Introduction

Archie Bleyer • Karen H. Albritton • Lynn A.G. Ries • Ronald Barr

Contents

1.1 Introduction

This is the first textbook of its type, a comprehensive treatise on cancer in adolescents and young adults who are 15 to 29 years of age when diagnosed. The impetus for this book is the lack of attention that has been paid to this age group, scientifically, therapeutically, psychosocially, and economically. During the past half-century, children (younger than 15 years of age) with cancer have been a singular focus of treatment and research. The advances among children with cancer have been among the most dramatic in the history of medicine, and the cooperative infrastructure that has supported this success has been among the most organized in the history of science. In 1971, the US National Cancer Act led to another highly organized effort that has significantly improved the outcome of adults with cancer, in whom the median age was at that time in the 60s. Meanwhile, substantially less attention has been given to the age group of cancer patients in between. Yet, cancer develops in 2.7 times more people in the 15 to 29 year age group than in those younger than 15 years of age, and the incidence of cancer has increased more rapidly in this older age group than in the younger population. Moreover, the relative improvement in the survival rate in young adults has not kept pace with that achieved in younger patients.

Reasons for this lack of progress certainly include issues specific to this age group: some inherent in the disease or the patient (differences in biology or intolerance of therapy), some inherent in the system (treatment by physicians less familiar with the disease, delay in recognition of malignancy, lack of available clinical trials, or failure to enroll patients on available trials),

Table 1.1 Incidence of invasive cancer in the period 1996–2001 reported according to age. Modified from Bleyer et al. [1]. *SEER* Surveillance, Epidemiology, and End Results

Age at diagnosis (years)	<5	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44
United States population, year 2000 census, in millions	19.175	20.549	20.528	20.219	18.964	19.381	20.510	22.706	22.441
Incidence of invasive cancer, 1996–2001, per million, SEER	206	111	125	203	352	547	843	1289	2094
No. of persons diagnosed with invasive cancer, year 2000, U.S.	3,954	2,281	2,566	4,105	6,675	10,602	17,085	29,269	46,993

and some influenced by the psychosocial milieu of the patient (unwillingness to participate in clinical trials, delays in seeking medical attention with symptoms of cancer, poor compliance with treatment). A further consideration is that the physical, emotional, and social challenges posed by cancer in adolescence and early adult life are often unique and especially difficult for patients, families, and healthcare providers alike.

In contradistinction to younger and older patients with cancer, until recently adolescents and young adults with cancer have had no national program to address their special problems. This review describes these issues relevant and specific to adolescents and young adults with cancer and their caregivers. The ultimate goal is to heighten awareness of a relatively neglected group of patients who, during the current half-century, deserve better.

A recently published monograph from the Survaillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) and the Children's Oncology Group of the United States describes the epidemiology of cancer between 15 and 30 years of age [1]. Previously, a brief summary of the epidemiology of cancer among 15- to 19-year-olds in the United States appeared in a monograph in 1999 [2], but neither monograph includes diagnostic or therapeutic considerations. The data reported in the more recent monograph are included in the epidemiology sections of this treatise, as provided by the SEER and the United States government [3], and are analyzed with the methods described in the monograph [4].

Each disease-based chapter follows a standard outline, beginning with the epidemiology of the disease including incidence, mortality, and survival rates, and risk factors/etiology, and continuing summaries of diagnosis, treatment, and outcome. Each of the disease-based chapters is authored by at least one pediatric oncologist and at least one academic oncologist who is an expert in the investigation of adult patients with cancer (medical oncologist, surgical oncologist, or radiation oncologist). Each chapter has been reviewed before publication by a member of our editorial staff and epidemilology sections were reviewed by an epidemiologist.

1.2 Epidemiology

1.2.1 Classification System

Invasive cancer refers to any malignancy except nonmelanoma skin cancer (squamous and basal cell carcinoma), in situ cancer of the breast or uterine cervix, or ovarian cancers of borderline significance. It does include low-grade brain tumors (e.g., "benign astrocytoma" and juvenile pilocytic astrocytoma) with low metastatic potential since these tumors can be fatal because of local growth. There are two basic systems of classification: the International Classification of Diseases for Oncology (ICD-O) and the International Classification of Childhood Cancers (ICCC). The ICD evolved first, and has been through several iterations

[5]. The ICCC was developed later [6] to better characterize the pediatric cancers than did the ICD. The ICD was based primarily on the site in the body where cancer arises (e.g., gastrointestinal tract, genitourinary system, respiratory system, and the breast), which is relatively easy to determine in the adult patient in part because most adult cancer at the time of diagnosis is localized. The vast majority of pediatric cancers are usually disseminated when they are diagnosed and only the tissue of origin can be determined. The ICD is therefore topographic and the ICCC is primarily histology-based. A proposal that synthesizes the ICCC and ICD systems for adolescents and young adults has been published [7]. More information on classification and how the epidemiology data were tabulated may be found in the monograph cited previously [1].

1.2.2 Incidence

In the United States, as in most economically advantaged countries of the world, 2% of all invasive cancer occurs in the 15-year interval between the ages of 15 and 30 years. This compares with cancer before age 15 years, which accounts for 0.75% of all cancers. There are 2.7 times more patients diagnosed during the second 15 years of life than during the first 15 years. At the turn of the millennium, in the year 2000, nearly 21,400 persons in the United State of 15 to 29 years of age were diagnosed to have invasive cancer (Table 1.1). Since the incidence of cancer increases exponentially as a function of age between 10 and 80 years of age (Fig. 1.1), approximately half of these patients are 25 to 29 years of age.

1.2.2.1 Age-Specific Incidence

Figure 1.1 shows the incidence of all invasive cancer in the United States from 1975 to 2000 as a function of 5-year age intervals from birth to 85+ years. The straight line in Fig. 1.1B, which is presented on a logarithmic scale, indicates that the incidence increases exponentially with age from 10 to 55 years, and throughout the adolescent and young adult years, which suggests that a common age-dependent oncogenic process is active, such as telomerase shortening, or that the mutation-to-malignancy rate constantly increases with age.

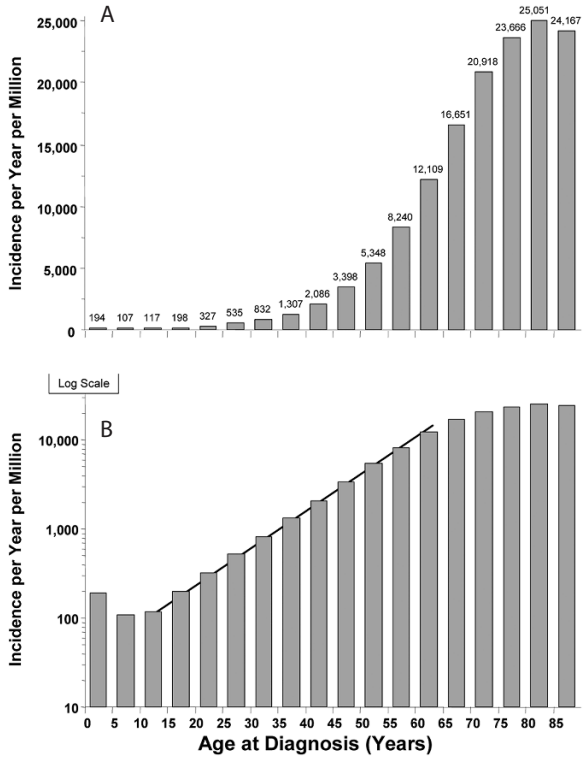

Figure 1.1

Incidence of all invasive cancer in the United States from 1975 to 2000 as a function of 5-year age intervals from birth to 85+ years. The ordinate is linear in A and logarithmic in B. The *straight line* in B indicates that the incidence is exponentially correlated with age from 10 to 55 years, and throughout the adolescent and young adult years. Surveillance, Epidemiology and End Results (SEER), 1975–2000

1.2.2.2 Gender-Specific Incidence

Figure 1.2 shows the incidence of all invasive cancer in the United States from 1975 to 2000 as a function of 5-year age intervals from birth to 85+ years separately for females (Fig. 1.2A) and males (Fig. 1.2B). Females demonstrate the exponential risk pattern from age 10 to 50 years. Males have a third peak that appears during the young adult age range, at approximately

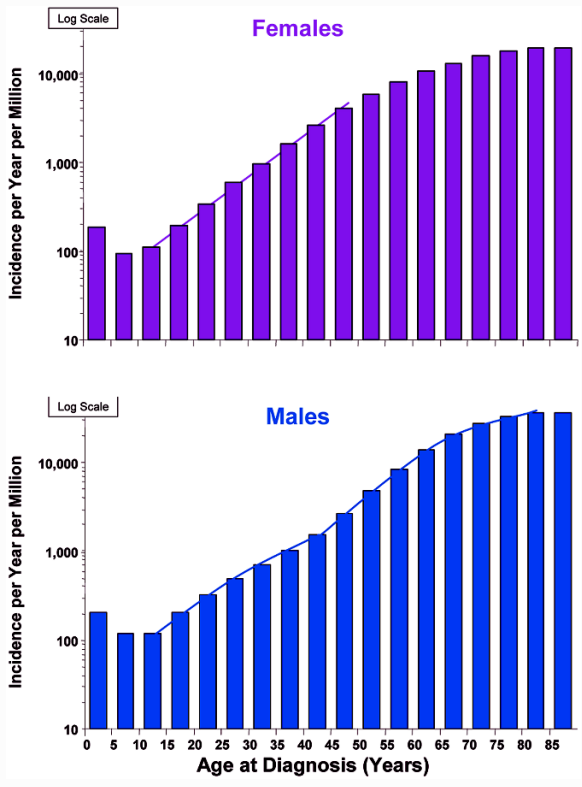

Figure 1.2

Incidence of all invasive cancer in the United States from 1975 to 2000 as a function of 5-year age intervals from birth to 85+ years among females (A) and males (B), each expressed on semi-logarithmic coordinates. SEER, 1975–2000

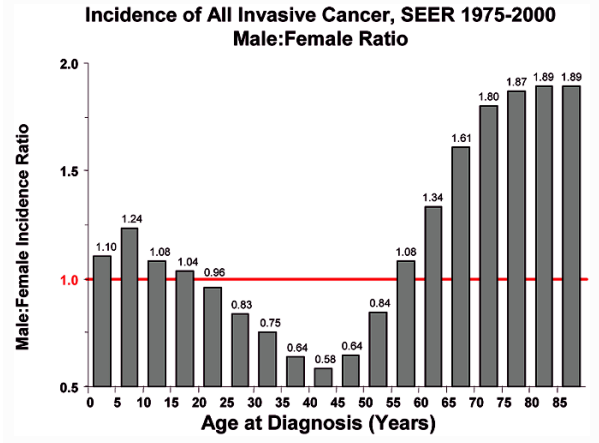

Figure 1.3

The relative risk of developing cancer in males versus females: dependence on age. SEER, 1975–2000

25 years of age. This intermediate peak may have occurred in males as a result of Kaposi sarcoma and HIV-related lymphoma during the AIDS epidemic of the 1980s and early 1990s. Alternatively, another age-dependent oncogenic mechanism may occur in young adult males that may also contribute to their risk.

