Chapter 1

EPIDEMIOLOGY OF CANCER AND AGING

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Epidemiology provides the initial clue to causes and mechanisms of diseases. It is well known that age is a risk factor for most common cancer and that incidence and prevalence of cancer increase with age[1]. In this chapter we explore the epidemiology of cancer and aging, in an attempt to understand the biologic interactions of these processes. In particular, we address the following questions:

1. Does aging enhance the susceptibility of older individuals to environmental carcinogens?

2. Is aging associated with increased risk of multiple malignancies?

3. Does the clinical behavior of cancer change with age?

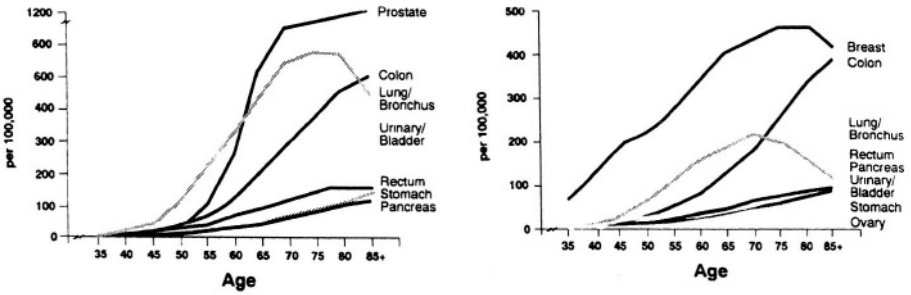
4. Does cancer increase the risk of death of older individuals?

In conclusion we will examine the clinical implications of these questions and propose a research agenda aimed to improve the control of cancer in the older aged person.

1. AGE AND CARCINOGENESIS

The incidence of common cancers increases with age (Figure 1). This association is universal [2] and is observed with the aging of any population around the world. A clear explanation of this phenomenon is the time-length of carcinogenesis, a stepwise process involving the activation of cellular oncogenes, and the suppression of anti-proliferative genes (anti-oncogenes) [3]. It is reasonable to assume that the duration of carcinogenesis reflects the number of stages involved in the pathogenesis of different tumors, and that this number be highest for tumors whose incidence peaks late in life, such as adenocarcinoma of the prostate and of the large bowel, or non-melanomatous skin cancer [3]. In the era of chemoprevention and recognition and elimination of environmental carcinogens, an alternative possibility should be considered. These interventions may cause the prolongation of one or more carcinogenic steps and, in so doing; they may delay the development of cancer. For example, the incidence of lung cancer has decreased for individuals less than 60, while it has increased for older individuals [4]. As a result, the peak incidence of lung cancer has become more and more delayed. Interestingly, these changes have paralleled the incidence of smoking cessation in the Western population. In this case it is reasonable to assume that the length of carcinogenesis has increased as a result of a prolongation of the late carcinogenic stages, from reduced intensity of exposure to tobacco smoke [3]. If this hypothesis is correct, one may expect to see a progressive delay in the appearance of common cancer and an increased incidence of neoplasia in advanced ages.

Figure 1. The incidence of common cancers increases with age.



The duration of carcinogenesis may not account completely for association of cancer and aging. . The incidence of some neoplasms, such as prostate and non-melanomatous skin cancer increases more rapidly with age, than it would be expected from the time-length of carcinogenesis alone [3]. These findings suggest that the concentration of cells in advanced carcinogenic stages increases with the age of an organism, enhancing the susceptibility of older individuals to environmental carcinogens [3]. This possibility is supported by a host of studies of experimental carcinogenesis, summarized in another chapter of this book [3] and also by epidemiologic observations [5-9]. Barbone et al reported the risk of lung cancer after exposure to an environmental pollutant in the Italian city of Trieste increased with the age of the subject at the time of exposure [6]. Since 1970, the incidence of non-Hodgkin's lymphoma has increased 80% for individuals 60 and over, and that of malignant brain tumors seven fold (or 700%) for individuals 70 and older [8, 9]. It is tempting to infer that older individuals develop cancer after exposure to new environmental carcinogens earlier than the younger ones, because of increased susceptibility to these substances. In other words, older subjects may represent a natural monitoring system for new carcinogens. Unfortunately this hypothesis may have proven true, at least in the case of brain tumors, as the incidence of these neoplasms is now increasing also for individuals aged 50 and older [8].

