National Cancer Institute

Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age

INCLUDING SEER INCIDENCE AND SURVIVAL: 1975-2000

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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A Children's Oncology Group and SEER Publication

CANCER EPIDEMIOLOGY IN OLDER ADOLESCENTS AND YOUNG ADULTS 15 TO 29 YEARS OF AGE

INCLUDING SEER INCIDENCE AND SURVIVAL: 1975-2000

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Finally, our appreciation goes to the numerous oncologists and medical teams who care for those with cancer, and the many older adolescent and young adult cancer patients and survivors, their families, and their care providers—without whom this work would not have been possible or meaningful.

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Front cover:

Satellite image is based on NASA "Visible Earth" imagery available at http://visibleearth.nasa.gov/.

With special thanks to the young adult cancer survivors pictured (listed in alphabetical order): Heidi Adams, Christine Baze, Sheri Cohen, Karen Dyer, Tamika Felder, Bethany Hartung, Kyle Stueck, Michael Lin, James Reed, Doug Ulman, Erin Zammett, Octavio Zavala

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LETTER FROM THE DEPUTY DIRECTOR OF THE NATIONAL CANCER INSTITUTE

Cancer, we have come to learn, is principally a disease of aging. Its likelihood increases as we get older, in part because *cancer does not occur at a precise moment in time, but rather is a process which can take many years to develop.* We also know that cancer's process is, at times, a very brief one, striking young children—the most defenseless among us.

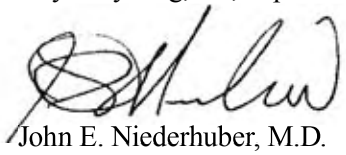
But there is one group that oftentimes gets lost in our healthcare system: young adults. Poised between adolescence and adulthood, these young adults are—as an age group—experiencing distinct physical changes as well as unique emotional hurdles. When the burden of cancer is added, it becomes part of this extraordinary and challenging time in their growth and development. Historically, though, little attention and few resources have been devoted to studying the incidence, biology, and treatment outcomes in this age group. The National Cancer Institute (NCI) is trying to change that fact.

In 2006 the NCI, in collaboration with the Lance Armstrong Foundation, is conducting a yearlong evaluation of the issues facing older adolescents and young adults with cancer. This Progress Review Group hopes to identify and prioritize the scientific, medical, and psychosocial barriers facing adolescent and young adult cancer patients and to develop strategies to improve their outcomes.

Likewise, with the establishment of the Adolescent and Young Adult Committee of the NCI-funded Children's Oncology Group (COG), research and education for and about young people will move forward a more-rapid pace.

This monograph is the first to collect detailed information about cancer incidence and outcomes in adolescents and young adults. It would not have been possible without the many institutions participating in the COG and adult treatment consortiums, or without the extensive data collection efforts of the NCI's Surveillance Epidemiology and End-Results (SEER) program.

The National Cancer Institute has challenged the United States to a goal: eliminate the suffering and death due to cancer by the year 2015. If we are to make that goal a reality, we must enhance the lives of all patients, whether they are young, old, or precariously positioned in between.



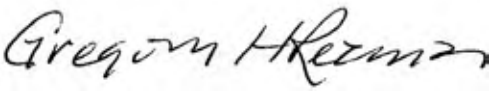
John E. Niederhuber, M.D.

LETTER FROM THE CHAIRMAN OF CHILDREN'S ONCOLOGY GROUP

Supported by the National Cancer Institute, the Children's Oncology Group (COG) designs and conducts clinical trials, correlative laboratory research and epidemiology studies of cancer in infants, children and adolescents. More than 200 member institutions in the U.S., Canada, Europe, Australia and New Zealand participate in these clinical trials, as we strive to improve survival rates and lessen the late effects of cancer treatment in this population. Older adolescent and young adult participation in our clinical trials is significantly lower than that of younger patients, and parallels the relatively worse treatment outcomes for each cancer type in this population.

The Adolescent and Young Adult Committee of COG was formed to focus research attention on this group, develop treatment protocols aimed at this population, increase participation in clinical trials by this population, and ultimately improve survival rates for older adolescents and young adults.

The following chapters highlight the initial efforts of this Committee in addressing the scope of the problem of adolescent and young adult under-representation in clinical trials and offer evidence that such a discrepancy may partially explain outcome differences. In addition, these chapters present information about biologic differences between specific cancer subtypes most common in younger children and those exhibited by the same cancers in adolescents and young adults, and offer plausible explanations for outcome differences as well as potential treatment strategies. The continued progress of these activities is a high priority of the COG and is expected to be the focus of future publication efforts.



Gregory H. Reaman, M.D.

LETTER FROM THE CANCER THERAPY AND EVALUATION PROGRAM OF THE NATIONAL CANCER INSTITUTE

Older adolescents and young adults with cancer are now the focus of national and international research investigating the tumor biology, treatment access, treatment compliance and psychosocial issues unique to this select age group of cancer patient. These investigations are being undertaken in an attempt to improve treatment regimens and boost the survival rates and quality of life for these young patients. I have the privilege to co-Chair, along with Drs. Karen Albritton and Michael Caligiuri, the *Progress Review Group (PRG) in Adolescent and Young Adult Oncology*, a year-long evaluation of the issues facing older adolescents and young adults with cancer, and co-sponsored by the National Cancer Institute and the Lance Armstrong Foundation. The *PRG* evaluation will bring critical attention to the specific needs of those with cancer in this age group.

This monograph was developed to gather population-based incidence, mortality, and survival data specific to cancers that occur in the AYA population, along with epidemiological data and risk factors for the development of age-specific cancers. This monograph uses both the International Classification of Childhood Cancer and the International Classification of Diseases-Oncology because cancers occurring in this age group span the pediatric-to-adult spectrum of diseases. We believe this monograph will help educate medical providers and the public about cancer incidence and survival in this age group, and provide the impetus for further research to improve the survival and the quality of life of these young people.

Barry Anderson, MD, PhD

LETTER FROM THE CHAIR OF THE CHILDREN'S ONCOLOGY GROUP ADOLESCENT AND YOUNG ADULT COMMITTEE

The primary goal of the Adolescent and Young Adult Committee of the Children's Oncology Group is to increase, through research and awareness, the knowledge about cancer in teenagers and young adults. We firmly believe this knowledge will improve the survival and quality of survival of a population that has not seen the same improvements as younger or older cancer patients. Through age-specific therapeutic studies of the cancers that occur in this age group, descriptive and interventional studies to decrease the burden of cancer, and studies to understand the processes of health access for this population, our committee strives to advance the emerging science of adolescent and young adult oncology.