Figure 1.3 demonstrates the dependence on age of the relative risk of developing cancer in males versus females. The male:female ratio has a nadir between the ages of 40 and 45 years, during which females are almost twice as likely to develop invasive cancer. At both ends of the age spectrum, in children and older adults, the ratio is reversed. Boys are 10 to 25% more likely than girls to develop cancer, and older adult males are much more likely than the opposite sex to suffer a malignancy. The switchover from a male predominance in childhood to a female predominance occurs in the 15 to19 year age group. Between the ages of 10 and 40 years, the male:female ratio declines linearly to the 40- to 45-year nadir.

1.2.2.3 Ethnicity-Specific Incidence

The dependence of cancer incidence on race and ethnicity as a function of age is shown in Figs. 1.4 and 1.5. The non-Hispanic white population has had the highest incidence during the first 40 years of life. Over the age of 40 years, African Americans have been at the highest risk. Americans of Hispanic/Latino, Asian, and Pacific Islander descent are the next most likely. American Indians and Native Alaskans have had the lowest incidence at all ages. Males and females each follow the race/ethnicity incidence patterns described above, with males demonstrating more marked differences (Fig. 1.6).

1.2.2.4 Types of Cancer

The common types of cancer and their relative proportion of all invasive cancers that occurred in 51,479 15-

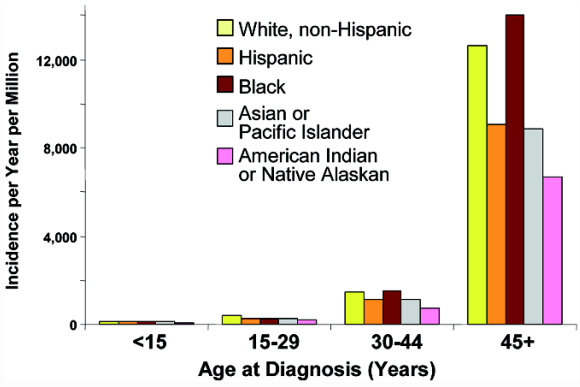

Figure 1.4

The incidence of all invasive cancer according to race/ethnicity as a function of age from birth to +45 years. SEER, 1990–1999

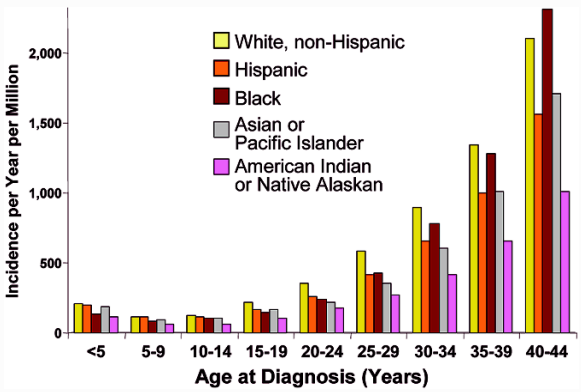

Figure 1.5

The incidence of all invasive cancer according to race/ethnicity as a function of 5-year age intervals from birth to 44 years. SEER, 1990–1999

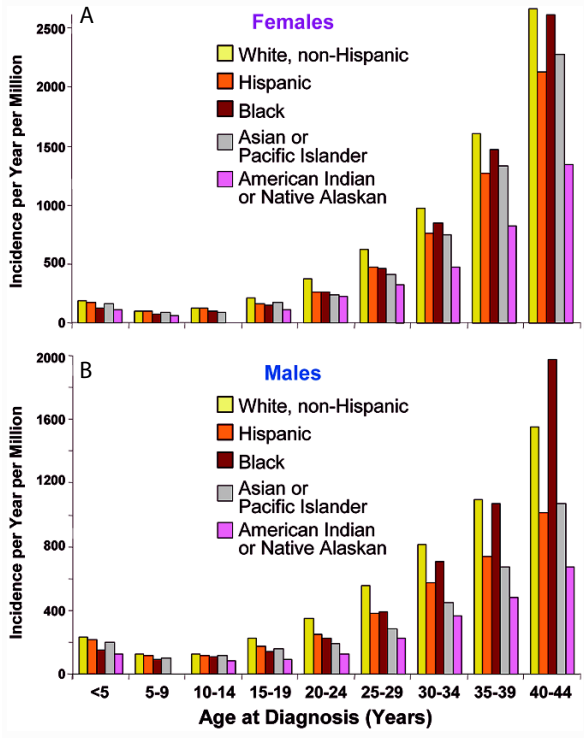

Figure 1.6

The incidence of all invasive cancer according to race/ethnicity as a function of 5-year age intervals from birth to 44 years among females (A) and males (B). SEER, 1990–1999

to 29-year-old Americans registered by SEER during the period 1975–2000 is shown in Fig. 1.7. Lymphoma accounted for the largest proportion, 19% of all cases, with Hodgkin lymphoma the most frequent, accounting for 12% of all cases by itself. Second in frequency was melanoma (11%) and testis cancer (11%), followed in rank order by female genital tract malignancies (10%, predominantly carcinoma of the uterine cervix and ovary), thyroid cancer (10%), soft-tissue sarcomas (8%), leukemia (6%), brain and spinal cord tumors (6%), breast cancer (5%), bone sarcomas (3%, predominantly osteosarcoma and Ewing tumor), and extragonadal germ cell tumors like teratocarcinoma and dysgerminoma (2%).

The distribution of the most frequent cancers within 5-year age intervals within the 15- to 29-year age range is shown in Figs. 1.8–1.10. The most dramatic changes in the types of cancer as a function of age between 15 and 29 years of age are melanoma (from 9th most frequent in the 15- to 19-year age group to 1st most frequent in the 25- to 29-year age group), leukemia (from 2nd most frequent to 11th), female genital tract malignancies (from 10th to 2nd most frequent), testicular carcinoma (8th to 3rd), and bone sarcomas (5th to 12th).

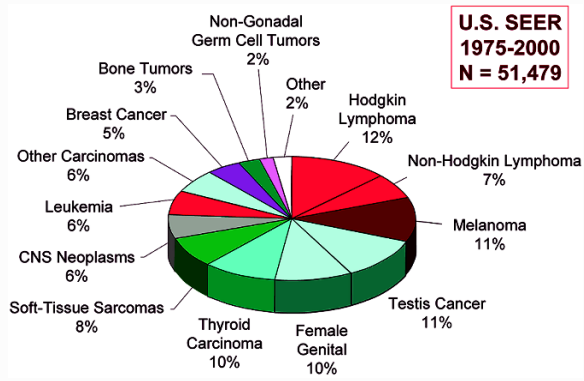

Figure 1.7

The common types of cancer and their relative proportion of all invasive cancers that occurred in 51,479 15- to 29-year-old Americans registered by SEER during the period 1975–2000

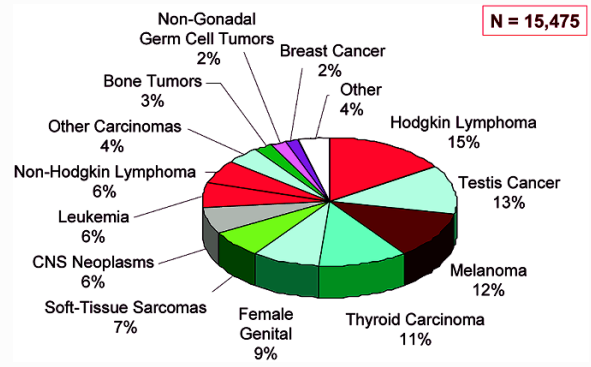

Figure 1.9

The distribution of the most frequent cancers within 5-year age intervals and within the 20- to 24-year age range. The total number of patients available for analysis was 15,475. SEER, 1975–2000

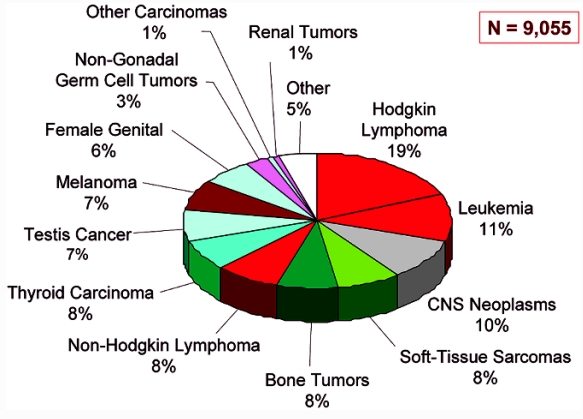

Figure 1.8

The distribution of the most frequent cancers within 5-year age intervals within the 15- to 19-year age range. The total number of patients available for analysis was 9,055. SEER, 1975–2000

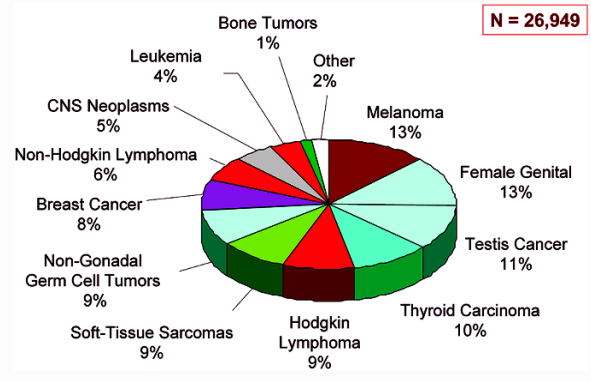

Figure 1.10

The distribution of the most frequent cancers within 5-year age intervals within the 25- to 29-year age range is shown in Figs. The total number of patients available for analysis was 26,949. SEER, 1975–2000

1.2.2.5 Trends in Incidence

Between 1975 and 2000, cancer increased in incidence in all age levels below 45 years of age (Fig. 1.11). Most of the increase in incidence in 25- to 44-year-olds occurred in males (Fig. 1.12), in large part due to increases in soft-tissue sarcoma (notably Kaposi sarcoma), non-Hodgkin lymphoma, and testicular carcinoma (Fig. 1.13). Among females less than 45 years of age, the greatest increases occurred in germ cell tumors (Fig. 1.14).

