

CANCER IN THE ELDERLY

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ABSTRACT

As the population expands, over the period from 2000 to 2050, the number and percentage of Americans over age 65 is expected to double. This population expansion will be accompanied by a marked increase in patients requiring care for disorders with high prevalence in the elderly. Since cancer incidence increases exponentially with advancing age, it is expected that there will be a surge in older cancer patients that will challenge both healthcare institutions and healthcare professionals. In anticipation of this challenge, researchers at the Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, Ohio are conducting a series of investigations focused on the intersection of aging and cancer. Studies will be addressed in the high priority research areas of 1) Treatment Efficacy and Tolerance, 2) Effects of Comorbidities, 3) Psychosocial Issues, and 4) Biology of Aging Cancer.

Population Aging

As life expectancy increases, many countries are experiencing an increase in older individuals, both in terms of absolute numbers and as a proportion of the total population (1–4). In the United States, this “aging” or “graying” of the population is being accentuated as the “baby boomers”, those born in post World War II America, from 1946–1964, approach age 65 and beyond. At the turn of the century, 13% of the American population, approximately 35 million individuals, were age 65 and over. By 2050, it is expected that this number will double and

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Final Revision December 22, 2005.

reach 70 million individuals over 65 years of age. In addition, because of the decreased birth rate, those over 65 will increase to constitute 20% of the American population. Not only will there be an increase in number of individuals older than 65, but the life expectancy of those over 65 has increased so that the numbers of those over 85 is expected to double to 8.9 million by 2050 and there will even be an increase in centenarians (1–4). This graying of the population will have important socioeconomic and political consequences. It will profoundly impact the health care industry as more resources and personnel will be required to care for the elderly. Even the very nature of healthcare services is likely to change as some of the unique needs of elder patients become more apparent.

The Intersection of Aging and Cancer

As the population ages, many diseases that predominantly affect older individuals will become more prevalent. Moreover many conditions that affect the elderly will occur in combination, thereby complicating care for any specific condition (5,6). Advancing age is a high risk factor for cancer, with persons over 65 accounting for 60% of newly diagnosed malignancies and 70% of all cancer deaths (7,8). The age adjusted cancer incidence rate is 2151/100,000 population for those over 65 compared to 208/100,000 for those under 65 (7,8). Similarly, the age adjusted cancer mortality rate for those over 65 is 1068/100,000 compared to 67/100,000 for those under 65 (7,8). Thus, the incidence of cancer in those over 65 is 10 times greater than in those younger than 65 and the cancer death rate is 16 times greater in patients over 65 compared to younger patients. More than 70% of the mortality associated with many cancers including prostate, bladder, colon, uterus, pancreas, stomach, rectum and lung occur in patients 65 and older (7,8). Even with a progressive decrease in the cancer incidence and death rate, aging of the population will be accompanied by a marked increase in the total number of patients with cancer and the need for physicians and caretakers to have special expertise in both oncology and geriatrics.

The graying demographics in the United States and the fact that cancer incidence in humans rises exponentially in the final decades of life, suggests that cancer may soon replace heart disease as the leading cause of death in this country. These demographics raise critical challenges to be met by American medicine. In addition to indicating the importance of preparing to deal with the increased burden of cancer, these data give rise to a number of questions regarding the relation of

aging to cancer. Why is cancer more prominent in older patients? Is cancer different in older patients? Should cancer be treated differently in younger and older patients? What can be learned about the biology of cancer in the elderly that can be applied to cancer research and treatment in general?