Since the inception of the Adolescent and Young Adult Committee, we have sought to raise awareness through numerous publications about cancer treatment and outcomes in this age group. The publication of the Adolescent and Young Adult Cancer Monograph has been a long-term goal of the Committee. Until now, the incidence and survival rates of cancer occurring in adolescents and young adults in the United States has been unknown—another "gap" between the fields of pediatric and adult oncology. No longer.

We are hopeful that this monograph will be a valuable resource for those working with these patients, and a tool in the development of cancer research dedicated to this age group, including the deliberations of the upcoming Adolescent and Young Adult Oncology Progress Review Group.

We are grateful to the young people for their participation in clinical trials, for their willingness to advocate for improvements in cancer care, and their courage in living life to the fullest.

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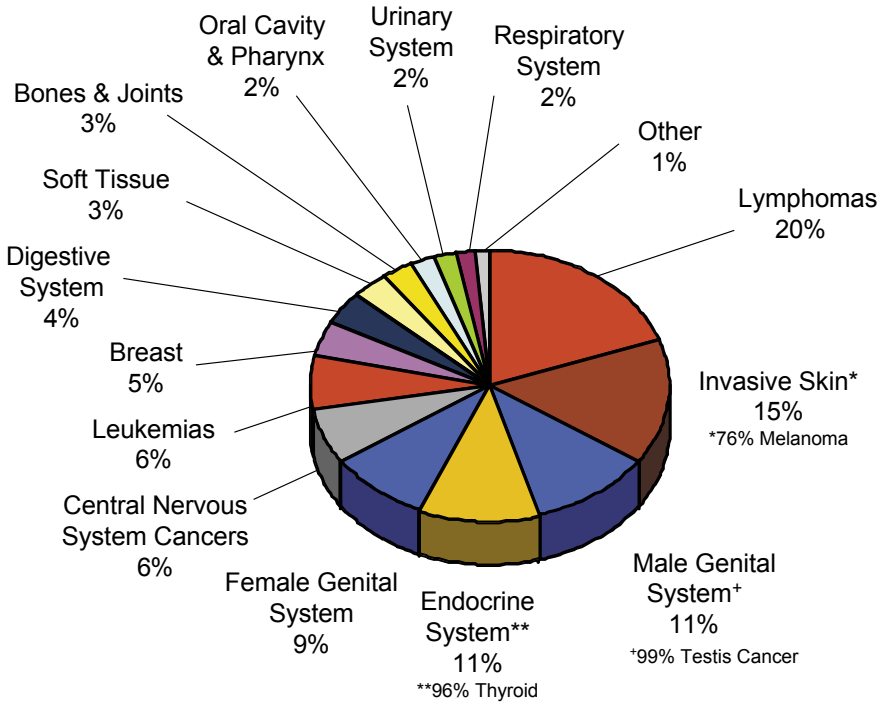
Chapter 1

Introduction

Cancer in 15-29 Year-Olds, U.S. SEER, 1975-2000



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HIGHLIGHTS

Incidence

- Cancer occurring between the ages of 15 and 30 years is 2.7 times more common than cancer occurring during the first 15 years of life, yet is much less common than cancer in older age groups, and accounts for just 2% of all invasive cancer.
- Cancer in adolescents and young adults is unique in the distribution of the types that occur. 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 non-gonadal germ cell tumors account for 95% of the cancers in this age group.
- The frequency distribution of cancer types changes dramatically from age 15 to 30, such that the pattern at the youngest age does not resemble the one at the oldest.
- The incidence of cancer in this age group increased steadily during the past quarter century.
- This increase is declining and at the older end of the age range appears to be returning to the incidence of the 1970s.
- Males in the 15- to 29- year age group have been at higher risk of developing cancer, with the risk directly proportional to age.
- Non-Hispanic whites have had the highest risk of developing cancer during this phase of life, and Asians, American Indians and Alaskan Natives the lowest.
- Males had a worse prognosis than females. African Americans/blacks, American Indian/Alaska Natives had a worse prognosis than white non-Hispanics and Asians.

Mortality & Survival

- At the beginning of the last quarter century, the diagnosis of cancer in 15- to 29-year-olds carried a more favorable prognosis, on the average, relative to cancer at other ages.
- Since then, there has been a lack of progress in survival improvement among older adolescents and young adults relative to all other ages.
- Survival improvement trends portend a worse prognosis for young adults diagnosed with cancer today than 25 years ago.
- The survival deficit is increasing with longer follow-up of the survivors, and is worse in males.
- Among 15- to 29-year-olds, non-Hispanic whites had the best survival and African Americans/blacks had the worst survival, with a 20% difference apparent by 5 years.
- Asians/Pacific Islanders had the second best survival, with Hispanics and American Indians/Alaska Natives next in sequence.

Risk Factors

- In general, there are relatively scant data to support either an environmental causation or an inherited predisposition to cancer in this age group.
- The majority of cases of cancer occurring before age 30 appear to be spontaneous and unrelated to either carcinogens in the environment or family cancer syndromes.
- Overall, family cancer syndromes appear to account for less than 5% of the cases of cancer in the age group. Melanoma, cervical carcinoma and Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin and Burkitt lymphomas accounting for the majority of environmentally induced malignancies (ultraviolet light, human papillomavirus, human immunodeficiency virus, and Epstein-Barr virus, respectively).
- Ultimately, a larger proportion of cases may be attributable to specific factors or genetic predisposition, but at present, most cancer in this age group appears to be sporadic and random.

INTRODUCTION

To our knowledge, this is the first treatise devoted exclusively to cancer in adolescents and young adults 15- to 29-years of age. A prior monograph from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI) of the United States reported the epidemiology of cancer in children younger than 20 years of age.[1] For many of the analyses in the current report, data for the age groups 0 to 15 years and 30 to 44 years are included for comparison. The SEER incidence data included in this introductory chapter were collected mainly between 1975 and 2001.

As in the prior monograph, and as routinely available in the SEER database,[2] five year increments (15 to 19 years, 20 to 24 years, 25 to 29 years, etc.) are utilized in most analyses. Only recently have data from SEER become available in shorter age intervals, but with the exception of this introductory chapter, these data are not presented in this monograph. Although the pediatric cancer monograph included a chapter about 15- to 19-year-olds,[3] the current monograph contains new and more varied analyses.

Each disease-based chapter follows a standard outline, beginning with incidence and followed by death rates, survival information and risk factors/etiology, in that sequence. Each of the disease-based chapters is authored by an expert epidemiologist, at least one pediatric oncologist, and at least one academic oncologist who is an expert in the care of adult patients with cancer (medical, surgical, gynecologic, and/or radiation oncologist).