There is evidence that the increase in incidence has declined among 15- to 29-year-olds, with a leveling off

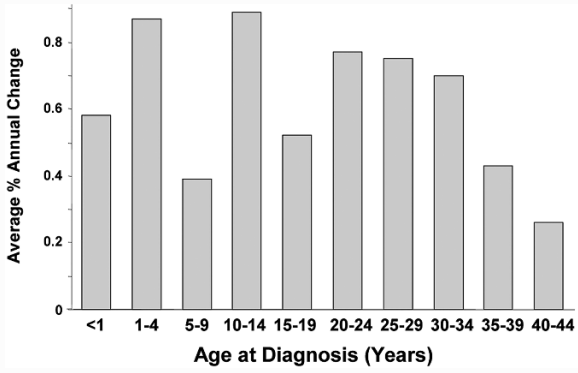

Figure 1.11
Change in the incidence of all invasive cancer between 1975 and 2001. SEER, 1975–2001

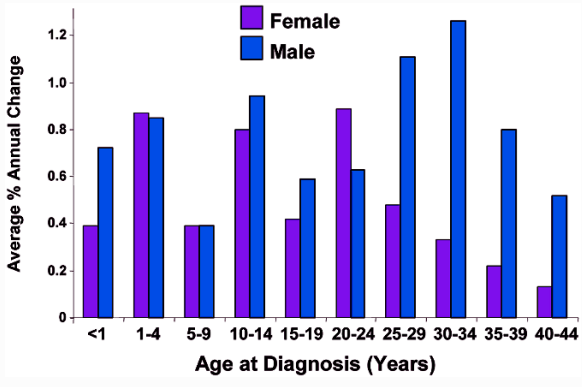

Figure 1.12
Change in the incidence of all invasive cancer between 1975 and 2001 according to gender. SEER, 1975–2001

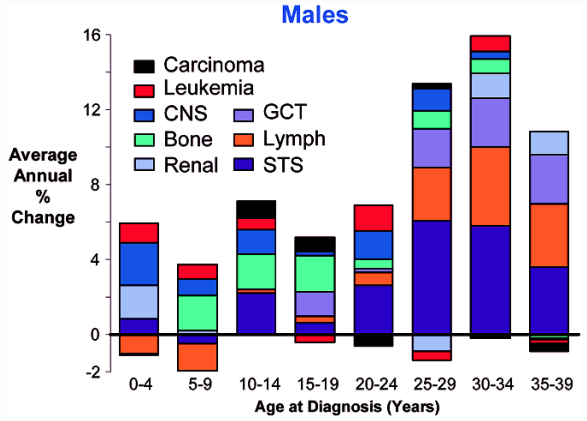

Figure 1.13
Increase in the incidence of cancer among males between 1975 and 1998, compiled from SEER data

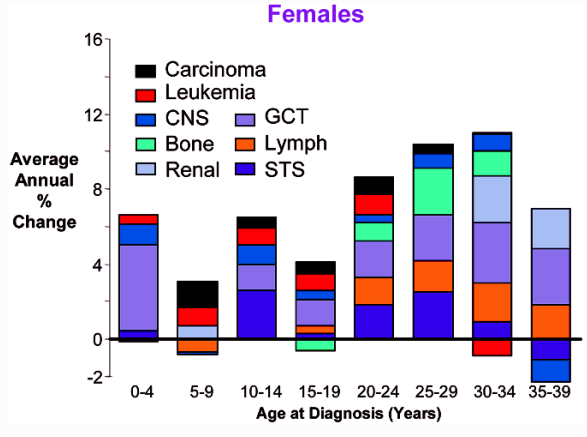

Figure 1.14
Increase in the incidence of cancer among females between 1975 and 1998, compiled from SEER data

of the incidence rate among 15- to 24-year-olds and a decrease after a peak in the late 1980s and early 1990s in 25- to 29-year-olds (Fig. 1.15). The latter is primarily due to cancers related to the HIV epidemic that occurred during the years before the rise in cancer incidence during the early 1980s in this age group.

1.2.3 Mortality and Survival

1.2.3.1 Age- and Gender-Specific Mortality

The national mortality rate of all invasive cancer as a function of age at death in shown in Fig. 1.16. Largely,

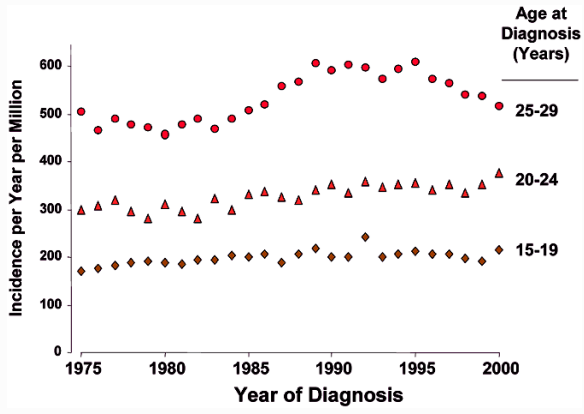

Figure 1.15

Change in the incidence of invasive cancer in three different age groups (15 to 19 years, 20 to 24 years, and 25 to 29 years) as a function of the year of diagnosis. SEER, 1975–2000

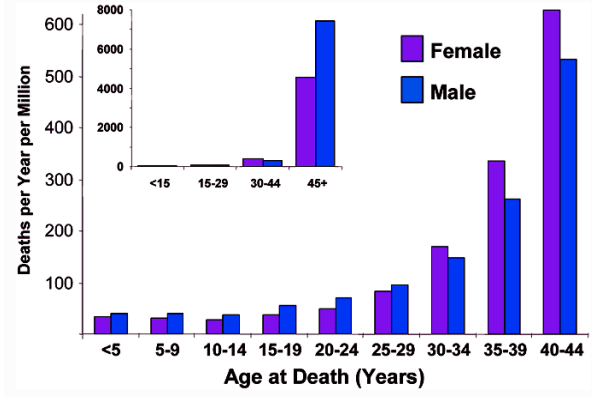

Figure 1.16

The national mortality rate of all invasive cancer as a function of age at death in the period 1975–2000

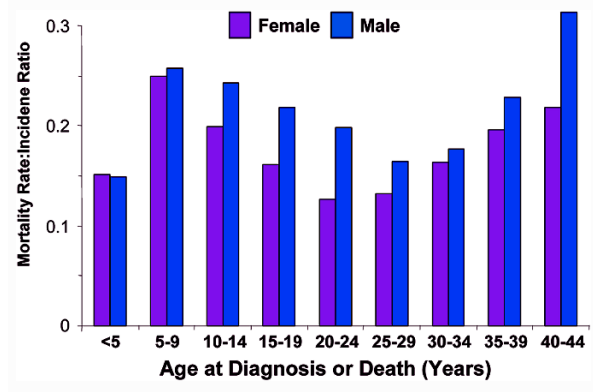

Figure 1.17

Ratio of national mortality rate to SEER incidence for all invasive cancer among males and females in the period 1975–2000

the age-dependent cancer mortality rate reflects the incidence profile (Fig. 1.6). More males die of cancer above age 45 years (Fig. 1.16, inset). From 30 to 45 years of age, deaths among females predominate. In younger patients, the mortality rate is higher among males (Fig. 1.16). Figure 1.17 shows the gender-specific ratio of the mortality rate to the incidence rate for the era 1975–2000. When the mortality rate is considered relative to the variation in incidence, it can be seen that, among all age groups from age 10 to 45 years of age, more men than women have died of cancer. This suggests that the cancers that occurred in adolescent and young adult males during 1975–2000 were more lethal than those in women, or that the treatment was less effective or efficacious.

1.2.3.2 Ethnicity-Specific Mortality

Figures 1.18 and 1.19 present the mortality rate for all invasive cancer according to ethnicity and age of death up to 45 years. The mortality rate generally reflects the incidence rate (Figs. 1.4 and 1.5), with the exception of the population of 15- to 44-year-old African-Americans, who had a higher mortality rate relative to their incidence than any of the other races/ethnicities evaluated.

1.2.3.3 Trends in Mortality

The mortality rate from invasive cancer declined during the period 1975–2000 in all age groups below age 45 years, but the least improvement occurred in the 20- to 44-year-olds (Fig. 1.20). This pattern – less progress among young adults than among children and young adolescents – is true for both genders (Fig. 1.21)

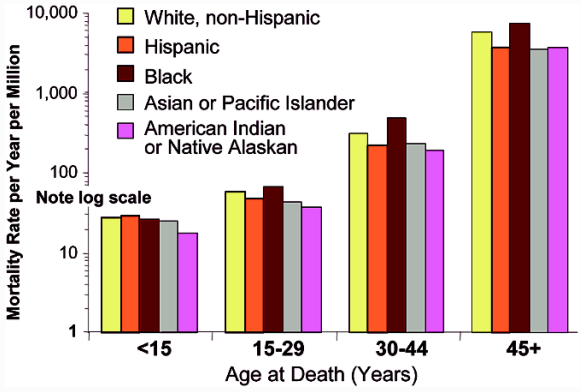

Figure 1.18

National mortality rate of all invasive cancer in the United States according to race, including American Indians/Alaskan natives, in the period 1990–2000, as a function of age from birth to 45+ years

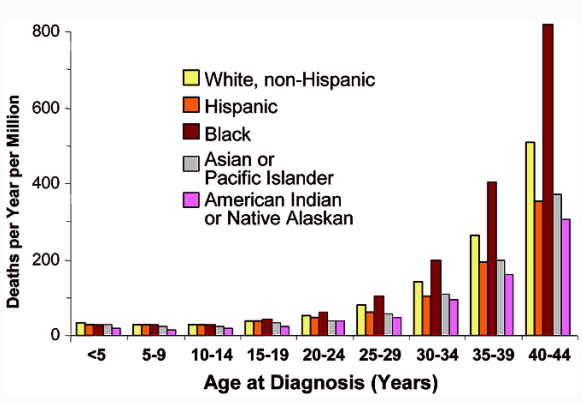

Figure 1.19

National mortality rate of all invasive cancer in the United States according to race, including American Indians/Alaskan natives, in the period 1990–2000, as a function of 5-year age intervals from birth to 44 years

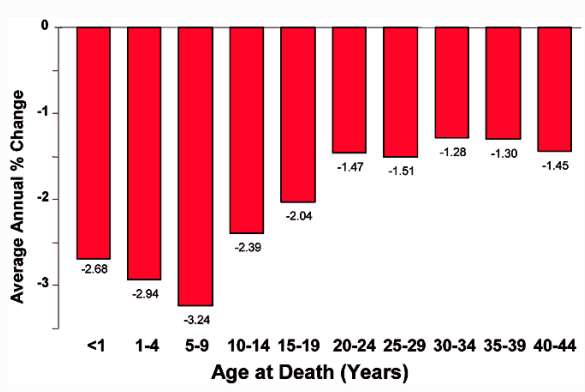

Figure 1.20

Change in the national mortality rate of all invasive cancer in the United States during the period 1975–2000

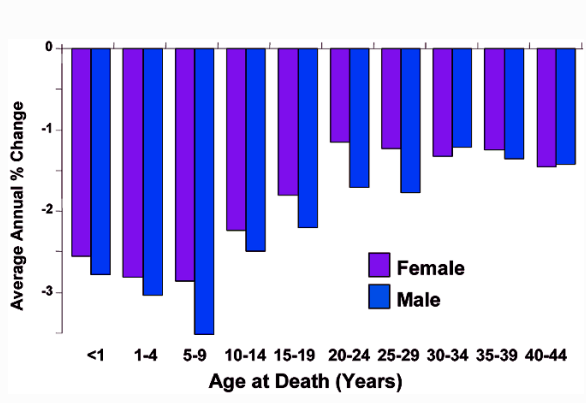

Figure 1.21

Change in the national mortality rate of all invasive cancer in the United States during the period 1975–2000, as a function of gender

and for whites and African Americans (Fig. 1.22). Among African Americans, however, the rate of progress in reducing cancer mortality was considerably lower, particularly among the 15- to 24-years olds (Fig. 1.22).