For completeness, other biological changes of aging, beside advanced carcinogenesis, may favor the development of cancer. Immune-senescence may facilitate the growth of highly immunogenic tumors [10], while proliferative senescence may result in loss of cellular apoptosis, and the production of tumor growth factors and proteolytic enzymes that promote the growth and the spreading of cancer respectively [11].

Does the incidence of cancer increase indefinitely with age? The answer to these question as become highly relevant with the progressive aging of the Western population and with the expansion of the oldest segment of the population (those 85 and older), that is increasing more rapidly than any other segment. [12]. The observations of Stanta et al, who performed more than 350 autopsies of individuals aged 95 and older and in more than 100 aged 100 and older suggest that beyond a certain age the incidence of cancer might decrease [13]. These authors reported that not only the incidence of cancer as cause of death and the incidence of clinical cancer, but also the incidence of occult cancer decreased after age 95. Of interest, the decline in cancer was associated with increased incidence of sarcopenia, and atrophy of multiple tissues, which suggest that at the upper extreme of age the anabolic processes are reduced to an extent that they cannot support the rapid growth of neoplastic tissues. An alternative possibility is that genes involved in longevity may also be involved in protection from cancer.

2. AGE AND MULTIPLE NEOPLASMS

As aging is a risk factor for cancer, it is reasonable to ask whether the incidence of multiple primary malignancies is more common in older persons and in particular whether an aging phenotype of increased cancer risk may be defined. The recognition of such phenotype would have important practical consequences, which include the ability to target certain individuals for cancer prevention and new insight in the molecular pathogenesis of cancer. Luciani and Balducci have considered two alternative hypotheses (Figure 2) [14]. According to both hypotheses the incidence of multiple primary malignancies increases with age. In model A this increment reflects only the general risk of cancer associated with aging, whereas in model B previous history of cancer is itself a risk factor for new neoplasms. Model B implies an aging phenotype associated with increased risk of multiple malignancies. After review of the literature, the authors concluded that model A was more likely that model B. Absolute conclusions are not possible, however, due to the limitation of existing data (Table 1).
Universal consensus is wanted for the definition of multiple primary malignancies. In the majority of study series the definition of Warren and Gates has been utilized [15]. This implies the fulfillment of two conditions: each tumor must present an independent clinical and pathologic picture and the possibility that one neoplasm be a metastasis of the other should be excluded. A number of serious limitations related to this definition are self-evident. First, it fails to distinguish between clinically relevant and irrelevant neoplasms as it is based on autopsy studies. Second it fails to address the issues related to multifocal tumors occurring in the same organ, that are defined by two questions: how can it be established that multifocal tumors are distinct tumors; and should multifocal tumors be considered multiple primary malignancies.

The development of multifocal tumors is a consequence of “field carcinogenesis “ implying that the same tissue may give origin to multiple neoplasms, as the whole tissue has been exposed to the same carcinogen for the same duration of time [16]. The development of multiple tumors in breast, large bowel, head and neck and bronchus support this theory [16]. The distinction of different tumors arising from the same organ may be problematic. The recognition of histologic differences (for example squamous cell carcinoma, adenocarcinoma or neuro-endocrine tumors) is by itself not a definitive proof of distinction, as it is well known that the same

Figure 2. Alternative hypotheses on the increased incidence of multiple primary malignancies with age [14]. Model A reflects only the general risk of cancer associated with aging. Model B implies an aging phenotype associated with increased risk of multiple malignancies.

