CANCER AND AGING
HANDBOOK
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You may open the window
And fail to see the fields and the river;
Even if you are not blind
You may be unable to enjoy the view of trees and flowers!

These verses of Fernando Pessoa are engraved on his monumental tomb in the Lisboa cathedral. They crystallize more eloquently than any scientific paper the urgency to study geriatric oncology. Diversity is a hallmark of aging. Individuals of the same chronologic age may differ substantially in life expectancy and tolerance of stress. When it comes to older individuals, the art of medicine consists in identifying those patients who are more likely to benefit from an aggressive treatment and those that are more likely to be harmed by it. In addition, the goals of treatment may change from patient to patient according to one’s physical stamina and one’s lifetime priorities. To a large extent, the management of an older individual is a social issue, involving the home caregiver and all the persons connected with the caregiver. It behooves the practitioner to ensure that the caregiver is appropriate for the patient’s need and that caregiving does not disrupt the caregiver’s family life.

The management of older individuals, including older cancer patients, involves a wisdom developed over a lifetime, thanks to time-consuming listening and painstaking collection and interpretation of clinical details. Only a practitioner willing to invest the time necessary to these endeavors will be able to provide safe and effective care to the older patient. In the management of older individuals with cancer, the practitioner needs to feel comfortable with uncertainty; to enjoy being creative in novel situations; to think outside the box; and to enrich with his/her own experience the dictates of medical textbooks, treatment guidelines, and clinical pathways. The best source of clinical evidence, the randomized clinical trials, are not very helpful for personalized care, because they cannot encompass the variety of conditions encountered in older individuals. A prominent geriatrician from the UK has defined evidence-based medicine as “evidence-biased medicine” [1], as the controlled conditions of clinical trials are rarely, if ever, reproducible in the practice arena.

There are other reasons for studying geriatric oncology beside the uniqueness of each cancer patient. They include the biological interactions of aging and cancer. Aging is a risk factor for carcinogenesis. This statement is confirmed by the association of smoking cessation with an epidemic of lung cancer in the elderly (people who no longer die of a coronary attack live long enough to develop lung cancer) [2] and that age is a risk factor for chemotherapy-induced acute myelogenous leukemia [3]. Also, the behavior of neoplasias may change with aging. For example, the prevalence of adverse prognostic factors increases with the age of patients with acute myelogenous leukemia [4], whereas breast cancer may become more indolent in the elderly [5]. The tumor host interactions represent a fascinating and largely unknown subject.
The problems of geriatric oncology are becoming everyday problems in the practice of oncology, given the rapid expansion of the aging population [6]. By the year 2000 50% of all malignancies occurred in the 12% of the population aged 65 and over; by the year 2030 it is predicted that individuals 65 and over will account for 20% of the population and 70% of all cancers in the United States [6]. This book, which gathers the contributions of some of the world’s best known experts in the field, could not be more timely.

Perhaps more than any other field of medicine, geriatric oncology is rapidly evolving. Nobody will be able to provide a final word, during our lifetimes, at least. This book should be considered as an important foundation supporting both the practitioner of oncology and the clinical and basic investigators in the area. It is necessary, every so often, to summarize where we are and to decide where we should be going. By providing such a beacon, the book will have fulfilled this goal.

In one of his first novels, Love and Pedagogy, Miguel de Unamuno stated: “The truth is the worst of all lies.” This paradox certainly applies to a medicine carved in stone rather than lived as an ongoing journey and a fascinating adventure. This book provides a current guide to practitioners and scientists involved in the journey.

LODOVICO BALDUCCI

REFERENCES

Since the 1980s there has been an unprecedented increase in the attention being paid to the topic of cancer and aging. This is reflected by a 2007 Institute of Medicine workshop on cancer in the elderly and several special journal issues on this topic [1–3]. This response is the direct result of three converging forces: the aging of the population, the age-sensitive nature of cancer, and innovations in medical care. The confluence of these factors represents a significant public health challenge for the future. This challenge is further complicated by a potential shortage of oncologists, geriatricians, and nurses due to the projected exponential increase in incidence and prevalence of cancer in older adults coupled with a reduction in healthcare professionals entering into these fields [4,5].