METHODS, CLASSIFICATION SYSTEM, AND DATABASES

Invasive cancer refers to any malignancy except squamous and basal cell carcinoma skin cancer, *in situ* cancers of any organ except bladder, or ovarian cancers of borderline significance. It does include juvenile pilocytic astrocytoma, a low-grade brain tumor with little metastatic potential. There are two primary site and histology groupings based on the *International Classification of Diseases for Oncology*[4,5] (ICD-O): the SEER site recode (http://www.seer.cancer.gov/siterecode/icdo3_d01272003/) and the *International Classification of Childhood Cancers* (ICCC). The ICD-O evolved as an expansion of the International Classification of Diseases (ICD) in order to code both primary site and histologic type, and has been through a number of revisions. The SEER site recode was developed mainly to group adult cancers by primary site. The ICCC was developed later[6] to better characterize pediatric cancers. The SEER site recode was based primarily on the site in the body where cancer arises (e.g. gastrointestinal tract, genitourinary system, respiratory system, and the breast). The majority of pediatric cancers are disseminated when they are diagnosed and only the tissue of origin can be determined. The SEER site recode is therefore mainly topographic and the ICCC is primarily based on histology. Further refinements have been proposed for adolescents and young adults to allow categorization of the epithelial tumors (carcinomas) that are much more common in this age group than in children.[7,8] The *Methods* chapter that follows provides more information on classification, and explains which SEER and national mortality databases were used and how the analyses were conducted.

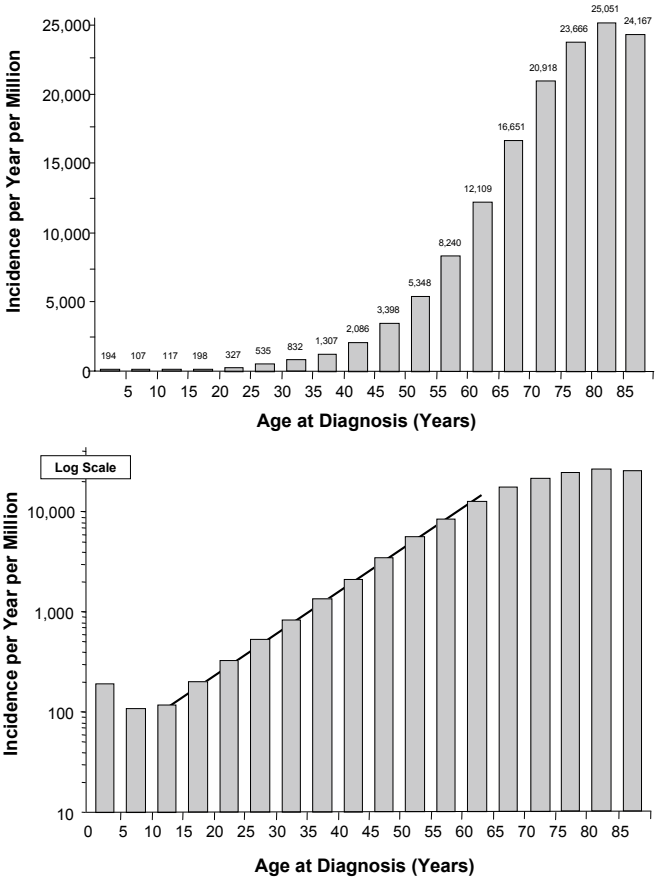

Figure 1.1: Incidence of All Invasive Cancer, SEER 1975-2000

Table 1.1: *Incidence of Invasive Cancer in Persons Younger Than 45 Years of Age*

AGE AT DIAGNOSIS (YEARS)	< 5	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44
U.S. 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 all invasive cancer per million per year, 1975-2000, SEER	206	111	125	203	352	547	833	1,289	2,094
Average annual % increase in invasive cancer, 1975-2000, SEER	1.0	0.4	0.9	0.7	1.0	1.9	1.6	1.1	0.4
Estimated incidence of invasive cancer per million, year 2000, U.S.	217	113	129	216	365	662	983	1,462	2,156
Estimated number of persons diagnosed with invasive cancer, year 2000, U.S.	4,153	2,314	2,638	4,374	6,928	12,830	20,162	33,197	48,385

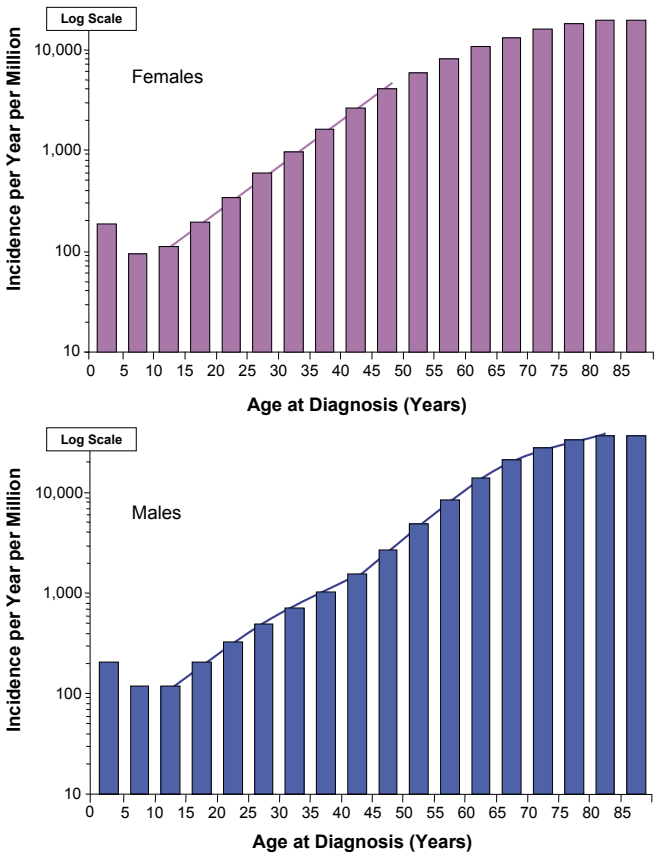

Figure 1.2: Incidence of All Invasive Cancer, SEER 1975-2000

INCIDENCE

In the U.S., 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 diagnosed before age 15, 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 15 to 29 years of age were diagnosed with invasive cancer (Table 1.1). Because the incidence of cancer increases exponentially as a function of age (Figure 1.1), approximately half of the 15- to 29-year-old patients are 25 to 29 years of age.