1.2.4 Survival

In the United States, cancer and suicide are the leading causes of nonaccidental death among adolescents and young adults. Among 20- to 39-year-olds, cancer causes more deaths than heart disease, HIV infection,

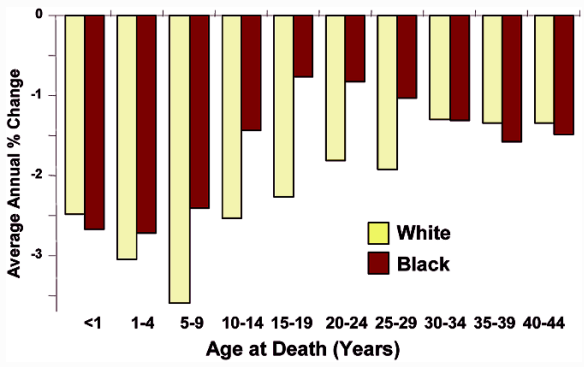

Figure 1.22

Change in the national mortality rate of all invasive cancer in the United States during the period 1975–2000, as a function of race

diabetes mellitus, chronic liver disease (including cirrhosis), cerebrovascular disease, and congenital anomalies (Table 1.2) [8]. In females, deaths caused by cancer occur at more than twice the frequency of the second leading cause of death caused by disease (Table 1.2).

Rates of survival up to 20 years after a diagnosis of invasive cancer is shown in Fig. 1.23 for all patients followed by SEER during the period 1975–1999, and in Figs. 1.24 and 1.25 for the females and males during this era, respectively. Among 15- to 29-year-olds and females 30 to 44 years of age, survival after an invasive cancer diagnosis was comparable to that in persons who were younger than age 15 years when diagnosed. In males older than 30 years, survival was worse. Above age 45 years, survival was considerably worse, and comparable in men and women, in large part due to death from causes other than cancer.

Survival as a function of race/ethnicity among 15- to 29-year-olds with cancer is shown in Fig. 1.26; the era is more recent (and the follow-up shorter), 1992–1999, since race/ethnicity data for other than whites and African Americans were not available until the 1990 census. American Indians and Native Alaskans have had the worst survival, with more than 35% of the patients dying within 2 years, nearly twice the death rate observed among other races/ethnicities. African Americans have had the second worst survival outcome.

Figures 1.27–1.29 display the average annual percent change (AAPC) in 5-year relative survival of patients diagnosed between 1975 and 1997, inclusive, as a function of age at diagnosis, in 5-year age increments [9]. Relative survival refers to adjustment of the observed survival relative to the survival expected from population norms of the same age, and thereby partially corrects for deaths due to causes other than cancer. The average annual percent change in survival

Table 1.2 Top eight causes of death due to disease in those aged 20 to 39 years in the United States in 2002 (accidents and homicides excluded). Modified from Jemal et al. (2005) [8]. *HIV* Human immunodeficiency virus, *Dis.* disease, *Cong.* congenital, *Cerebrovasc.* cerebrovascular

	Male & Female	Deaths		Males	Deaths		Females	Deaths
1	Suicide	10,684	1	Suicide	8,771	1	Cancer	5,403
2	Cancer	10,029	2	Heart diseases	5,590	2	Heart diseases	2,640
3	Heart diseases	8,230	3	Cancer	4,626	3	Suicide	1,913
4	HIV disease	4,597	4	HIV disease	3,206	4	HIV disease	1,391
5	Diabetes mellitus	1534	5	Diabetes mellitus	905	5	Cerebrovasc. Dis.	740
6	Chronic Liver Dis.	1327	6	Chronic Liver Dis.	852	6	Diabetes mellitus	629
7	Cerebrovasc. Dis.	1482	7	Cerebrovasc. Dis.	742	7	Chronic Liver Dis.	475
8	Cong. Anomalies	983	8	Cong. Anomalies	552	8	Cong. Anomalies	431

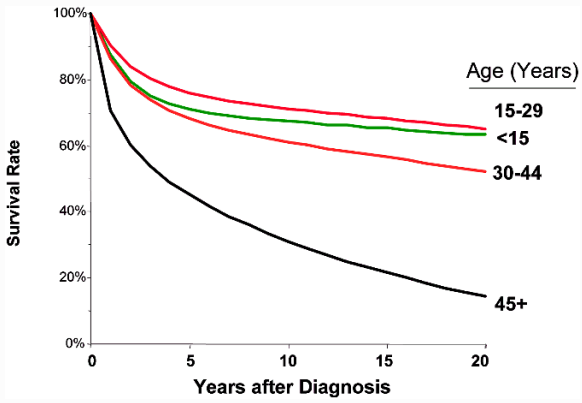

Figure 1.23

Rates of survival up to 20 years after a diagnosis of invasive cancer according to age, in the period 1975–1999 (SEER)

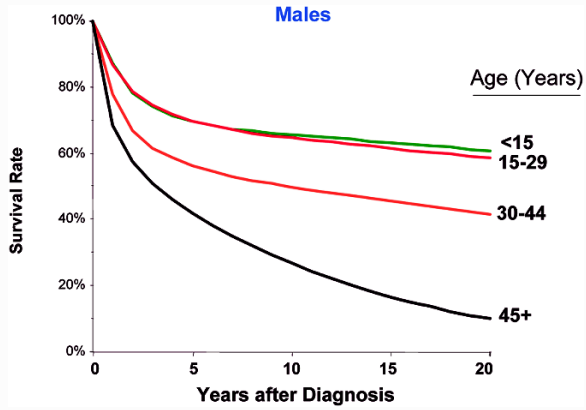

Figure 1.25

Rates of survival among males up to 20 years after a diagnosis of invasive cancer according to age, in the period 1975–1999 (SEER)

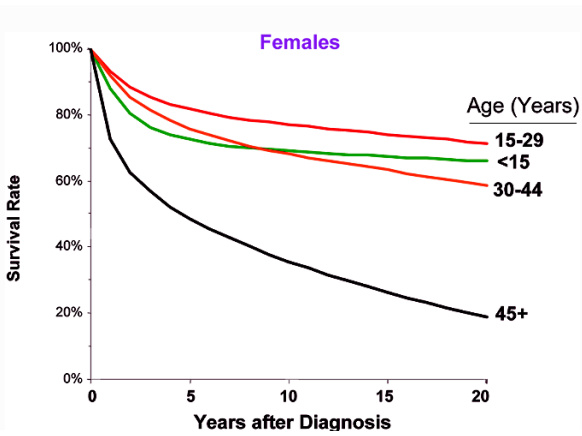

Figure 1.24

Rates of survival among females up to 20 years after a diagnosis of invasive cancer according to age, in the period 1975–1999 (SEER)

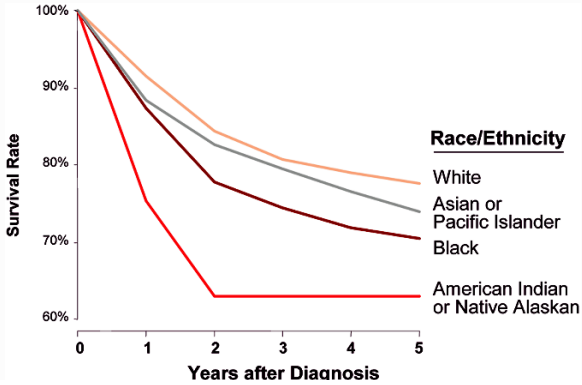

Figure 1.26

Short-term survival as a function of race/ethnicity among 15-to-29-year-olds diagnosed with invasive cancer during the period 1992–1999 (SEER)

for females and males are evaluated separately in Figs. 1.28 and 1.29. An explanation of how SEER applies the AAPC and relative survival parameters is given in Bleyer et al (2006) [10].

Steady progress in improving the 5-year survival rate has occurred among children and older adults. Between 15 and 45 years of age, however, progress in survival improvement has been a fraction of that achieved in younger and older patients, and among patients 25 to 35 years of age, there has been no evidence of an improvement in survival from all invasive cancers considered together since 1975 (Fig. 1.27).

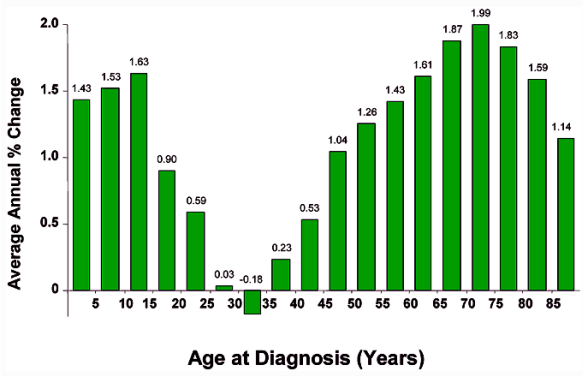

Figure 1.27

Change in the 5-year relative survival rate of all invasive cancer in the period 1975–1997 (SEER) as a function of 5-year age increments

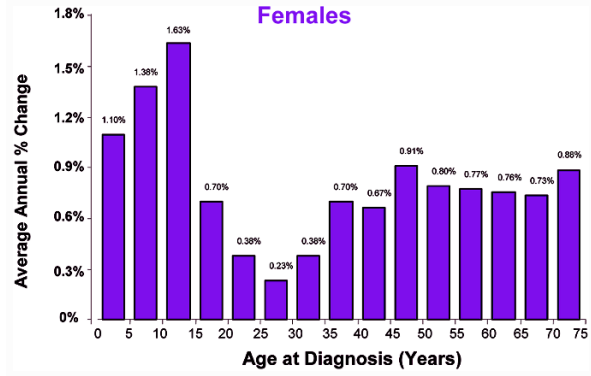

Figure 1.28

Change in the 5-year relative survival rate of females with invasive cancer in the period 1975–1997 (SEER) as a function of 5-year age increments

Most of the older adolescent–young adult deficit has occurred among males (Fig. 1.28), but females have not been spared (Fig. 1.29).