These trends provide both challenges and opportunities. A central challenge is building the evidence base from epidemiologic, clinical trial, and behavioral research focusing on care for older adults across the cancer care continuum. Unfortunately the science of cancer care in the elderly population lags far behind what is known in children and other adults with cancer. Therefore, much of what is being practiced is extrapolated from studies of younger cohorts or based on clinical judgment. Another challenge is our capacity to respond to the complex healthcare needs of older adults given the projected shortages of geriatric/gerontology-trained healthcare workers. We believe that the answer to this question is multifaceted and will require thinking “outside the box” to (1) test new models of cancer care; (2) encourage new physicians to pursue geriatric fellowships; (3) provide broader geriatric and gerontology training for primary-care physicians and nurses; and (4) foster research and clinical collaboration among geriatricians, gerontologists, adult oncologists, and behavioral scientists. This latter endeavor is important as each of these disciplines contributes different perspectives, all essential to providing quality care to the growing population of older adults.

With challenges come opportunities. As we age, we become more heterogeneous in terms of physical and psychosocial health as a result of our previous lifestyles, environmental exposure, and genetic composition. Cancer care for older adults will likely be based on individualized approaches that account for this heterogeneity as well as the needs and preferences of the individual. This will likely require a paradigm shift from population-based medical care and healthcare to patient-centered care, which, we believe, will ultimately result in the highest-quality and most cost-effective care.

This multidisciplinary book was written by some of the most prominent international experts in the field of cancer and aging. The chapters in this book provide a synthesis of findings from current epidemiologic, behavioral, and clinical trial research across the entire continuum of cancer care, from prevention and screening, to treatment and survivorship, to end-of-life care. This book also includes a section on emerging issues in cancer care for older adults, including chapters focusing on caregivers, comprehensive
geriatric assessment, the economic cost of treating older adults with cancer, and finally a discussion of multidisciplinary models of care. For some topics in this book, the evidence is still nascent, and the authors were challenged to provide recommendations for future research in these areas. In doing so, they raise some interesting questions about the complex issues facing older adults before, during, or after the diagnosis of cancer.

We believe that this book will demonstrate that the answer to addressing one of the biggest public health challenges of our time does not rest within any one discipline and that a broader knowledge and multidisciplinary approach is required to care for older adults at risk for, or living with, cancer. Our hope is that this information will be useful for healthcare providers, medical students, public health professionals, and policymakers who care for, or make policies that pertain to, the health of older adults.

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PART I

CANCER AND AGING IN CONTEXT
CHAPTER 1

Epidemiology of Cancer in the Older-Aged Person

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1.1 INTRODUCTION

Age is a risk factor for most cancers. In the United States 50% of all malignancies occur in men and women over the age of 65, which represents 12% of the population. With the current growth rate of the older population, it is estimated that 70% of all cancers will occur in the elderly by the year 2030 [1,2]. This finding is a call to face incoming cancer epidemics in a population that has been grossly understudied. As in other fields of geriatrics [3], clinical epidemiology will have a critical role in determining the best cancer care in older heterogeneous adults.

In this chapter we will examine how clinical epidemiology may help us to gain insight into the biology and the management of cancer in the older person. In closing we will explore new epidemiological approaches to determine benefits and risk of cancer treatment in older individuals.

1.2 AGE AND CANCER BIOLOGY

Clinical epidemiology helps us understand the interaction of aging with carcinogenesis and tumor behavior. The study of the incidence of cancer in advanced age may shed light on age-related factors that favor cancer development. Likewise, comparison of the natural history of cancer in younger and older individuals indicates that some cancers may become more aggressive and others more indolent with aging.

1.2.1 Aging and Carcinogenesis

The increased incidence of cancer in the older person may be due to three not necessarily mutually exclusive mechanisms. These include duration of carcinogenesis, increased susceptibility of older tissues to environmental carcinogens, and changes in body environment (chronic inflammation, increased resistance to insulin) [4].