Age-Specific Incidence

Figure 1.1 shows the incidence of all invasive cancer in the U.S. from 1975 to 2000 as a function of 5-year age intervals from birth to 85+ years. The upper panel displays a linear ordinate and the lower panel uses semi-logarithmic coordinates. The straight line in the lower panel indicates that the incidence is exponentially correlated with age from 10 to 60 years. That adolescents and young adults have an exponential risk of developing cancer as they age suggests a biologic mechanism that is age-dependent, such as telomerase shortening or a mutation-to-malignancy rate that increases constantly with age, and that most cancer before age 30 is not due to environmental carcinogens.

Gender-Specific Incidence

Figure 1.2 shows the corresponding incidence in females (upper panel) and males (lower panel), each expressed on semi-logarithmic coordinates. Females demonstrate the exponential risk pattern from age 10 to 50 years. Males instead have 2 exponential risk patterns, from 10 to 40 years and 40 to 80 years. This suggests that another age-dependent mechanism is operative in young adult males. This pattern may be attributable also to the cancers that occurred in males during the 1980s and early 1990s as a result of the human immunodeficiency virus, namely Kaposi sarcoma and HIV-related lymphoma.

Figure 1.3 demonstrates how dependent on age is the relative risk of being diagnosed with cancer in males versus females. The male:female ratio has a nadir at 40 to 44, years, during which females are almost twice as likely as males to be diagnosed with invasive cancer. At both ends of the age spectrum—in children and older adults—the ratio is reversed. Boys are 10–25% more likely than girls to be diagnosed with cancer, and older adult males are much more likely to develop cancer than females. The transition from a male predominance in childhood to a female predominance in the middle years of life occurs during late adolescence/early adulthood. The male:female ratio declines linearly from the 10- to 14-year age group to the 40- to 44-year age group.

Racial/Ethnic Differences in Incidence

The dependence of cancer incidence on race and ethnicity as a function of age is shown in Figure 1.4 for all ages in 15 year-intervals up to age 44, and as one group for older persons. In Figure 1.5, it is shown for 5-year age intervals up to age 45. Non-Hispanic whites had the highest incidence during the first 40 years of life. Over age 40, African Americans/blacks had the highest incidence, followed by white non-Hispanics and Americans of Hispanic/Latino, Asian, and Pacific Islander descent. American Indians/Alaska Natives had the lowest cancer incidence at all ages. Males and females follow similar race/ethnicity-incidence patterns to those described above up to age 40 (Figure 1.6). The conversion to a higher incidence in African Americans/blacks occurs in males between age 40 and 44 and in females at an older age (Figures 1.4 and 1.6).