To determine whether the early-adult survival gap was apparent at follow-up time points earlier and later than 1 year, 1- and 10-year relative survival intervals were examined and compared with the 5-year relative survival (Fig. 1.30) [10]. In this analysis, the survival rates during the 1995–1999 era were compared with those of the 1975–1999 era and expressed as the percentage improvement since the earlier era, and individual year-to-year age groups were evaluated instead of the 5-year age groupings. All three survival parameters (1-, 5- and 10-year survival rates) showed the same profile (Fig. 1.30A), with a nadir in progress occurring between the ages of 25 and 40 years (the red zone in Fig. 1.30). The 10-year survival pattern showed an even greater disparity with progress made in other age groups, than either the 1- or 5-year follow-up data. As in the analyses that utilized the average percent change method, young adult males exhibited a more striking deficit than females of the same age group (Fig. 1.30B).

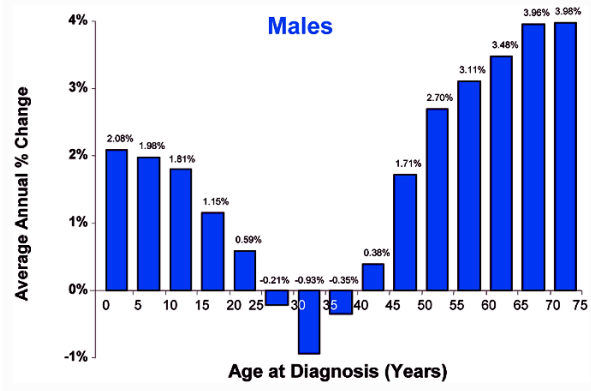

Figure 1.29

Change in the 5-year relative survival rate of males with invasive cancer in the period 1975–1997 (SEER) as a function of 5-year age increments

1.2.4.1 Conditional Survival

Conditional survival expresses change in prognosis for survivors as a function of their time since diagnosis [11]. When applied to cancer, this matrix estimates the risk of dying after an interval of survival and allows survivors and their healthcare providers to know what the risks are at intervals after diagnosis, and to base prognostication and follow-up accordingly [12, 13].

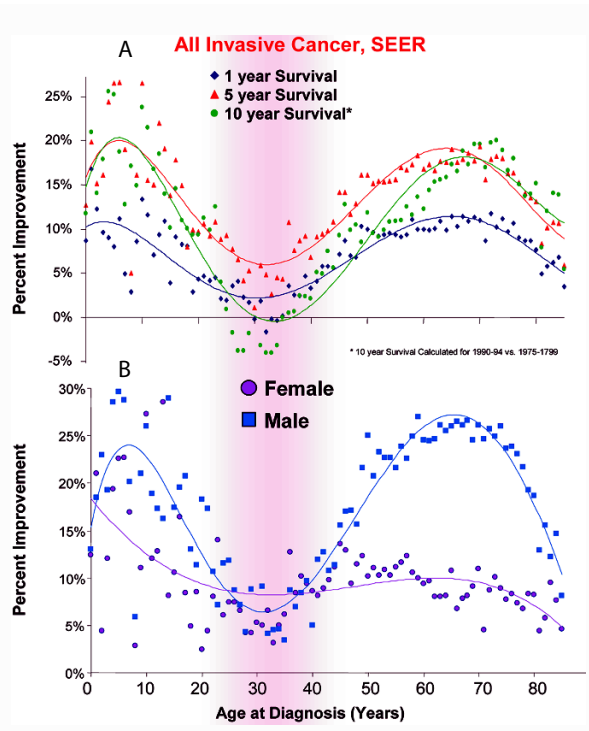

Figure 1.30

A Comparison of the 1-year (*blue diamonds*), 5-year (*red triangles*), and 10-year (*green circles*) survival rates during the period 1995–1999 compared with those of the period 1975–1999, expressed as the percentage improvement since the earlier era, as a function of individual year-to-year age groups (SEER). B Percentage improvement in overall survival among females (*pink*) and males (*blue*) as a function of age at diagnosis during the period 1995–1999. The *red zone* indicates a nadir in progress between the ages of 25 and 40 years

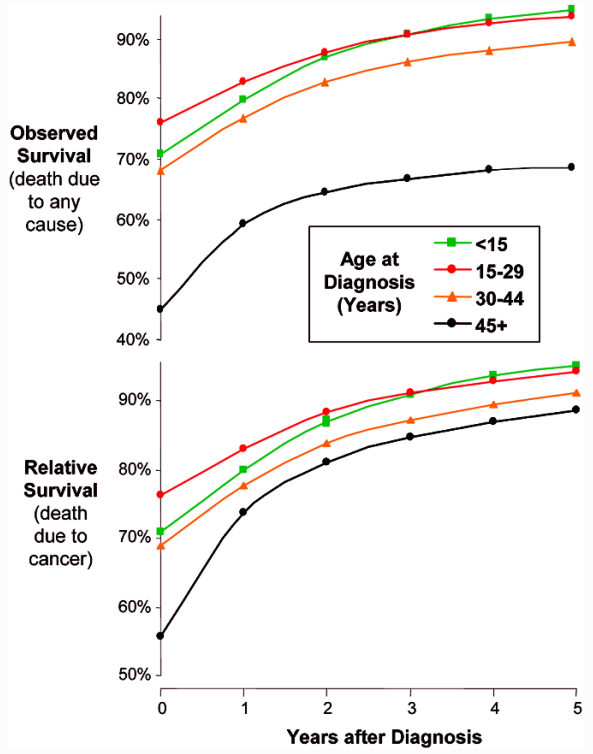

Figure 1.31

Improvement in 5-year conditional survival (freedom from death of any cause) for four age groups: younger than 15 years, 15–29 years, 30–44 years, and 45 years and older when diagnosed with all invasive cancer, during the first 5 years following diagnosis (SEER, 1975–2000). *Upper panel* Observed survival (freedom from death by any cause); *lower panel* relative survival (freedom from death due to cancer)

The NCI SEER database was used to determine the conditional survival of 15- to 29-year-olds diagnosed with cancer during the period 1975–2000 and to compare their results with younger and older patients diagnosed during the same interval. In Fig. 1.31, the observed conditional survival is shown for four age groups: younger than 15 years, 15 to 29 years, 30 to 44 years, and 45 years and older when diagnosed with cancer. The upper panel shows absolute survival (freedom from death of any cause) and the lower panel depicts relative survival (freedom from death attributable to having had a diagnosis of cancer). Whereas 15- to 29-year-olds diagnosed with cancer during the past quarter century had a better prognosis at diagnosis (as shown by the values in Fig. 1.31 at time zero), their probability of survival thereafter did not increase as rapidly as it did in younger and older patients, particularly for relative survival.

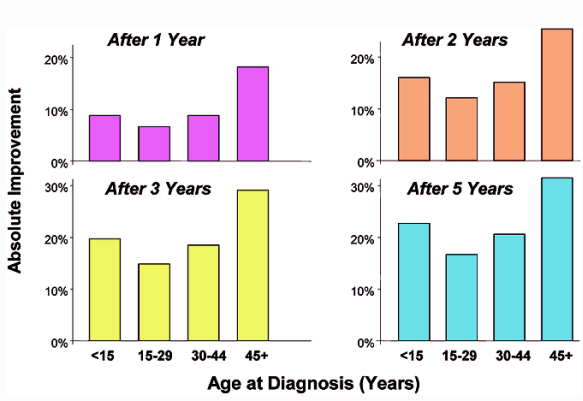

Figure 1.32

Comparison of improvement in 5-year conditional relative survival (freedom from death by cancer) at 1, 2, 3, and 5 years after diagnosis of any invasive cancer as a function of age at diagnosis (SEER, 1975–2000)

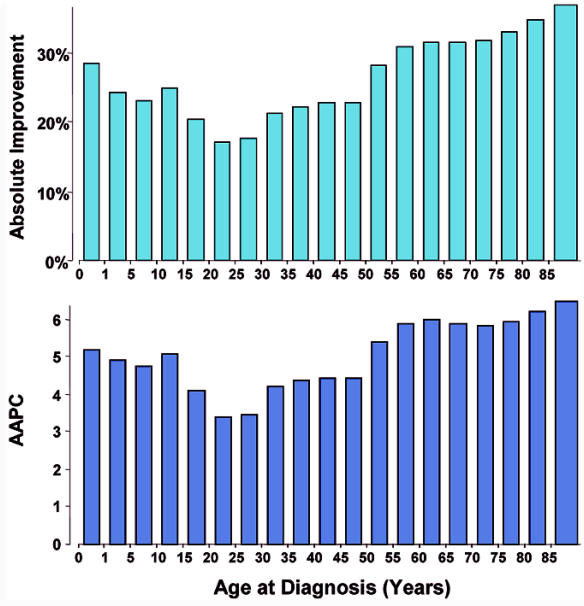

Figure 1.33

Improvement in 5-year relative conditional survival (freedom from death due to cancer) 5 years after diagnosis of all invasive cancer as a function of age at diagnosis from birth (<1 year) and then at 5-year age groups to 85+ years (SEER, 1975–2000). *Upper panel* Absolute improvement from 1975 to 2000; *lower panel* Average annual percent change (AAPC) during the period 1975–2000

Conditional survival in all SEER-registered patients with cancer at 1, 2, 3, and 5 years after diagnosis as a funktion of age is shown in Fig. 1.32. A deficit among 15- to 29-year-olds is apparent at the earliest follow-up and continues at the same magnitude throughout the 5-year postdiagnosis period.

