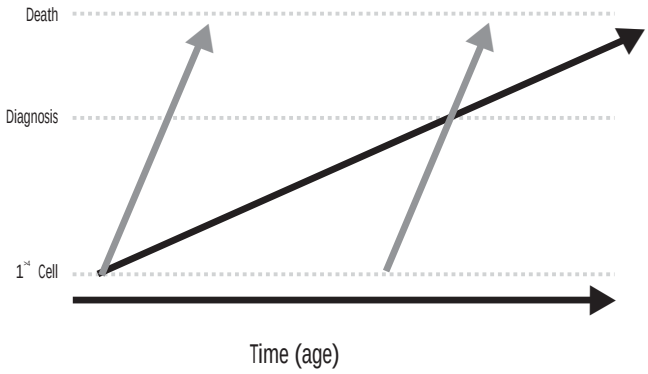
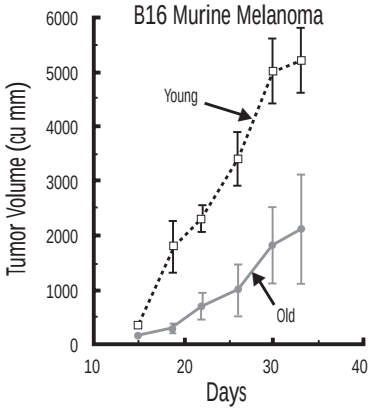


Figure 2



tumors that take a long time to develop and grow ("Seed Hypothesis"; Fig. 1). However, it is also clear that genetically identical cells growing in experimental animals of disparate ages have different rates of growth (Fig. 2) and different patterns of spread.

It is now clear that tumor cells are, indeed, different in young and old hosts. Thus, older women with breast cancer are more likely to have tumor cells that express estrogen and progesterone receptors, less accumulation of abnormal p53 and laminin, less lymphovascular invasion, less DNA ploidy, fewer cells in division, and more favorable histologies. Such is typically observed for all the common epithelial tumors, including colon, lung, and prostate—tumors for which the median age is older than 70 years. Yet, "soil" factors are also demonstrably influential. To the extent that aging influences those host-derived tissue factors that contribute to the tumor microenvironment, it might be less favorable for cell proliferation, tumor growth, and spread. Thus, host-derived angiogenesis and other growth factors, nutritional adequacy, and matrix protein alterations might, in composite, present a less favorable environment for tumor growth in senescent tissues ("Soil Hypothesis").

At the cellular and subcellular level, common processes of aging and cancer are becoming more clearly defined. It is no surprise that cancer is generally an old person's disease. Although this has been appreciated for a long time, clinical advances in oncology have been slow in developing.

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CROSS-CUTTING ISSUES IN WORKING GROUP REPORTS

	Working Groups						
	1	2	3	4	5	6	7
Cancer Center Role							
Collaborate with SEER	■		■			■	
Enhance research linkages with other cancer centers to increase population size for research	■			■			■
Provide organized, multidisciplinary research infrastructure		■	■		■		■
Advocacy for access, quality care, and funding				■		■	
Conduct pilot studies			■	■		■	
Test and evaluate new practice guidelines						■	
Incorporate best care into clinical trials						■	
Collaborate with local care providers to develop innovations in delivery of care						■	
Research Questions							
What is the impact of comorbidities on older cancer patients and the care they receive?	■	■	■			■	
Does and should treatment differ in older and younger patients?	■			■			
What type of care do older cancer patients need?	■	■	■	■	■		
What type of care do elderly cancer patients receive?	■		■				
Research Priorities							
Explore existing research	■					■	
Develop and test interventions		■	■	■	■	■	
Develop validated assessment instrument		■	■	■	■	■	
Incorporate cancer center expertise into NCI projects	■	■	■				
Learn more about cancer in elderly populations	■	■	■	■	■	■	■
Research Barriers							
Cancer centers are not well suited to the kinds of research needed	■			■			
More experts in different fields, with relevant experience, are needed to do research			■	■	■	■	
Need more multidisciplinary, multi-institutional collaboration	■	■		■	■		
Antiaging bias of many researchers		■	■				
Recruiting older patients into clinical trials and studying them is difficult, costly, time consuming		■	■		■		■
Research tools for this population are lacking		■	■		■	■	
Healthcare system is not set up to provide appropriate care to the elderly				■		■	