Research at the Aging-Cancer Interface

Anticipating the surge in cancer patients among older Americans, in 2001 the National Institute of Aging and the National Cancer Institute (NIA-NCI) convened a workshop to identify priorities and stimulate research efforts to improve the outlook for this group of patients (8). The Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, Ohio is one of eight centers in the United States to be awarded a NIA-NCI-funded P20 Program Development Grant to stimulate research at the intersection of aging and cancer. Aging-Cancer P20 Grants were awarded also to cancer centers at Memorial Sloan Kettering, University of Pittsburgh, University of Iowa, University of South Florida, University of Wisconsin, University of Colorado and University of Washington. To address the interaction of aging and cancer these institutions are pursuing research in eight high priority areas identified by the NIA and NCI workshop (8). Investigations at the Case Comprehensive Cancer Center are focused in four of these research priority areas, 1) treatment efficacy and tolerance, 2) effects of comorbidities in patients with cancer, 3) psychosocial issues, and 4) biology of aging and cancer.

Treatment Efficacy and Tolerance in Older Patients with Cancer

In the area of treatment efficacy and tolerance, several early phase agents are being evaluated in clinical trials in elderly patients along with their pharmacodynamics and pharmacokinetics. At the same time, important studies are being conducted on age bias or "ageism" as a factor in selecting or recommending prevention, screening, therapy or other clinical approaches based on age rather than evidence-based medicine. In a retrospective review of 81 patients with treatable head and neck cancer, 96% of those under age 65 were treated with radiation and two chemotherapy agents, which is the standard of care at our institution (9). In contrast, only 62% of those over age 65 received radiation therapy along with two chemotherapy agents. In another retrospective review, conducted at multiple institutions, therapeutic interventions were examined for 131 elder patients with ovarian can-

cer (10). Of those between the ages of 70–79 years, 89% underwent debulking surgery and 87% received platinum based combination chemotherapy. Of those women above 80 years old, only 61% underwent debulking surgery and 46% received platinum based combination chemotherapy. These studies support the concept that when appropriate treatment has been identified, older patients are less likely to receive the standard of care.

While less aggressive therapy may be warranted in some older individuals, there is little evidence to demonstrate comparable or even beneficial outcomes with reduced intensity regimens. Future studies are clearly needed to provide a basis for determining how tumors in elder patients, including those with comorbidities, respond to therapy; how therapeutic agents are metabolized by elder patients; what types and how severe are the toxicities produced in elderly patients; how therapeutic maneuvers and their toxicities affect quality of life and outcomes; and how toxicities may be ameliorated so that older patients can obtain full course regimens and optimal benefits from therapy.

Effects of Comorbidities on Cancer

Since patients are likely to acquire an increasing number of maladies with increasing age, strategies to prevent, screen or treat cancer in older subjects will potentially be impacted by a variety of comorbidities (5,6). A new approach at Case Western Reserve University to evaluate the impact of comorbidities in patients with cancer has been to establish a Cancer-Aging Linked Database (CALD) for patients in the State of Ohio (11,12). The CALD accesses and merges information from a series of databases including the Ohio Cancer Incidence Surveillance System (cancer is a reportable disease in Ohio), the Ohio Death Certificate File, Census Block Data which provides an assessment of income, education and socioeconomic status, Medicaid and Medicare Enrollment and Claims Files, Home Health Outcome and Assessment Information System and Long-Term Care Minimum Data Set.

Using the CALD resource, it has been possible to identify comorbidities: geriatric syndromes, such as incontinence, depression and dementia as well as disabilities leading to functional impairment in patients 65 and older with breast cancer, colorectal cancer and prostate cancer. While these data will be used to evaluate relationships between comorbidities, geriatric syndromes and functional limitation on choice of therapy and therapeutic outcomes, they have already been useful in

identifying the marked overlap of patients with combinations of two or more of these complicating conditions.

While still early in its use to study effects of comorbidities, the CALD methodology has already produced additional interesting observations (11,12). Thus, preliminary findings indicate that geriatric syndromes, such as depression and dementia, are associated with late stage diagnosis of breast cancer. Also of interest is the observation that older patients with breast cancer are less likely to get recommended therapy. In contrast, the stage of diagnosis for colorectal cancer is not associated with comorbidity, geriatric syndromes or disability. These observations clearly indicate that physicians involved in elder care must be made aware of these disparities to more effectively orient their cancer screening and treatment strategies.