The conditional relative survival 5 years after diagnosis is further analyzed in Fig. 1.33 for 5-year age intervals. The upper panel demonstrates the absolute percent improvement in conditional survival from 1975 to 2000. The lower panel shows the AAPC, using the same method as shown for change in survival at diagnosis (Fig. 1.27). In both cases, the 20- to 29-year age group had the least improvement in conditional survival, and those 15 to 19 years of age at diagnosis had the next worst improvement

These profiles may be interpreted to mean that during the past 25 years, young adults with cancer have not enjoyed the improved prognosis with the passage of time since diagnosis to the extent that younger and older patients have. This deficit in progress is in addition to the deficit in survival improvement measured at diagnosis described above and shown in Figs. 1.27–1.30).

The reason for a deficit in conditional survival among young adults relative to younger and older patients is not known. One explanation is that the kinds of cancer that occur in this age group are distinctly different than those that occur in younger and older persons. It is possible that the mix of sarcomas, lymphomas (both Hodgkin and non-Hodgkin lymphoma), leukemia, thyroid cancer, melanoma, testicular carcinoma, breast cancer, and carcinoma of the uterine cervix that occurs in young adults may not have the same year-to-year improvement as the array of cancers in younger and older patients. It is possible that it may take longer in the young adult age group than 5 years after diagnosis to realize an eventual overall gain that matches younger and older patients. Another possibility is that the therapeutic gains made in younger and older patients have not occurred to the

same degree in young adults and older adolescents – an explanation that has been applied to the deficit in survival at the time of diagnosis. Either way, however, survival at diagnosis and conditional survival up to 5 years after diagnosis indicates that young adults and older adolescents deserve a better trend in outcome than that which has occurred during the last quarter century.

1.2.5 Etiology and Risk Factors

As in younger patients, little is known about the causes of cancer in adolescents and young adults. Whereas cancers in infants and young children are likely to be influenced strongly by congenital and prenatal factors, and cancers in the elderly population are most strongly linked with environmental causes, the cancers in young adults and older adolescents may be a combination of both. Very few cancers in this age group have been attributed directly to single environmental or inherited factors. An exception is clear cell adenocarcinoma of the vagina or cervix in adolescent females, with most cases caused by diethylstilbestrol taken prenatally by their mothers in an attempt to prevent spontaneous abortion. Radiation-induced cancer may occur in adolescents and young adults after exposure during early childhood. In fact, many of the adolescent and young adult cancers that have been linked to an identifiable cause are second malignant neoplasms in patients who were treated with chemotherapy and/or radiotherapy for a prior cancer.

Given that the duration of exposure to potential environmental carcinogens is directly proportional to age, it is not surprising that tobacco-, sunlight-, or diet-related cancers are more likely to occur in older adolescents than in younger persons. With the probable exception of melanoma, cancers known to have been related to environmental exposures in older adults have not been implicated with any certainty to environmental agents in 15- to 30-year-olds. In most people, it appears to take considerably longer than one or two decades for these environmentally related cancers to become manifest. The logical hypothesis is that adolescents who develop cancer after a carcinogenic exposure have a predisposing genotype. For example, melanoma is more common among Australian adolescents than among those elsewhere in the world, as described above. The Australia data does suggest that solar exposure may be able to induce skin cancer before the end of the second decade of life, at least in that part of the world.

Besides intense sun exposure, exposure to other environmental carcinogens, including tobacco, recreational drugs, alcohol, and sexually transmitted diseases, begins or intensifies during this age period. Cancer control efforts to reduce teenage exposure to these carcinogens are unlikely to affect rates of cancers in adolescents, but should decrease rates in adults.

Lymphoma, sarcoma, melanoma, and cancer of the breast, thyroid, colon, and liver may also occur at higher frequency during this period of life in persons with inherited conditions (see Chaps. 9, 11, 12, 16–18, and 20). On aggregate, however, these cancers account for only a small proportion of the cancers that occur during adolescence and early adulthood.

1.3 Diagnosis

1.3.1. Signs and Symptoms

With few exceptions, the signs and symptoms of cancer in young adults and older adolescents are similar to those of the same cancer in younger and older patients. Nonetheless, knowing the most common sites of disease in this age group helps in directing the evaluation of the symptoms and in formulating the most appropriate differential diagnosis. The examiner who is not aware of the prominence of sarcomas, thyroid and testicular cancer, and melanoma in this age group may overlook these possibilities when taking the history and performing the physical examination.

Because of the psychological and social factors that affect adolescents and young adults, patients in this age range may be at higher risk for a delay in diagnosis, a factor that may impact their cancer survival. In a study of the interval between symptom onset and diagnosis (lag time) in 2,665 children participating in Pediatric Oncology Group therapeutic protocols between 1982 and 1988, Pollock and colleagues found by multivariate analysis that for all solid tumors except Hodgkin lymphoma, lag time increased as age increased [14]. In addition, data from the University of Texas

MD Anderson Cancer Center indicates, that among 15- to 29-year-olds with newly diagnosed, previously untreated cancer, the lag time to diagnosis was correlated with the quality of health insurance. Those with public or no health insurance had statistically longer lag times in five of the six cancers evaluated [15, 16]. In multivariate analysis, only the type of cancer and quality of health insurance were significantly correlated with lag time. Gender, age subgroup, race/ethnicity, religion, marital status, rural vs. urban residence, and median household income and population density of the zip code of residence were not correlated.

The reasons for delay in seeking medical care and obtaining a diagnosis are multiple:

1. Adolescents and young adults have a strong sense of invincibility. Out of denial, they may delay seeing a physician for symptoms. Even when seen, they may give poor historical information, especially to a physician untrained to "read between the lines" of an adolescent's history. Some of the most advanced disease presentations occur in adolescents. We have had older adolescents with extraordinarily large masses of the breast, testes, abdomen, pelvis, and extremity that they had harbored for months because they were too embarrassed to bring the problem to anyone's attention.
2. Too many young adults are not receiving routine medical care. Young adults and older adolescents have the lowest rate of primary care use of any age group in the United States [17]. Regardless of health insurance status, adolescents and young adults are more likely than younger children to lack a usual source of care. Without a primary physician who knows the patient's baseline heath status, the symptoms of cancer can be missed.
3. Physicians may be poorly trained or unwilling to care for adolescents and young adults.
4. Adolescents and young adults are not "supposed to" have cancer. Clinical suspicion is low, and symptoms are often attributed to physical exertion, fatigue, and stress.
5. Young adults are the most underinsured age group, falling in the gap between parental coverage and programs designed to provide universal health insurance to children (Medicaid and Children's Health Insurance Programs), and the coverage supplied by a full-time secure job. Lifetime uninsured rates for those who present for care peak for females between ages 15 and 17 years (19%) and for males between ages 18 and 21 years (24%). True uninsured rates are likely to be higher, as those who do not present for care may not do so because of lack of insurance [18–21].

Given the lack of routine care, empowering young adults and older adolescents for self-care and detection is important. Certainly, self-examination of the skin and, in females, of the breasts should be encouraged. However, at this age, it may be most difficult to teach the importance of early detection of cancer, because at no other time in life is the sense of invincibility more pervasive. Adolescents should be taught especially to examine themselves for cancers that increase in incidence during this time period. This is particularly true for testicular self-examination, a subject that is obviously difficult to bring up and teach at this age. On the other hand, there is little evidence that testicular self-examination screening is effective. The American Cancer Society encourages self-examination of the skin and breasts, and increasing the awareness of testicular cancer in young men, but routine testicular self-examination is not recommended. Teaching testicular cancer awareness to high school and college students may not be as difficult as it may seem. A preliminary assessment of teaching testicular self-examinations showed that anxiety was no greater in students who were exposed to presentations on testicular cancer and testicular self-examination than in those who did not receive this training [22]. In addition, efforts should be made to educate teenagers about the treatment and cure rates of cancer in children and young adults in order to dispel the fatalistic perception that arises from knowing older individuals (grandparents and others) who have died from cancer.

1.3.2 Radiologic and Pathologic Considerations

A diagnosis in adolescents and young adults may be more favorably facilitated compared to children. Young adults are able to describe and localize signs and symptoms of the malignancy and biopsy specimens are more

easily obtained. Knowing the most common sites and histology of malignancies in the age group assists in evaluating symptoms and in selecting the most appropriate imaging and biopsy procedures. Noninvasive imaging without the need for sedation, endoscopy, and minimally invasive surgery are all available for patients in this age group. Although these are used more often in adolescents and young adults than in children because they are easier to obtain, it is possible that they are underused in this group in comparison with older patients, because of a lack of insurance and other economic constraints, difficulty taking time off from work, transportation limitations, and a lack of understanding on the part of the professional staff as to what diagnostic and staging procedures are appropriate.

1.4 Treatment

As is true at any age, treatment depends on the type and stage of the tumor. In general, however, the therapeutic management of cancers in adolescents and young adults differs from that in adults because of physiologic, psychological, and social differences. Although there is a dearth of publications that address these issues, several provide advice on how to manage the cancers that occur in this age group [23–33].

1.4.1 Choice of Treatment Setting and Specialist

A central, complex issue is the appropriate specialist to manage the treatment of the young adult and adolescent – a pediatric oncologist or an adult oncologist (medical, radiation, surgical, or gynecologic oncologist). Leonard and his colleagues surmised that, at least in the United Kingdom, adult oncologists are "untutored in arranging ancillary medical, psychological, and educational supports that are so important to people who are facing dangerous diseases and taxing treatment at a vulnerable time in their lives" and "unpracticed in managing rare sarcomas," and pediatric oncologists "have little to no experience in epithelial tumors or some of the other tumors common in late adolescence" [34]. The (admittedly biased) American Academy of Pediatrics issued a consensus statement in 1997, in which it indicated that referral to a board-eligible or board-certified pediatric hematologist-oncologist and to pediatric subspecialty consultants was the standard of care for all pediatric and adolescent cancer patients [35]. A wider consensus panel that included adult oncologists, the American Federation of Clinical Oncologic Societies, also concluded that "payors must provide ready access to pediatric oncologists, recognizing that childhood cancers are biologically distinct" and that the "likelihood of successful outcome in children is enhanced when treatment is provided by pediatric cancer specialists" [36]. However, neither of these statements defines an age cutoff for the recommendation.

Currently, the choice of specialist is made haphazardly and probably depends on the decision of the referring physician. Younger children obtain care primarily from pediatricians who refer to pediatric centers and specialists. Young adult and older adolescent patients are seen by a breadth of specialists for their presenting symptoms of cancer. These include internists, family physicians, gynecologists, emergency room physicians, dermatologists, gastroenterologists, neurologists, and other specialists. These physicians may have very different referral patterns [37]. In addition, when a referral of a young adult or adolescent patient is made to an oncologic subspecialist, the latter may be a medical, radiation, surgical, or gynecologic oncologist, or other oncologic specialist.