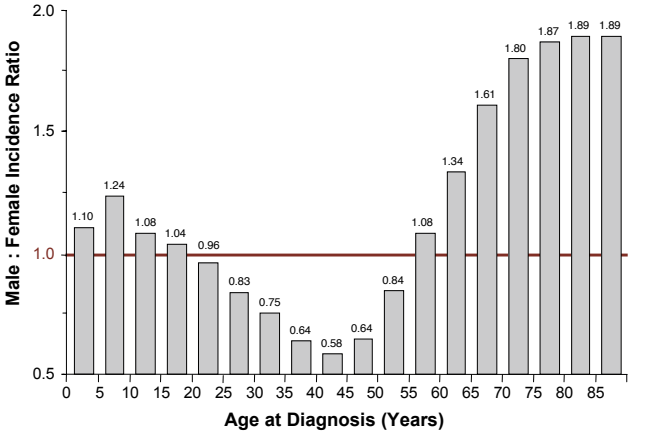

Figure 1.3: Incidence of All Invasive Cancer, Male:Female Ratio, SEER 1975-2000

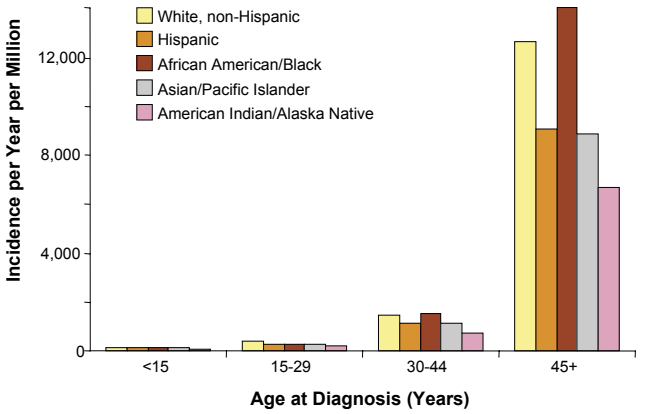

Figure 1.4: Incidence of All Invasive Cancer by Race/Ethnicity, SEER 1990-1999

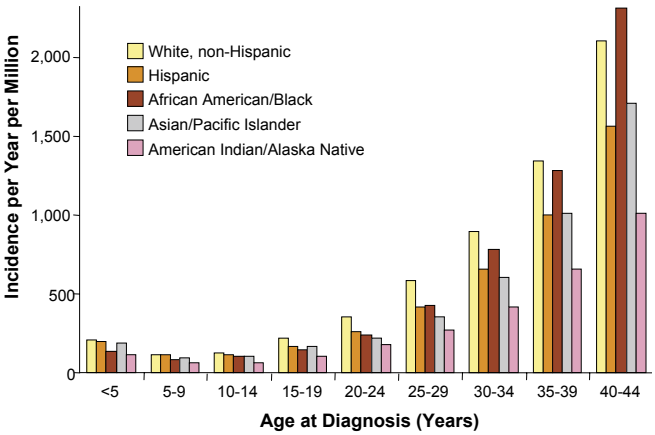

Figure 1.5: Incidence of All Invasive Cancer by Race/Ethnicity, SEER 1990-1999

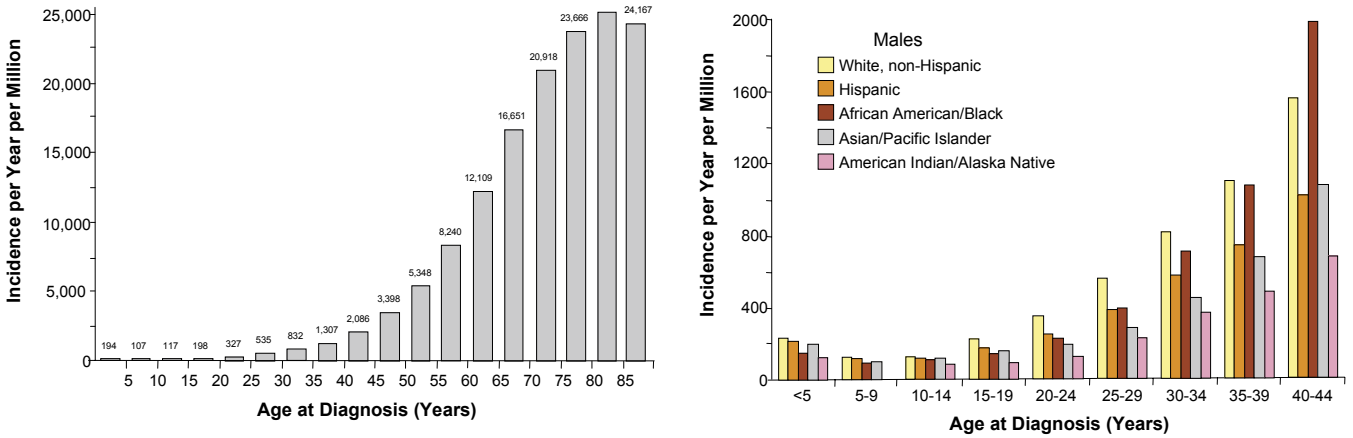

Figure 1.6: Incidence of All Invasive Cancer by Race/Ethnicity, SEER 1990-1999

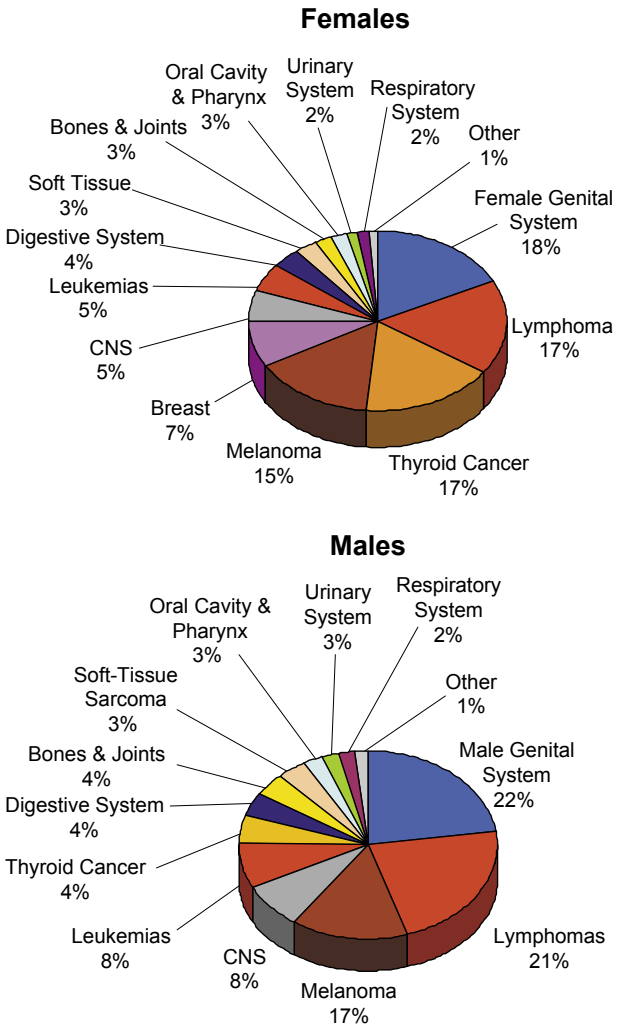

Figure 1.7: Cancer in 15- to 29-Year-Olds by Primary Site (SEER Site Recode) U.S., SEER 1975-2000

Types of Cancer

The common types of cancer and their relative proportion of all invasive cancers that occurred in 60,824 15- to 29-year-old Americans registered by SEER from 1975 to 2000 are shown in the pie diagram on the first page of this chapter, according to the SEER site recode. Lymphoma accounted for the largest proportion, 20% of all cases, with Hodgkin lymphoma alone accounting for 12% of all cases. Next in frequency were invasive skin cancer (15%) and male genital system cancer (11%), followed in rank order by endocrine system cancer (11%), female genital tract malignancies (9%—predominantly of the uterine cervix and ovary), brain and spinal cord tumors (6%), leukemias (6%), breast cancer (5%), digestive tract malignancies (4%—predominantly of liver and colon), soft-tissue sarcomas (3%), bone sarcomas (3%—predominantly osteosarcoma and Ewing sarcoma), cancers of the oral cavity/pharynx, urinary tract, and respiratory system (each 2%), and other, including extragonadal germ cell tumors such as teratocarcinoma and dysgerminoma (1%).

The distribution of the most frequent cancers in the U.S. among 15- to 29-year-olds according to gender is shown in Figure 1.7. The most striking difference between males and females in the 15- to 29-year age range is the much higher frequency of thyroid cancer in females. In both males and females, malignancies of the genital tract are the most frequent type of cancer followed closely by lymphomas (and thyroid for females).

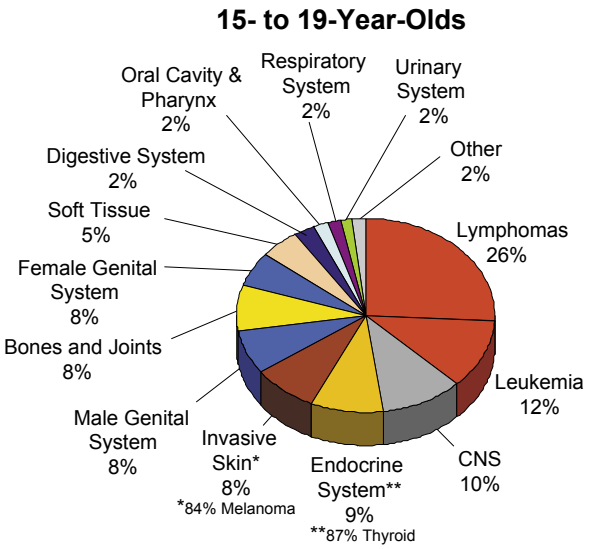

Figure 1.8: Cancer in 15- to 19-Year-Olds by Primary Site (SEER Site Recode) U.S., SEER 1975-2000