The CALD study outlined above approaches questions of aging and cancer from the view point of intersecting large databases. At the same time, studies of cohorts of older adults in the City of Cleveland and in a retirement community in Florida are being used to study the impact of comorbidity on cancer prevention (13,14). These studies indicate that cancer screening decreases among the elderly in general; however, it is particularly deficient among those with co-morbid health problems. Moreover, age was found to be a greater predictor than comorbidity for physicians not referring elderly patients for screening. Most interestingly, it was observed that patients who are assertive health care consumers or who have assertive health care advocates, are more likely to be recommended for cancer screening and cancer care. These studies indicate the importance of educating senior citizens and their caregivers to be more assertive advocates for their own health care.

Psychosocial Issues

Case Western Reserve University has an established group of investigators focused on psychosocial issues in patients with cancer and their families. Their concentration on older adults identified multiple interesting issues, many of which require follow-up with focused interventions, such as the need to encourage older patients and their caregivers to be proactive and assertive advocates for improving their own health care. While this approach has already been shown to impact the quality of life in older patients, it remains to be determined how it will affect cancer prevention, detection and outcomes. Studies to evaluate health worries and psychological distress among older adult cancer survivors have shown that about one-third of long term survivors worry about recurrence and second malignancies and may develop

anxiety and depression in association with these concerns (15,16). Many cancer survivors were found to experience psychological distress around six months after diagnosis; this is frequently the time that therapy is concluded or decreased in intensity. These findings support the need for ongoing interactions between patients, their caregivers and their physicians to provide monitoring and reassurance.

Age group comparisons have been an important focus in research on psychosocial issues. In a secondary analysis of data in the Study to Understand Prognosis and Preferences for Risks of Treatment (SUPPORT), Case investigators compared care preferences, treatment decision making and outcomes for hospitalized middle-aged (aged 45–64 years) and older (65 years or older) patients with advanced cancer (17,18). In this group analysis, fewer older than middle-aged patients preferred treatment focused on life prolongation or the option of cardiopulmonary resuscitation, a specific action (18). Older patients who preferred such treatment over comfort care received more aggressive care; however middle-aged patients' preferences were not associated with aggressiveness of care. Interestingly, aggressive terminal care resulted in high hospital cost but did not significantly impact survival outcomes for patients in either age group. When communicating with patients about care decisions, physicians should be sensitive to possible age differences in patients' treatment goals and expectations about outcomes.

In another study, comparing young-old (aged 60–74 years) and old-old (aged 75–90 years) long term cancer survivors, age group differences were found in health maintenance activities and lay sources of decision making support (19). Fewer health maintenance activities and lay sources of support were reported by old-old survivors during active treatment and in long-term survivorship. Health care providers should be attentive to aging and cohort-related differences in assessing older adult's preferences and barriers to health promotion, both during active treatment and in long-term survivorship.

Biology of Aging and Cancer

Many studies at Case Western Reserve University investigating fundamental biologic interactions of aging and cancer focus on DNA metabolism and DNA Repair Processes. For example, recent studies of microsatellite instability in hematopoietic stem cells derived from the bone marrow of older patients showed more high level aberrations than did hematopoietic stem cells from bone marrow of younger adults or cord blood samples from neonates (20). These studies suggest pro-

gressive decreases in the DNA mismatch repair process in hematopoietic stem cells of older individuals. Defects in this process may contribute to the progressive increase in acute leukemia and myelodysplastic syndrome in older individuals. Other studies investigating biologic interactions focus on questions of whether the poor prognosis associated with selected tumors in older patients is due to more aggressive tumors or less resistance by the host. Thus, an *in vitro* model using brain slices to examine astrocyte migration has been adapted to investigate whether the more rapid demise of older patients with brain tumors may be associated with differences in the tumor or in the brain substrate (21). Initial studies using U87 human glioma cells, show that the migration of injected U87 cells is impaired in brain slices representing the mature CNS environment and that the tumor cells rarely cross the boundary between gray and white matter. In contrast, U87 cells injected into brain slices obtained from aged rats, migrate widely throughout the CNS and readily traverse the borders between gray and white matter. These observations suggest, that compared to tissue in younger individuals, normal brain tissue in older adults is more susceptible to tumor spread and may contribute to the decreased survival associated with age. Studies are in progress to determine whether differences in susceptibility to tumor spread in younger and older brains is associated with growth factors, adhesion molecules or other factors affecting structure.