The switch from predominantly pediatric specialist management to adult management occurs not at age 21 years, or even at age 18 years, as might be expected, but around age 15 years. A cancer registry review in Utah, a state that has only one pediatric oncology treatment facility, showed that only 36% of oncology patients aged 15–19 years were ever seen at the pediatric hospital [38]. A study of the National Cancer Data Base found that, for nearly 20,000 cases of cancer in adolescents aged 15–19 years, only 34% were treated at centers that had NCI pediatric cooperative group affiliation [39]. Research is only now being done to ascertain the reasons for this practice pattern.

The answer to which specialist is most appropriate certainly varies from case to case. Patients at any age who have a "pediatric" tumor, such as rhabdomyosarcoma, Ewing sarcoma, and osteosarcoma, will probably benefit from the expertise of a pediatric oncologist,

at least in the form of consultation. Children younger than age 18 years and their parents may benefit from the social and supportive culture of a pediatric hospital regardless of the diagnosis. Individuals between the ages of 16 and 24 years may have varying levels of maturity and independence, and the choice of physician and setting for their care should be determined individually. Pediatric oncologists may be less adept at a nonpaternalistic relationship with the patient (and potentially his or her spouse) and less inclined to consider issues such as sexuality, body image, fertility, and the like. Adult oncologists are more accustomed to dose delays and adjustments, and may be less willing to be aggressive with dosing that can be tolerated by the younger patient.

In the end, the decision should be based in large part on which setting will provide the patient with the best outcome. If these are equivalent, "social" or "supportive" factors should weigh into the decision. Little comparative outcome data are available. Stock and colleagues compared patients between the ages of 16 and 21 years who were registered on either a pediatric (Children's Cancer Group, CCG) or adult (Cancer and Leukemia Group B, CALGB) treatment protocol between 1988 and 1998. The remarkably significant results were a 6-year event-free survival of 64% for those treated on the CCG study and 38% for those treated on the CALGB study [40]. At the University of Texas MD Anderson Cancer Center, results of treatment for acute myeloid leukemia (AML) in adults improved substantively after treatment derived from pediatric trials was introduced into the institution's trials [41]. The analysis of data from the National Cancer Database revealed that adolescents (ages 15–19 years) with non-Hodgkin lymphoma, leukemia, liver cancer, and bone tumors have a survival advantage if treated at an NCI pediatric group institution [23].

The British, although hindered by the limited size of their patient population (only 600 cancer cases per year between the ages of 13 and 20 years), have pioneered the solution of treating young adult and adolescent patients at a unique "adolescent oncology unit" [42]. This provides the adolescent with age-specific nursing care, recreation therapy, and peer companionship. Perhaps it is appropriate to have as a goal, centers and oncologists devoted solely to the care of this group of patients. This topic has its controversies and is discussed further in Chap. 33.

1.4.2 Surgery

In general, surgery is performed more readily and anesthesia is easier to administer in larger patients. Another advantage is that young adults are generally healthier than older patients. The main disadvantage in fully grown patients relative to children is that the older patients generally have fewer compensatory mechanisms to overcome the deficits and disabilities resulting from the surgical resection of large tumors. Decisions to use sedation and anesthesia commonly employed in younger children (e.g., topical anesthetic for venipunctures) should be individualized to the adolescent/young adult patient, but should not be dismissed as unnecessary just because of the patient's "maturity."

1.4.3 Radiation Therapy

Compared to children, adolescents and young adults are less vulnerable to the adverse effects of ionizing radiation. This is particularly true for the central nervous system, the cardiovascular system, connective tissue, and the musculoskeletal system, each of which may be irradiated to higher doses and/or larger volumes with less long-term morbidity than in younger patients. By analogy, older adolescents who are still maturing may be more vulnerable to radiation toxicities than older persons at those sites and tissues that are still undergoing development such as the breast and gonads. Breast cancer, for example is more likely in women who received radiation for Hodgkin lymphoma if the radiation was administered between the onset of puberty and the age of 30 years [43]. Remarkably little is actually known about the differential normal-tissue effects of radiotherapy in patients between 15 and 30 years of age.

1.4.4 Chemotherapy

The acute and chronic toxicities of chemotherapeutic agents are generally similar in children, adolescents, and young adults. Exceptions are that older patients in

this age range may experience a greater degree of anticipatory vomiting, have a somewhat less rapid recovery from myeloablative agents, and have fewer stem cells in the peripheral blood available for autologous rescue. Adolescents and young adults certainly can tolerate more intensive chemotherapeutic regimens than older adults, because of better organ (especially renal) function. This should encourage those treating patients in this age group to push the limits of dose intensification. At the University of Texas MD Anderson Cancer Center, the more rigorous pediatric regimen for acute lymphoblastic leukemia (ALL) was adopted successfully years ago. Subsequently, the center also integrated the more intensive AML regimen used by pediatric oncologists into the adult therapy program for AML. In London, Verrill and his colleagues found the use of pediatric regimens for the treatment of young adults (ages 16 to 48 years) with Ewing sarcoma "rational and feasible" without excessive dose delays or modifications [44].

Adherence to therapeutic regimens, particularly oral chemotherapy, is also much more problematic in teenagers and young adults than in younger and older patients [45–48].

1.4.5 Psychosocial and Supportive Care

The greatest difference in the management of adolescents and young adult patients is in the supportive care, particularly psychosocial care, that they require. These patients have special needs that are not only unique to their age group but also broader in scope and more intense than those at any other time in life.

Young adult and older adolescent patients are on the cusp of autonomy, starting to gain success at independent decision-making, when the diagnosis of cancer renders them "out of control" and often throws them back to a dependent role with parents and authority figures (by circumstance and/or by choice). Sometimes the patient has become distanced from his or her nuclear family but has not yet developed a network of adult support relationships. The young adult or adolescent patient usually has many new roles they are just trying to master when the cancer diagnosis hits: high school student, college student, recent graduate, newlywed, new employee, or new parent. How can they succeed when, in addition to all of these stresses, cancer intervenes? How can they plan and begin their future when they suddenly realize that they may not have one? What will happen if they cannot graduate, keep their friends, finish their education, get a good job, marry, have children, or be whatever they aspire to be?

Because of the complex issues of dependence, decision-making during cancer therapy is different for the patient, family, and physician of an adolescent/young adult than for either younger patients (which is more paternalistic) or for the older adult (more patient-centered). The young adult patient may wish to make his or her own decisions, but his or her understanding of the illness may be incomplete or flawed [49].

Honing social and interpersonal skills is an important developmental milestone during adolescence. Cancer treatment for these patients must accommodate this important developmental process. We have discharged a patient from the intensive care unit to allow her to attend her senior prom, and readmitted her when the party was over. Yet boundaries must be set, so that treatment effectiveness is not compromised to keep a "social calendar." Certainly, cancer therapy causes practical problems in social arenas. Adolescent and young adult patients, who are developmentally dependent on peer-group approval, often feel isolated from peers by their experience; the cancer patient's issues are illness and death, while their peers are consumed by lipstick and homework. All adolescents agonize over their personal appearance and hate to be singled out or to appear different. In adolescents with cancer, having to be isolated from peers and society by having a disease that makes them different and having to be treated separately is often devastating. In addition, many of the adverse effects of therapy can be overwhelming to an adolescent's or young adult's self-image, which is often tenuous under the best of circumstances. Weight gain, alopecia, acne, stunted growth, and mutilating surgery to the face and extremities are examples of adverse consequences that can be devastating to an adolescent's self-image. In particular, hair loss is cited over and over as a huge blow to the adolescent or young adult (especially the female) with cancer.

Other challenges include the time away from school, work, and community that therapy requires and the

financial hardships that occur at an age when economic independence from family is an objective. There may be guilt if not attending to these responsibilities, or stress and fatigue if trying to keep up a semblance of normal activity.

This is a period when sexuality, intimacy, and reproduction are central. A young adult is supposed to attract a mate and reproduce. However, the young adult with cancer may feel or look unattractive, may be uninterested in or unable to have sex, and may be infertile. A feeling of impotence can pervade.

Most patients are in a relationship or hope to be in one. However, the relationship will be tested by the strain of the cancer diagnosis and its therapy. Patients may wonder whether the partner stays in the relationship out of guilt or sympathy. Some significant others may feel ignored by medical staff because they are not formally a "family member." After treatment, commitment to the relationship in the face of fear of relapse or infertility can be difficult for both parties. Those contemplating having children often worry about passing on a genetic predisposition to cancer.

A wide range of financial situations is seen in the young adult population. Some patients are still happily dependent on their parents. Some are just striking out on their own but, without a long-standing job or savings, may have to return to dependence on parents or get public assistance. Others are trying to begin a career, but long work absences threaten their job security or growth. As stated above, this age range is the most medically uninsured. As a result, many young adult patients incur high medical bills, and at a time in life when they may least be able to afford them. Future insurability is certainly a stressful issue for all of these patients.

Medical professionals caring for the adolescents and young adults may be used to the psychosocial problems more common in either younger children or older adults. Extra effort, including patient and family support groups specifically geared to this age bracket, should be made to uncover and address these needs, to increase compliance, reduce stress, and improve the quality of life during cancer therapy. Established theories of developmental behavior should be used to systematically improve our care of these patients. As Christine Eiser states, "only by seeing adolescents with cancer as adolescents will we ultimately be acceptable as sources of support" [50]. Only by seeing young adults with cancer as young adults will we ultimately be able to optimize their care.

1.4.6 Lack of Participation in Clinical Trials

More than 90% of children with cancer who are younger than 15 years of age are managed at institutions that participate in NCI-sponsored clinical trials, and 55 to 65% of these young patients are entered into clinical trials. In contrast, only 20 to 35% of 15- to 19-year-olds with cancer are seen at such institutions, and only approximately 10% are entered into a clinical trial [51, 52]. Among 20- to 29-year-olds, the participation rate is even lower, with fewer than 10% being seen at member institutions of the cooperative groups, either pediatric or adult, and only approximately 1% of 20- to 29-year-olds entering clinical trials of the pediatric or adult cooperative groups. Among older patients, the trial participation rate is higher, putatively between 3 and 5%. The high proportion of older adolescent and young adults who are not entered into clinical trials is referred to as the "adolescent and young adult gap." This gap has been observed throughout the United States and spares no geographic region or ethnic group [53].

The reasons for the gap are to a large extent unknown and are undoubtedly multifactorial, as explained in Chap. 5. A factor that does not explain the discrepancy is the participation of minority adolescent patients in clinical trials. Although minority patients are known to be underrepresented in visits to physician offices [54], they have equal or higher rates of entry into clinical trials. The participation rate of older adolescent patients is lower than rates of younger patients of corresponding ethnicity and socioeconomic status.