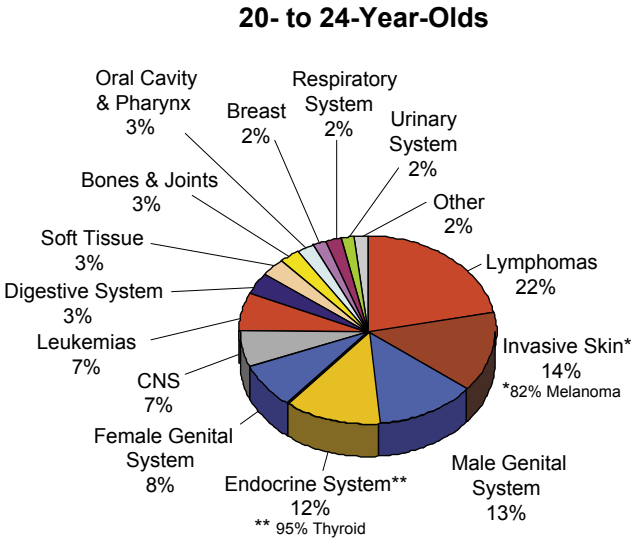

Figure 1.9: Cancer in 20- to 24-Year-Olds by Primary Site (SEER Site Recode) U.S., SEER 1975-2000

The distribution of the most frequent cancers by 5-year age intervals within the 15- to 29-year age range is shown in Figures 1.8, 1.9, and 1.10. The most dramatic changes in the types of cancer as a function of age (15 to 29 years) occurred in melanoma (from 5th most frequent in the 15- to 19-year age group to 1st most frequent in the 25- to 29-year age group, when gender is not considered), leukemia (from 2nd most frequent to 9th), and CNS tumors (3rd to 7th).

Trends in Incidence

Between 1975 and 2000, cancer increased in incidence for all age groups younger than 45 years (Figure 1.11). Between 25 and 45 years of age, most of the increase in overall cancer incidence occurred in males (Figure 1.12). Those cancers with the greatest change in incidence during this interval are shown in Figures 1.13 and 1.14.

The increase in incidence among 25- to 39 -year-old males (Figure 1.12) was due in large part to increases in soft tissue sarcoma (notably Kaposi sarcoma), non-Hodgkin lymphoma, and testicular carcinoma (Figure 1.13). Among females younger than 45 years of age, the greatest increase occurred in germ cell tumors (Figure 1.14).

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

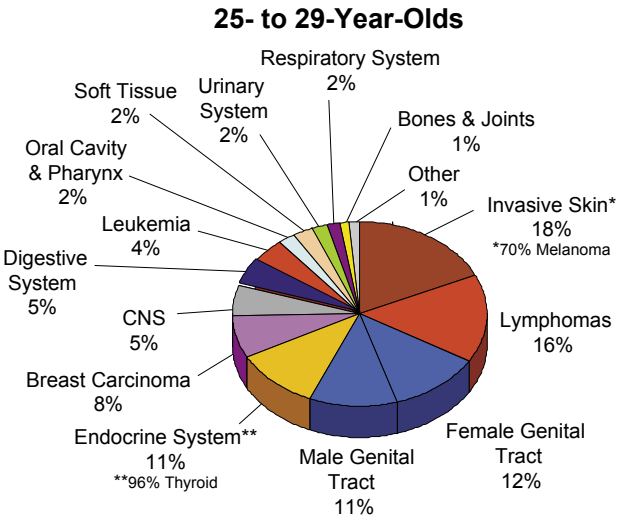

Figure 1.10: Cancer in 25- to 29-Year-Olds by Primary Site (SEER Site Recode) U.S., SEER 1975-2000

incidence among 15- to 24-year-olds and a decrease in 25- to 29-year-olds (after a peak in the late 1980s and early 1990s) (Figure 1.15). That sarcoma and lymphoma accounted for most of the increase in cancer in males between 25 and 40 years of age (Figure 1.13) suggests that the peak in incidence in this age group was primarily due to Kaposi sarcoma and non-Hodgkin lymphoma as a result of the human immunodeficiency virus epidemic.

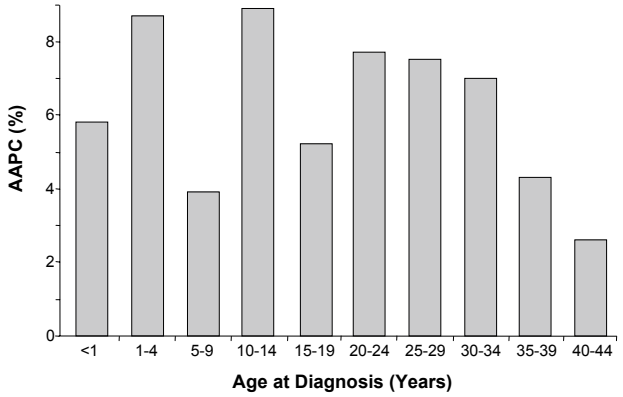

Figure 1.11: Average Annual Percent Change (AAPC) in Incidence of All Invasive Cancers, SEER 1975-2001

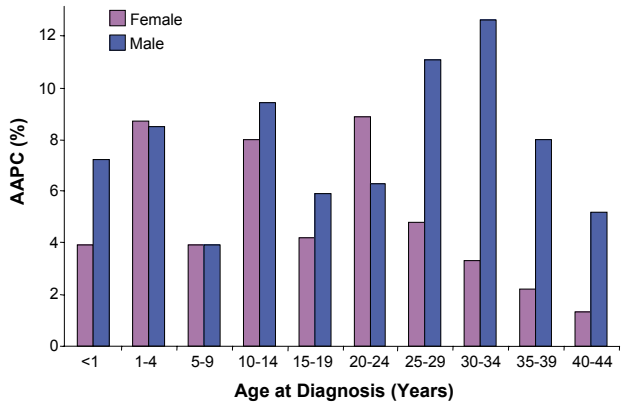

Figure 1.12: Average Annual Percent Change (AAPC) in Incidence of All Invasive Cancer by Gender, SEER 1975-2001

OUTCOME

Age- and Gender-Specific Mortality

National mortality of all invasive cancer as a function of age at death is shown in Figure 1.16. By and large, the age-dependent cancer death rate reflects the incidence profile (Figure 1.1). More males than females die of cancer over age 45 (Figure 1.16; inset). From 30 to 44 years of age, deaths among females predominate. In patients younger than 30 years, mortality is higher in males (Figure 1.16).

Because mortality varies with incidence—the more patients diagnosed with cancer the higher the death rate would be expected to be—the gender-specific ratio of the death rate to incidence for the era 1975 to 2000 is shown in Figure 1.17. Among all age groups—from 10 to 45 years of age—more males than females have died of cancer when the death rate is considered relative to the variation in incidence. This suggests that the cancers that occurred in adolescent and young adult males during the period 1975 to 2000 were more lethal than those in women or that the treatment was less effective.