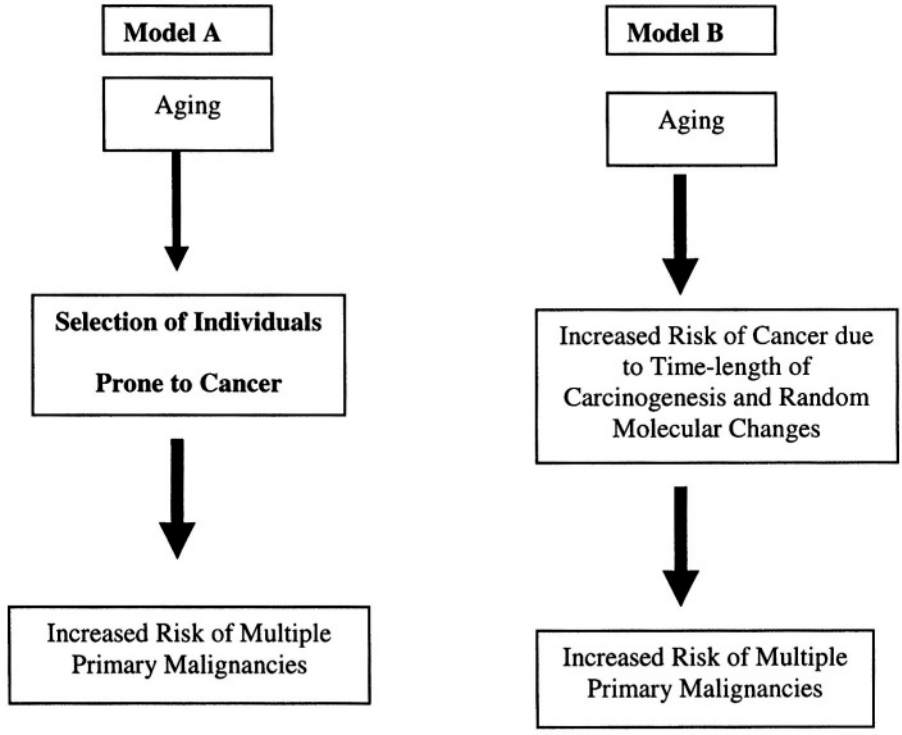


Table 1. Methodological difficulties related to the diagnosis of multiple primary malignancies

- Definition
- Clinical and pathologic recognition
- Influence of previous cancer treatment
- Selection bias
- Limitation of existing sources of data
- Tumor registries
- Autopsy series

epithelial stem cell can give origin to different neoplastic phenotypes [14] Mortel proposed that two tumors arising in the same tissue be considered independent when the tissue separating the two neoplasms does not show

neoplastic infiltration [17]. Though helpful, this criterion appears inadequate on two accounts: it relies on the correctness of individual observations, and it excludes the possibility of surface metastases.

Last but not least, there is an age-specific problem related to the association of age with multiple primary malignancies. This involves the decision whether one should consider that age at which the first or the subsequent tumors did occur. Conceptually, it appears reasonable to consider affected by age-related multiple primary malignancies only those patients whose first cancer was diagnosed during adulthood, but we recognize that this proposal only shifts the problem to the definition of adulthood.

One common problem in the definition of multiple primary malignancies is whether the subsequent neoplasms are metastases of the initial one. This difference can be established with absolute certainty only when the tissue of origin of the original and subsequent tumor is different (for example epithelial and mesenchymal neoplasms). Electron microscopy and immune-histochemistry have also helped to identify tumors of origin from different tissues [14]. In the case of some tumors, specific characteristics, such as the presence of hormone receptors in breast cancer allow establishing whether a tumor occurring in different organs is a metastasis of the original neoplasm.