The dramatically lower clinical trial participation rate by young adults may help to explain the lower-than-expected improvement in their outcome relative to younger and older patients. A report on 38,144 young adults with sarcoma diagnosed during the period 1975–1998 and followed by the United States SEER program may provide insight into the relative lack of progress [55]. In this study, the average annual percent change in 5-year survival as a function of

patient age was compared with national sarcoma treatment trial data obtained on 3,242 patients entered onto NCI-sponsored trials during 1997–2002. For bone and soft-tissue sarcomas (except Kaposi sarcoma), the least survival improvement occurred between the ages of 15 and 45 years. For Kaposi sarcoma, the pattern was reversed, with the greatest survival increase occurring in 30- to 44-year-olds. The lowest participation rate in NCI-sponsored sarcoma treatment trials was found to be among the 20- to 44-year-olds. For Kaposi sarcoma patients, the highest accrual rate was found among the 35- to 44-year-olds. The age-dependent survival improvement and clinical-trial accrual patterns were directly correlated (soft-tissue sarcomas, $p < 0.005$; bone sarcomas, $p < 0.05$; Kaposi sarcoma, $p = 0.06$), regardless of whether the accrual profile demonstrated a decline or a peak (Kaposi sarcoma) during early adulthood. Thus, the lack of survival prolongation in 15- to 44-year-old Americans with non-Kaposi sarcomas may be a result of their relative lack of participation in clinical trials. If so, reversing the shortfall in survival among young adults with sarcomas, as was accomplished in Kaposi sarcoma patients, should benefit from increased clinical trial availability, access, and participation.

Studies of younger children have certainly shown a survival advantage to children enrolled in clinical trials for ALL [56], non-Hodgkin lymphoma [57], Wilms tumor [58], and medulloblastoma [59]. Similar analyses of data for adolescents are sparse. In the United States and Canada, a comparison of 16- to 21-year-olds with ALL or AML showed that the outcome was superior in patients with either cancer treated on CCG trials than in those not entered [60]. In France, The Netherlands, and North America, older adolescents with ALL treated in pediatric clinical trials have fared considerably better than those treated on adult leukemia treatment trials [61–63]. In Germany, older adolescents with Ewing sarcoma who were treated at pediatric cancer centers had a better outcome than those treated at other centers [64]. In Italy, young adults with rhabdomyosarcoma fared better if they were treated according to pediatric standards of therapy than if treated ad hoc or on an adult sarcoma regimen [65].

On the other hand, a population-based study of 15- to 29-year-olds with acute leukemia in England and Wales showed no difference between patients treated on national clinical trials and those not entered, or between those managed at teaching hospitals as opposed to nonteaching hospitals [66]. This observation appears to be exceptional, however, in that subsequent national AML trials in the United Kingdom have shown some of the best results reported to date [67].

1.4.7 Quality of Survival

The quality of survival, both during and after therapy, is a critical issue for adolescents and young adults. Quality of life is poor during the months and years when most adolescents and young adults with cancer are treated, and the acute and delayed toxicities of cancer therapy are undeniably among the worst associated with the treatment of any chronic disease. The acute toxicities of nausea, vomiting, mucositis, alopecia, weight gain (or excessive loss), acne, bleeding, and infection are generally harder for adolescents to cope with than for either younger or older persons. Delayed complications may be of low concern to patients in this age group during treatment, but after therapy has been completed these complications can be frightening and real. Cardiomyopathies, growth disturbances, and neuropsychological side effects are examples of adverse late effects that are hard to describe in a meaningful way before initiating therapy to an adolescent or young adult. A particularly tragic example of an unanticipated late effect is the development of a second malignancy in a patient cured of their original disease.

Many adolescent and young adult cancer survivors cite fertility as a primary concern that impacts the quality of their life. Most do not recall an adequate discussion of the risks of infertility or methods to decrease the risks with their physician at the initiation of therapy. The risk of infertility for an individual is difficult to predict. Direct radiation exposure of the gonad had been studied more extensively than other chemotherapy exposures. Permanent ovarian damage occurs between 5 and 20 Gy, with higher doses required in younger females [68]. The male germinal epithelium is much more sensitive to radiation-induced damage, with changes to spermatogonia resulting from as little as 0.2 Gy. Testicular doses of less than 0.2 Gy had no significant effect on follicle-stimulating hormone

(FSH) levels or sperm counts, whereas doses between 0.2 and 0.7 Gy caused a transient dose-dependent increase in FSH and a reduction in sperm concentration, with a return to normal values within 12 to 24 months. No radiation dose threshold has been defined above which permanent azoospermia is inevitable; however, doses of 1.2 Gy and above are likely to be associated with a reduced risk of recovery of spermatogenesis. The time to recovery, if it is to occur, is also likely to be dose dependent [69]. Cranial radiation impairs gonadal hormone synthesis and can result in a decreased production of luteinizing and follicle-stimulating hormones. Alkylating chemotherapeutic agents carry a high risk of infertility, but the exact dose required or the rates associated with combination agents are unavailable. Recommendations for preservation, evaluation, and counseling have recently become available [70–73].

The quality-of-life issues that arise during and after cancer therapy have been the focus of studies in children and older adults, but have not received the same attention or study in adolescents and young adults. A few studies have found certain trends that should be tested in future studies. A higher risk-taking behavior has been noted among survivors of Hodgkin lymphoma occurring during childhood and adolescence [74], an observation that does not appear to be limited to this disease. On the other hand, evidence also suggests that adolescent and young adult cancer survivors show better attendance and performance at school and work [75]. Persistent anxiety over relapse, death, or late effects is likely to be higher in adolescents who were cognitively aware of the severity of their illness than in those treated in early childhood (the Damocles syndrome) [76]. The paucity of quality-of-life data in this age group is another manifestation of the general neglect of these patients.

1.5 Summary

Cancer is 2.7 times more likely to develop in a patient at the age of 15 to 30 years than during the first 15 years of life, and yet is uncommon relative to older ages, accounting for 2% of all invasive cancer. Malignant disease in persons 15 to 30 years of age has no age counterpart. It is unique in the distribution of the types that occur, with Hodgkin lymphoma, melanoma, testis cancer, female genital tract malignancies, thyroid cancer, soft-tissue sarcomas, non-Hodgkin lymphoma, leukemia, brain and spinal cord tumors, breast cancer, bone sarcomas, and nongonadal germ cell tumors accounting for 95% of the cancers in the age group. In the mere 15 years of the age span, the frequency distribution of cancer types changes dramatically, such that the pattern at age 15 years does not resemble that at age 30 years. It is unique with regard to the physical nature and emotional needs of the hosts that develop it, and in the current failure to improve survival prolongation or mortality reduction relative to other age groups. Adolescents and young adults with cancer also face unique psychosocial challenges in the arenas of self-image, independence/dependence, finances, and relationships. Fortunately, the incidence increase observed during the past quarter century is declining, and in the older end of the age range appears to be returning to incidence rate of the 1970s.

Males in the age group have been at higher risk of developing cancer, the risk being directly proportional to age in the group. Non-Hispanic white people have had the highest risk of developing cancer during this phase of life, and Asians, American Indians and Native Alaskans the lowest. Males have had a worse prognosis, as have African-American, American Indians, and native Alaskans among the races/ethnicities evaluated.

The most disturbing epidemiologic finding is the lack of progress in survival improvement among older adolescents and young adults relative to all other ages. Whereas the diagnosis of cancer in this age group used to carry a more favorable prognosis, on the average, relative to cancer at other ages, survival improvement trends portend a worse prognosis for young adults diagnosed with cancer today. During the last 25 years, the incidence of cancer in this age range has increased more and the reduction in cancer mortality has been lower than in younger or older patients.

Proposed reasons for this gap in outcome include lack of health insurance and poor participation by older adolescents and young adults with cancer in clinical trials: in the United States, only approximately 1% of 15- to 29-year-olds with cancer are entered onto clinical trials, in contrast to more than 50% of younger patients.

Despite the fact that there are nearly three times as many cases of cancer in individuals who are 15–29 years of age as in those less than 15 years of age. Yet the former has its own organized cooperative oncology group and the latter does not. Adolescent and young adult oncology patients should be viewed as a distinct age group that, like pediatric, adult, and geriatric patients, has unique medical and psychosocial needs. This mindset will help bring the problem into focus and will help those caring for adolescents or young adults to find solutions. A specific discipline for this special population is just beginning to evolve. Meanwhile, resources should be devoted to educating the public, health professionals, insurers, and legislators about the special needs of these patients. The overriding issues to be addressed are the lagging improvements in survival and the special psychosocial needs of this age group.

To address this problem, the United States NCI and the NCI-sponsored pediatric and adult cooperative groups have launched a national initiative to improve the accrual of adolescents and young adults with cancer into clinical trials. In North America and Australia, the newly formed Children's Oncology Group has taken a leadership role in this effort. In conjunction with the NCI and NCI-sponsored adult cooperative groups, four initiatives were identified as priorities for development: (1) improving access to care through understanding barriers to participation; (2) developing a cancer resource network that provides information about clinical trials to patients, families, providers, and the public; (3) enhancing adolescent treatment adherence (compliance with protocol-prescribed therapy); and (4) increasing adolescent accrual and adult participation in sarcoma trials designed specifically for patients in this age group. However, reasons other than poor clinical trial participation, such as undescribed differences in biology, delays in diagnosis, poor compliance or intolerance of therapy, and treatment by physicians less familiar with the disease, may also be contributing to this outcome disparity [77], and need to be studied.

Surviving adolescence and young adulthood is difficult enough, even when all is well and health is not limiting. Cancer makes this phase of life extraordinarily more challenging and demanding. The medical community caring for these patients should pay special attention to the unique transitions faced by adolescents and young adults with cancer at the times of diagnosis, informed consent, initiation of therapy, school and employment reentrance, completion of therapy, post-treatment follow-up, and switching from pediatric to adult care [78, 79]. Ideally, specialized adolescent and young adult cancer units should be developed in the anticipation that the centralization of care and the availability of age-targeted clinical trials will lead to improved treatment, survival, and quality of life.

Thus, cancer during adolescence and early adult life is an underestimated challenge that merits specific resources, solutions and a national focus. Future research should elucidate why the outcomes have lagged behind and identify the efforts, including better clinical trial accrual, that will remedy the disparity. Finally, more scholarly and focused attention on the unique psychosocial needs of this population will improve the quality of their cancer care and the quality of their survival.

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