Racial/Ethnic Differences in Mortality

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

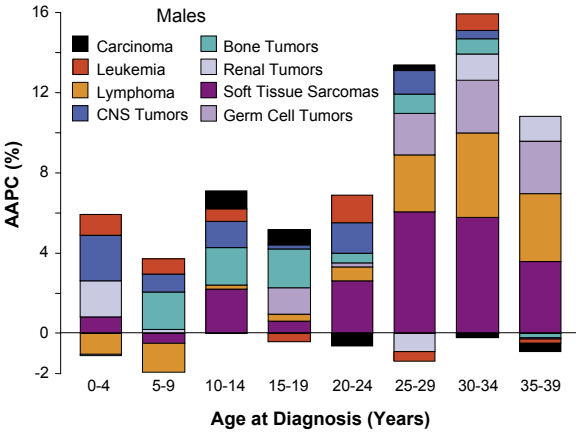

Figure 1.13: Average Annual Percent Change (AAPC) in Cancer Incidence in Males, SEER 1975-1998

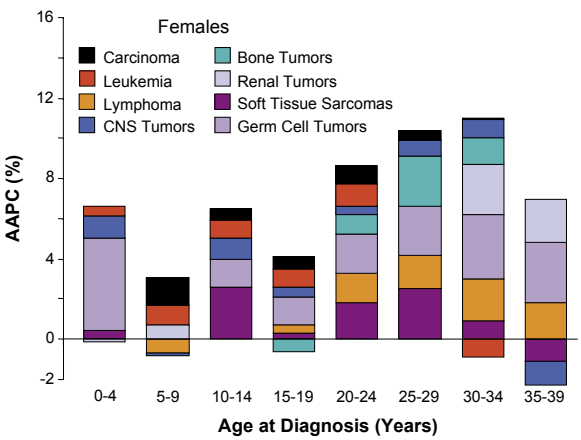

Figure 1.14: Average Annual Percent Change (AAPC) in Cancer Incidence in Females, SEER 1975-1998

Trends in Mortality

Mortality from invasive cancer declined between 1975 and 2000 in all age groups younger than age 45, but the least improvement occurred in 20- to 44-year-olds (Figure 1.20). This pattern—less progress in reducing cancer mortality for young adults than for children and young adolescents—is true for males and females (Figure 1.21) and for white non-Hispanics and African Americans/blacks (Figure 1.22). Among African Americans/blacks, however, the rate of progress in reducing mortality was considerably lower, particularly in 15- to 24-year olds (Figure 1.22).

Survival

Survival up to 20 years after a diagnosis of invasive cancer is shown in Figure 1.23 for all patients followed by SEER from 1975 to 1999, and in Figures 1.24 and 1.25 for females and males, respectively, during this era. Among both female and male 15- to 29-year-olds, survival after an invasive cancer diagnosis was comparable to that in persons who were younger than age 15 when diagnosed. In males older than 30, survival was worse. Above age 45, survival was considerably worse than for younger age groups, and comparable in men and women.

Survival as a function of race/ethnicity among < 15, 15- to 29-, 30- to 44-, and 45+ year-olds with cancer in the period 1992 to 1999 is shown in Figure 1.26. The era is more recent and the follow-up shorter because race/ethnicity data for other than whites and African Americans/blacks were not available until the 1990 census. Among 15- to 29-year-olds, non-Hispanic whites had the best survival and African Americans/blacks had the worst survival, with a 20% difference apparent by 5 years. Hispanics, Asians/Pacific Islanders and American Indians/Alaska Natives had an intermediate survival. American Indians/Alaska Natives had a more rapid cancer death rate during the first two year than non-Hispanic whites, Hispanics and Asians/Pacific Islanders, and then reached a relative plateau not seen in the other races/ethnicities. During the 1990s, 27% of American Indians/Alaska Natives with cancer died within two years, more than twice the death rate observed among non-Hispanic whites.

When compared to younger and older cancer patients, 15- to 29-year-olds had an intermediate survival for each

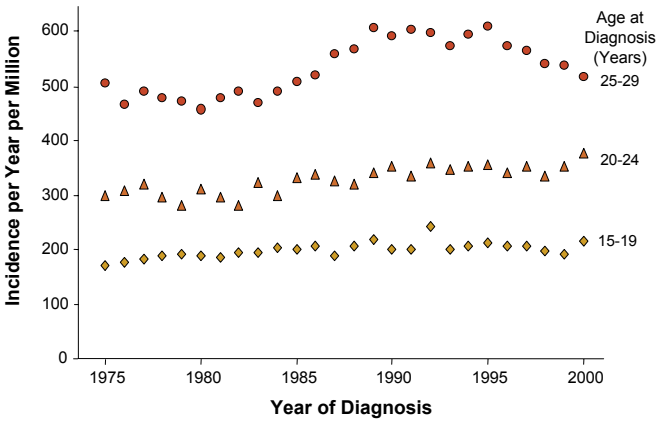

Figure 1.15: Incidence of Invasive Cancer by Year of Diagnosis, SEER 1975-2000

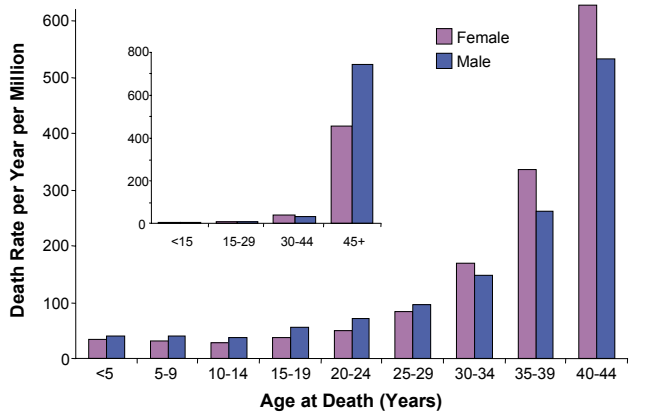

Figure 1.16: National Mortality by Gender for All Invasive Cancer, 1975-2000

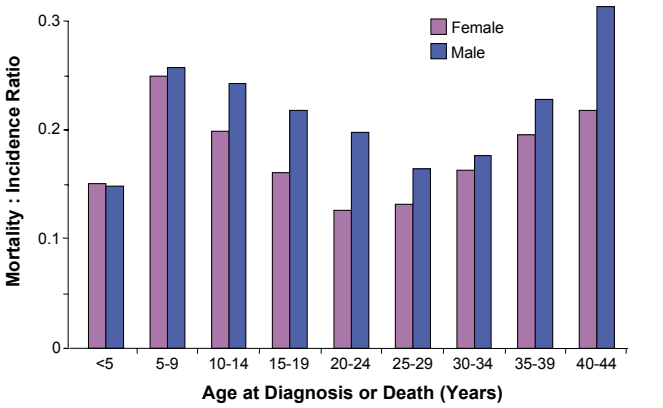

Figure 1.17: Ratio of National Mortality to SEER Incidence, All Invasive Cancer by Gender 1975-2000