The changing epidemiology of lung cancer supports the fact that aging is associated with cancer because carcinogenesis is a time-consuming process. As of 2005 the median age of lung cancer was around 71 years, up from 55 years in the mid-1970s [5]. This shift is arguably due to smoking cessation that is associated with a rapid decline in cardiovascular mortality. Ex-smokers now do live long enough to develop lung cancer [6,7]. Indeed, ex-smokers or never smokers account for an increasing proportion of newly diagnosed lung cancer [8]. Figure 1.1 summarizes the age-related changes in lung cancer mortality over a 20-year period.

A number of experimental studies have shown that some older tissues are primed to the action of environmental carcinogens and are more likely to undergo malignant transformation than younger tissues when exposed to the same dose of carcinogens [4]. Clinical epidemiology suggests that this is the case in older humans as well for the following reasons:

• The incidence of some cancers, such as prostate and colon cancer, increases more rapidly with age. This finding suggests that older tissues are more susceptible to environmental carcinogens. In support of this theory, the rate of malignant transformation of adenomatous polyps becomes more rapid with the age of the patient [2].

• Since the 1970s there has been a dramatic increase in the incidence of certain tumors, such as non-Hodgkin’s lymphoma and malignant brain tumors in older individuals [9,10]. This finding suggests the possibility that older people develop cancer more quickly than younger ones when exposed to new environmental carcinogens.

• Age is a risk factor for the development of myelodysplasia and acute myelogenous leukemia after anthracycline-based adjuvant chemotherapy of breast cancer or after treatment for lymphoma [11,12].

• In a more recent longitudinal study of the population of Bruneck, Italy, individuals with shortest leukocyte telomeres had more than a threefold increase in the risk of cancer with respect to those with the longest telomeres [13]. According to a
number of studies, summarized in Reference 14, telomere length is a mirror of the functional age of a person.

There is no convincing epidemiologic evidence supporting the association of cancer with changes in body environment, including immune-senescence, endocrine senescence, and proliferative senescence of fibroblasts. This possibility is suggested by the increased incidence of lymphatic tumors in presence of immune suppression and increased incidence of colon cancer in the presence of obesity [15]. Epidemiology has also produced some hypothesis-generating information related to the prevention of cancer in older individuals. This includes reduced incidence of cancer of the large bowel with regular use of aspirin [16] and reduced incidence of breast cancer in patients treated with selective estrogen receptor modulators (SERMs) or aromatase inhibitors for the adjuvant treatment of breast cancer.

### 1.2.2 Aging and Tumor Behavior

The clinical behavior of some tumors changes with the age of the patient (Table 1.1) [17]. The table highlights two important facts, emerging from clinical epidemiology:

1. Contrary to common belief, some neoplasms become more aggressive and more lethal with aging.
2. The change in tumor behavior involves at least three mechanisms: intrinsic cellular changes and changes in the tumor host and in the treatment received. If one tries to compare the growth of the cancer to that of a plant, the changes in growth rate depend on the seed, the soil, and the gardener.

It has always been known that age is a poor prognostic factor for acute myelogenous leukemia (AML), due to changes in the biology of the disease, which include higher prevalence of multidrug resistance, of unfavorable cytogenetics, and of NPM1 unmutated and fli3 mutated tumors [18]. At least in part, these changes may be explained by the fact that AML in older patients is preceded by myelodysplasia, a disease that affects the early hematopoietic progenitors.

Age is a poor prognostic factor for both aggressive and indolent non-Hodgkin’s lymphomas [19]. Increased circulating concentrations of interleukin 6 (IL6), a powerful

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Clinical Behavior in the Aged</th>
<th>Mechanism</th>
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<tr>
<td>Acute myelogenous leukemia</td>
<td>More resistant to treatment</td>
<td>Increased prevalence of unfavorable genomic changes and of resistance to chemotherapy</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>Age is a poor prognostic factor</td>
<td>Increased circulating concentrations of interleukin 6 and increased risk of undertreatment</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>More indolent</td>
<td>Increased prevalence of hormone-receptor-rich tumors; endocrine senescence</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>More lethal</td>
<td>Unknown</td>
</tr>
<tr>
<td>Malignant brain tumors</td>
<td>More lethal</td>
<td>Increased prevalence of unfavorable genomic changes</td>
</tr>
</tbody>
</table>
stimulator of lymphocyte replication, may, in part, explain, this finding [20]. In the case of large cell lymphomas, clinical epidemiology suggests another important possibility: inadequate doses of chemotherapy. A systematic review demonstrated that individuals 60 and older had the same outcome as did younger adults if they received the same dose intensity of chemotherapy [21]. The review does not address the important question as to whether the undertreatment of the aged was justified by comorbidity and poor functional reserve, but it underlines the possibility that undertreatment may be responsible for some of the age-related prognostic changes in cancer, such as decreased survival in patients 60 and over with large cell lymphoma.