The treatment of cancer may be itself a cause of new cancer, and enhance the risk of a second malignancy in patients who have received antineoplastic treatment. The association of acute myelogenous leukemia with cytotoxic chemotherapy [18] is well known. Cervical cancer has been associated with an increased risk of cancer of the bladder, small intestine, ovary, bones, and of multiple myeloma, but only in patients who had been treated with radiation therapy [19].

A number of selection biases may convey the impression that multiple primary malignancies after diagnosis of an initial cancer. Undoubtedly, patients with a diagnosis of cancer do receive more diagnostic tests, to stage the initial cancer and to establish the presence of recurrences. These tests may reveal concomitant occult malignancies. For example, staging of non-Hodgkin's lymphoma led to the diagnosis of a number of unsuspected renal cell carcinomas [14]. In addition to these diagnostic biases, there is a survival bias. That is the patients who survive the first cancer are more likely to carry the diagnosis of subsequent cancers as a consequence of the fact that they live longer [14]. Though not properly a "selection bias" another source of error may be the changing incidence of certain malignancies with time. For example, non-Hodgkin's lymphoma appeared more common in patients with previous diagnosis of renal cell carcinoma, before it was realized that this association reflected the increased incidence of lymphoma in the general population during that period of time [20].

The main source of information on multiple primary malignancies is tumor registries and autopsy studies. Tumor registry studies are cohort studies, whose value varies with the quality of the registry as well as with the quality of cancer care provided during the time covered by the registry. For example, studies performed during a time when women received routine mammographic screening are more likely to demonstrate the association of breast cancer with other malignancies, because breast cancer was diagnosed at an earlier stage and associated with a more prolonged survival. In general tumor registry studies showed that the risk of second malignancies increased with the duration of survival since the diagnosis of the initial neoplasm [14]. Autopsy studies are by there own nature selective, as they depend on the ability of physicians to obtain autopsy and on the willingness of patients' family to allow the procedure. These cross-sectional studies showed that the prevalence of multiple malignancies increased with the patient's age, but it was consistent with the general risk of cancer for that age [14]. In conclusion, both autopsy and registry studies demonstrated that the diagnosis of multiple primary malignancy was more likely in patients of advanced age, but age was not a risk factor for increased risk of multiple primary malignancies. These studies favored model B over model A in figure 1. It should be noticed that increased likelihood of association was found between certain types of cancer including smoking related cancer [16], papillary cancer of the kidney and cancer of the bladder and of the prostate [21], and breast and uterine cancer [22]. The latter was observed only in women aged 70 and older.

The increased possibility of multiple primary malignancies in older individuals has important clinical consequences:

- The development of a new lesion in patients with history of cancer should be investigated to rule out the possibility of a new and curable malignancy and should not be dismissed as a recurrence off the previous cancer. .
- Previous history of cancer should not prevent aggressive treatment of new cancer. It is not unusual for an older individual to carry a diagnosis of two or more primary malignancies, all of which have been curable.

3. AGE AND NATURAL HISTORY OF CANCER

It is well established that the biology of some malignancies may change with the age of the patient due to at least two underlying mechanisms (Table 2). One may think metaphorically of the tumor as a plant, whose growth is affected by changes in the seed (the neoplastic cell) and the soil (the aging tumor host). In the case of AML the seed is responsible for

reduced responsiveness to chemotherapy and decreased likelihood of complete remission after chemotherapy-induced marrow aplasia [23]. A possible explanation for the worse prognosis of NHL in the aged [24] include the fact that aging is associated with increased circulating concentrations of IL-6 [25] one of the most powerful lymphatic growth factors [26]. Both seed and soil may conspire in making breast cancer a more indolent disease in older women: the prevalence of slowly proliferating [27], hormone-responsive tumors increase with the age of the patient, while endocrine senescence and, paradoxically, immune senescence may disfavor its growth. The role of immune senescence has been revealed in a couple of studies showing that the

Table 2. Age and behavior of common malignancies.