Summary

In summary, the number of older persons with cancer is expected to significantly increase because of the overall aging of the population and the fact that cancer incidence and mortality rises exponentially in the 50–85 year old age groups. The increased caseload of older patients with cancer will present great challenges to all components of the health care systems. As a result, there is a great need for clinical research to identify and implement evidence-based, best practices to eliminate pain and suffering from cancer in older patients, enhance their quality of life and extend their meaningful survival. At the same time, there is an important role for education of healthcare providers, the elderly and their caregivers to eliminate age bias, institute best practices for screening and prevention and achieve optimal care for older patients with cancer. Research on the biology of cancer in the elderly is already showing important differences between young and old and should provide insight and strategies that can significantly inform future approaches to cancer research and treatment.

ACKNOWLEDGMENTS

This work was supported in part by the Case Western Reserve University, School of Medicine, the Case Comprehensive Cancer Center and NIH Grant P20 CA103736.

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DISCUSSION

Boxer, Ann Arbor: Nate, are there any prospective studies where people are looking at individuals over 65 who are in very good health? With this emphasis on our population on exercise and diet, I'm just curious if some of the healthy senior citizens behave, in terms of their response to chemotherapy, like younger patients, and shouldn't that be emphasized if it's a valid assumption?

Berger, Cleveland: As I think you are well-aware, many clinical trials had one reason or another to eliminate patients over 65. And now I think exactly the opposite has become necessary to understand how to most effectively treat older patients. Randomized trials are being conducted looking at older versus younger patients, both in their response and in their toxicity, and although I didn't get a chance to talk about it, pharmacokinetic and pharmacodynamic analysis are being performed as part of Phase I and Phase II trials.

Bast, Houston: I know that these studies are difficult to interpret, but as it now stands, in which cancers do you find equivalent activity in patients over 80 versus under 80? Are there studies to show that aggressive treatment of head and neck cancer in individuals over 80 produces results comparable to those achieved in younger patients.

Berger: For the studies that I showed you, both the ovarian cancer study and the head and neck cancer study, patients who received a full course of therapy had similar outcomes. There was somewhat more toxicity in some of the older patients who underwent the treatment. But the outcomes were reasonably similar.

Barondess, New York: Dr. Berger, when you talk about incidence or prevalence as a function of age, you're talking about clinically evident cancer, a very late stage event in the course of a set of diseases that in many instances have been present for a very long time at a level below clinical recognizability. I wondered what your thought was about why this disease accumulates increasingly at older ages. Do you think it's primarily the persistence of initiating factors or biological processes that are inexorable once they start, or is it some failure in the host response such as immune surveillance or whatever else it might be?

Berger: I think there are two general answers. One is, we think there really is biology involved here. Whether it's inexorable or not is difficult to say. However, it certainly

appears to be cumulative and cooperative in that initial changes appear to facilitate accumulation of further changes. These cumulative processes almost certainly contribute to the exponential increase in age-associated cancers. You are certainly correct when you talk about the incidence being those cases that are discovered. And as I indicated, our studies suggest that a number of conditions, such as dementia for example, have an impact on the diagnosis of breast cancer, and race has an impact on the diagnosis of colon cancer. So we think there are probably many people in nursing homes or institutionalized with Alzheimer disease who have breast cancer or prostate cancer that never gets diagnosed. These may be having an important impact on our statistics that say that the incidence of breast cancer is improving. We don't know. There are large populations that need to be screened.