It is well established that metastatic breast cancer is associated with a more indolent course in older women, which include higher prevalence of bone and skin metastases in lieu of visceral and brain metastases. This finding may be due to increased prevalence of well-differentiated, hormone-receptor-rich tumors, endocrine senescence that disfavor the growth of hormone sensitive cancer, and availability of several forms of endocrine treatment [22]. Nevertheless, despite a more indolent course, breast cancer is still a lethal disease in older women and should be treated aggressively. Also, not all breast cancers in older women are indolent. Even in the oldest ages at least 20% of tumors are hormone receptor poor and very aggressive. Age is a risk factor for early death in glioblastoma multiformis and malignant astrocytoma [9].

Epidemiological observations have identified important age-related differences in tumor behavior that have led to the discovery of underlying molecular or physiologic mechanisms. In addition, clinical epidemiology has revealed that inadequate treatment might have been responsible for poorer outcomes among older patients.

### 1.2.3 Age and Clinical Presentation of Cancer

Heterogeneity in terms of function and life expectancy is a hallmark of aging [23,24]. The practitioner managing older patients is faced with a number of issues, including whether (1) cancer screening and cancer treatment may reduce cancer-related mortality in patients with limited life expectancy and (2) older individuals are able to tolerate aggressive cancer treatment. Clinical epidemiology has given important insights into these issues.

A number of older studies summarized in Goodwin et al. [25] demonstrate that the majority of cancers were diagnosed at a more advanced stage in older compared with younger adults. The reasons for delayed diagnosis are poorly understood and may involve decreased awareness of early symptoms of cancer in the aging population and their providers. It is possible that symptoms such as pain, constipation, malaise, or weight loss be mistakenly ascribed to preexisting diseases or even to age itself. Another potential cause of delayed diagnosis is limited access to healthcare. One reversible cause of delayed diagnosis is reduced utilization of effective screening interventions such as mammography or colonoscopy by older individuals [26]. Disturbingly, lack of physician recommendations might have been the major cause of underutilization of these life-saving procedures by the elderly. Thus, public and professional education may reduce the cancer-related mortality of older individuals.

**Multiple Malignancies**  As aging is a risk factor for cancer, it should not be unexpected for older cancer patients to present with more than one malignant disease. Excluding non-melanomatous skin cancer, approximately 20% of cancer patients 70
and older have more than one neoplasm in their lifetime [27]. This association may be explained by several factors, such as:

- The phenomenon of field carcinogenesis, which explains how patients who experience a previous cancer are susceptible to a second neoplasm in the same organ, as all cells of that organ have been exposed to the same carcinogen
- More frequent clinical monitoring of individuals with previous history of cancer (e.g., frequent utilization of CT scans or MRI may explain the association between lymphoma and renal cell carcinoma)
- Carcinogenic effects of previous cancer treatment, including chemotherapy-induced AML in patients who received adjuvant chemotherapy from previous cancers [11,12].
- Increased prevalence of indolent malignancies, including prostate cancer and chronic lymphocytic leukemia in older individuals

At present there is no evidence of a special genetic profile that renders certain older individuals more susceptible to multiple neoplasms requiring more intense monitoring. Also, a history of multiple neoplasms does not appear to increase the risk of an older patient to die of cancer [27].