Tumor	Change in behavior
Acute myelogenous leukemia (AML)	Less responsive to chemotherapy after age 60 due to higher prevalence of Multi Drug Resistance (MDR). Less likely to yield remission after marrow aplasia, because the pluripotent hemopoietic stem cell may be involved by the disease The course of the disease may be more indolent than in older individuals due to higher prevalence of "smoldering acute leukemia" and "hypoplastic acute leukemia"
Non-Hodgkin's lymphoma, low and intermediate grade	Age may be associated with decreased response rate to chemotherapy and decreased remission duration. The worst prognosis may be due to increased circulating concentrations of Inteleukin-6 in older individuals
Breast Cancer	Diagnosed at more advanced stage in older women. Growth rate appears lower and may be due to a combination of factors, including higher prevalence of slow-growing, hormone-responsive tumors, endocrine senescence and immune senescence
Lung cancer, non small cell	More likely to be diagnosed at an early stage after age 70 Slower growth rate after age 70 Mechanism of change unknown
Ovarian cancer	Prognosis is worse with age, irrespective of stage and of treatment; mechanism unknown
Cancer of the large bowel	No clear relation between age and tumor behavior

growth of primary breast cancer was inversely related to the degree of mononuclear cell infiltration [10, 28], suggesting that these cells produce a cytokine promoting neoplastic growth. The statement that breast cancer becomes more indolent with age contrasts with some reports that age over 75 is associated with more advanced disease and reduced survival [29-31]. The contradiction may be only apparent, as the worst prognosis in women aged 75 and older may reflect lesser utilization of mammographic screening and of adjuvant treatment, and increased risk of mortality from comorbid conditions. Several lines of evidence suggest that breast cancer becomes more indolent with age including reduced risk of life-threatening hepatic and lymphangitic lung metastases, and reduced local recurrence rate after partial mastectomy [32-36].

In the case of non-small cell lung cancer a more indolent course is suggested by reports from different centers that lung cancer presented at an earlier stage in older than in younger individuals [37-39]. These reports may be fraught a referral bias, however, as only older patients with resectable tumors might have been referred to the centers for treatment. It is possible that lung cancer after age 70 involved preferentially ex-smokers, in whom reduced exposure to tobacco smoke resulted in more indolent tumors. While several studies have shown that age is associated with decreased treatment response and survival in women with ovarian cancer, the mechanism of this change has not been clarified[40].

The study of the natural history of cancer relies mainly on old reports, of questionable methodology, as in the last twenty years the majority of cancer patients have received some form of antinoplastic treatment. From a clinical standpoint the critical question is whether there are circumstances in which the management of cancer in older individuals may cause worse complications than the neoplasm itself. Clearly, the natural history of cancer is only one aspect of this decision that involves also the life expectancy and the functional reserve of individual patients [41, 42]. In addition is important to notice that major advances in cancer treatment may have minimized the risk of complications. These include more limited surgery, safer general anesthesia, laser surgery, cryosurgery, radiofrequency tumor ablation, radiosurgery, brachytherapy, conformal field radiation therapy, low dose weakly chemotherapy, and antidotes to chemotherapy-related toxicity, such as hemopoietic growth factors, and targeted therapy. In general, the same treatment of cancer that is beneficial to younger patients appears beneficial to the older ones, albeit to a lesser extent. Though the risk of local recurrence after partial mastectomy decreases with age, radiation therapy improves the chance of breast preservation even for older women [43]. Adjuvant hormonal therapy reduces the risk of breast cancer recurrence and death for women younger than 50 and older than 70[44], while adjuvant chemotherapy may be