1.2.4 Clinical Profile of the Older Cancer Patient

At least three studies have explored function and comorbidity of older cancer patients and have revealed that 70% of individuals over 70 years of age reported dependence in one or more instrumental activities of daily living (IADL) and that significant comorbidity was present in 40–90% of patients [28–30]. The prevalence of memory disorders, malnutrition, and dependence in one or more basic activity of daily living was present in as many as 20% of patients [28–30]. These studies revealed that the majority of older cancer patients needed some assistance in receiving and managing cancer treatment. When compared with an age-matched population without cancer, older cancer patients appeared to be in better health, but with reduced number of comorbid conditions and reduced prevalence of functional dependence. The impression that cancer may be a disease of “healthy elderly” is reinforced by the low prevalence of neoplastic diseases among patients living in institutions [31]. Thus, clinical epidemiology suggests that the majority of older individuals with cancer may benefit from cancer treatment if they have adequate medical and social support.

A study in 2000 was particularly provocative as it showed that women 80 and older diagnosed with breast cancer have a longer life expectancy than do women of the same age without breast cancer, according to SEER data [32]. These data may be misleading, however, because in the majority of the patients with breast cancer, the cancer was diagnosed at mammography. It is reasonable to expect that only the healthiest octogenarians might have been chosen to undergo mammography.

1.2.5 Age and Cancer Management

Diversity is a hallmark of the aged population [23,24]. The influence and the interactions of comorbidity, polypharmacy, geriatric syndromes, and social support on cancer diagnosis and outcome are best studied in large databases where this information is
prospectively collected. So far the main source of information related to the prevention and treatment of cancer in older people has been the Surveillance, Epidemiology, and End Results (SEER) program. SEER is the US National Cancer Institute–funded cancer registry representing four main geographic areas of the United States and includes information on cancer in approximately 21% of the US population [32]. When coupled with the Medicare data, SEER allows us to study the benefits and risks of cancer treatment in individuals 65 and older.

Indeed, SEER has been the source of important, albeit inadequate, information. Through SEER we have learned that

- Women aged 70–79 had a twofold reduction in breast cancer mortality if they underwent at least two mammographic examinations [33–35]. The benefit was present even in women with moderate comorbidity [35].
- Androgen deprivation in older men was associated with increased risk of bone fractures when the treatment was protracted longer than one year [36]. Androgen deprivation was also associated with increased risk of diabetes and myocardial infarction.
- Age was a risk factor for chemotherapy-induced acute leukemia, and this effect was enhanced by the use of hemopoietic growth factors [11,12].
- Age was a risk factor for anthracycline-induced chronic cardiomyopathy [37].

In other areas, however, the information provided by SEER has been inconclusive, as is the issue of whether cancer chemotherapy is a cause of dementia in older breast cancer patients [38,39]. The main limitation of the SEER data is the absence of information related to the function, severity of comorbidity, cognition, social support, and geriatric syndromes. This information is crucial to the advancement of geriatric oncology for several reasons: (1) function, comorbidity, and geriatric syndromes determine the so-called active life expectancy that is as important as survival and disease-free survival as treatment outcome in the older population [17]; (2) this information predicts the risk of mortality of older individuals [23,24]; and (3) a number of more recent and yet largely unpublished studies showed that function, cognition, comorbidity, risk of falls, and other geriatric syndromes may be used to predict the risk of complications from cancer treatment in older individuals [40,41]. Only by collecting a host of pretreatment information may we be able to fine-tune our predictions and decide for which patients cancer treatment may be beneficial or detrimental. New tumor registries, including the Endhoven registry in the Netherlands, have made a concerted effort to collect this prospective information.

1.3 CONCLUSIONS

Clinical epidemiology has a unique role in the study of older cancer patients. In the case of carcinogenesis and cancer behavior, clinical epidemiology has been the dictionary allowing us to translate bench findings into clinical data. It has demonstrated that older individuals are more susceptible to carcinogens than younger ones, and that the clinical behavior of cancer changes with age, due to a combination of “seed and soil” factors. From a clinical standpoint, clinical epidemiology has demonstrated that older cancer patients are generally healthier than older individuals without cancer, and that age is a
risk factor for delayed diagnosis and undertreatment of cancer. Clinical epidemiology is the best available approach to establish whether cancer treatment benefit older patients in terms of active life expectancy and which age-related factors may influence the treatment toxicity and the disease outcome. For this purpose it is important to have a prospective collection of data related to function, comorbidity, geriatric syndromes, and social support.

REFERENCES