beneficial to older post-menopausal women [45]. Likewise, age does not seem to reduce the benefits of adjuvant chemotherapy in patients with stage III cancer of the large bowel[46]. The only situations in which the natural history of cancer may suggest to forgo the use of antineoplastic treatment include smoldering AML and early stage prostate cancer in man aged 70 and older. Though smoldering acute leukemia is an obsolete term, this definition may still be helpful to encompass two conditions: hypoplastic acute leukemia, that is AML with a marrow cellularity lower than 10% and AML associated with Myelodysplasia, with a percentage of blasts in the bone marrow between 20 and 30%, that does not undergo any significant change over three months. In both cases the predominant clinical picture is pancytopenia, the incidence of leukostasis is negligible, cytotoxic chemotherapy is associated with low therapeutic response and high risk of early mortality, while supportive treatment with transfusion of blood products and possible erythropoietin may allow months of quality survival [47]. The value of local treatment of early prostate cancer in patients aged 70 and over has been debated [48]. A study in which patients aged 60 to 75 were randomized to observation and radical prostatectomy demonstrated that surgery was associated with decreased risk of prostate cancer-related deaths, but not overall survival benefits [49, 50].

4. PROFILE OF THE OLDER CANCER PATIENT

Aging is associated with reduced functional reserve of multiple organ systems, increased prevalence of comorbidity, memory disorders, depression, malnutrition, polypharmacy and functional dependence [51]. It is legitimate to ask whether these conditions may interfere with the treatment of cancer and may reduce the patient's life expectancy and tolerance of treatment to the point that treatment is futile or even harmful.

In three studies, cancer patients aged 70 and older had undergone a comprehensive geriatric assessment prior to the institution of treatment, with similar conclusions [52-54]. Some form of functional dependence was present in up to 70% of patients, some form of comorbidity in up to 90%, depression, malnutrition and memory disorders in approximately 20% and polypharmacy in 40%. . A review of the Surveillance, Epidemiology and End Results (SEER) data also revealed that some form of comorbidity was present in the majority of cancer patients aged 65 and older [55]. These studies show the benefits of a comprehensive evaluation of older individuals that allows an estimate of life expectancy and tolerance of treatment, recognition of conditions that should be reversed prior to treatment and the utilization of a common language in the definition of older individuals [56]. As a result of

these studies should be highlighted the need to adjust the doses of chemotherapy to the renal function of older individuals, to investigate anemia, that is a risk factor for mortality, functional dependence, and chemotherapy related toxicity, the management of depression, and the provision of a home caregiver in patients at risk to develop functional dependence during cancer treatment.

Another series of study compared the survival and the general function of older cancer patients with that of individuals of same age without cancer. Diab et al review the SEER breast cancer experience and showed that for women aged 75 and older breast cancer was not associated with a change in survival. Unexpectedly, breast cancer was associated with a more prolonged survival in women aged 80 and older. This observation suggests that breast cancer may affect preferentially women in best general condition, who might have lived even longer if they had not developed breast cancer[57]. This hypothesis is supported by two other studies. Repetto et al compared functional dependence and comorbidity of patients 65 and older with and without cancer admitted to two general hospitals in Italy and found that cancer patients had lower prevalence of both conditions [58]. In a retrospective study of the population of Cusumano, Italy, Ferrucci demonstrated that patients who developed cancer had the highest degree of function and the lowest of comorbidity [59]. Similar conclusions were drawn by Stanta et al from autopsy studies of elderly persons with and without cancer [13].

It is reasonable to surmise that cancer is preferentially a disease of healthy elderly individuals and that the treatment of cancer in these individuals may result in prolongation of survival and quality of life improvement.

CONCLUSIONS

A review of the epidemiology of cancer and age allows concludes:

- Age is a risk factor both for cancer and carcinogenesis, at least up to age 95;

- Multiple primary malignancies are more common in older individuals. In many case each of these neoplasms is amenable to cure or life-prolonging treatment. Possible exceptions include localized low grade prostate cancer in men aged 70 plus and smoldering acute leukemia

- The biological behavior of cancer may be altered with age: in some cases the neoplasm may become more resistant to chemotherapy, in other cases more aggressive and in other cases more indolent;

- Cancer is prevalently a disease of healthy elderly individuals whose life expectancy and quality of life may be compromised by cancer.

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