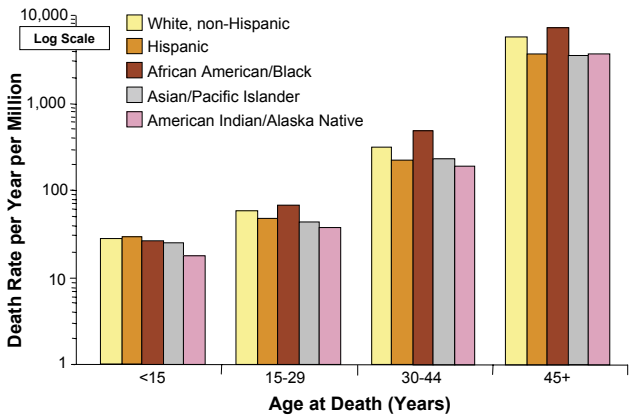

Figure 1.18: National Mortality by Race/Ethnicity for All Invasive Cancer, U.S., 1990-2000

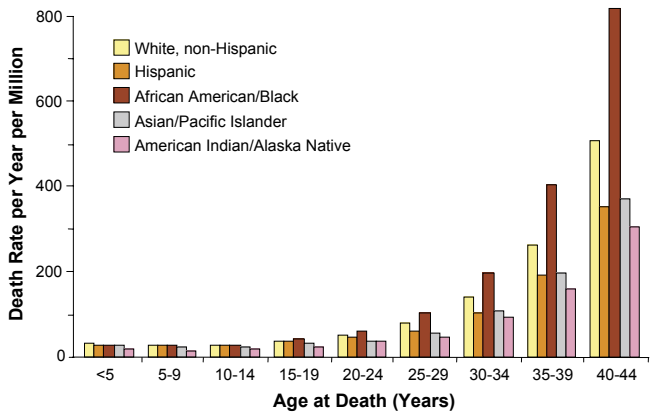

Figure 1.19: National Mortality by Race/Ethnicity for All Invasive Cancer, U.S., 1990-2000

of the races/ethnicities (Figure 1.26). The higher cancer death rate in African Americans/blacks observed in older adults is equally apparent in 15- to 29-year-olds but not in < 15-year-olds, in whom the worst initial survival occurred in American Indians/Alaska Natives and the ultimate survival appeared similar for races/ethnicities other than non-Hispanic whites (Figure 1.26). Also, in 30- to 44-year-olds the plateau on the survival curve in 15- to 29-year-old American Indians/Alaska Natives was not observed. And in comparison to both < 15- and 15- to 29-year age groups, the survival curves among 30-to 44-year-olds clearly separated, with the order of best-to-worst survival being non-Hispanic whites, Asians/Pacific Islanders, Hispanics, American Indians/Alaska Natives, and African Americans/blacks.

Figure 1.27 depicts the 5-year survival rate of 15- to 29-year-olds diagnosed with cancer during 1975 to 1997 by year of diagnosis. Little improvement in survival is noted during the 23 years of SEER tracking.

Figures 1.28 and 1.29 display the average annual percent change 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 (see Chapter 2, *Methods*, for an explanation of how SEER derives this parameter). 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 (ibid).

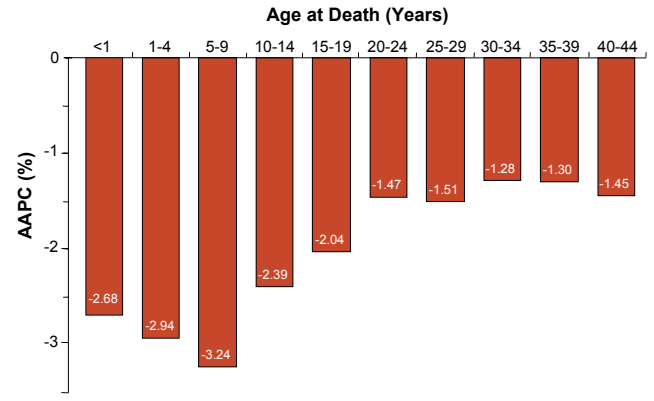

Figure 1.20: Average Annual Percent Change (AAPC) in National Mortality for All Invasive Cancer, U.S., 1975-2000

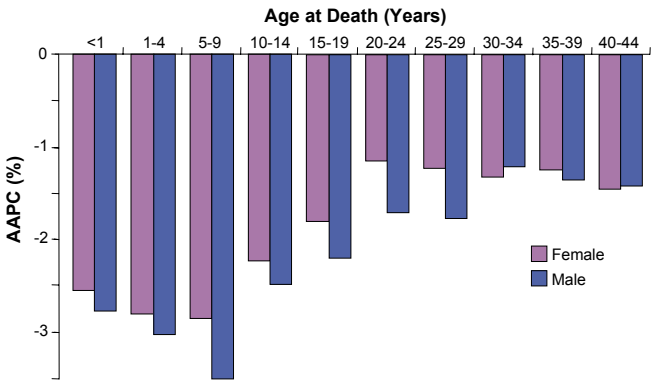

Figure 1.21: Average Annual Percent Change (AAPC) in National Mortality for All Invasive Cancer by Gender, U.S., 1975-2000

Steady progress in improving the 5-year survival rate has occurred in children and older adults. For patients between 15 and 45 years of age, however, progress in survival improvement has been a fraction of that achieved in younger and older patients. For patients between 25 and 35 years of age, in fact, there has been no evidence for an improvement in survival (Figure 1.28). Most of the older adolescent/young adult deficit occurred in males, but females have not been spared (Figure 1.29). Among females, the least amount of improvement occured in 25- to 29-year-olds; among males it was in 25- to 39-year-olds.

To determine whether the young adult survival gap was apparent at follow-up time points other than every five years, the 1- and 5-year relative survival rates were compared. In this analysis, individual year-to-year age groups were evaluated instead of 5-year age groupings, and the survival rates during the 1995 to 1999 era were compared with the 1975 to 1999 era rates and expressed as the percentage improvement since the earlier era. Both survival parameters (1- and 5-year survival rates) showed the same profile (Figure 1.30), with a nadir in progress between age 25 and 40 years (the vertical red band in the Figure). The 5-year survival pattern showed a greater disparity than the pattern at 1-year, indicating that the survival deficit gap increased with longer follow-up of the patients. As in the analyses that utilized the average percent change method, young adult males had a more striking deficit than females in the same age group (Figure 1.31).

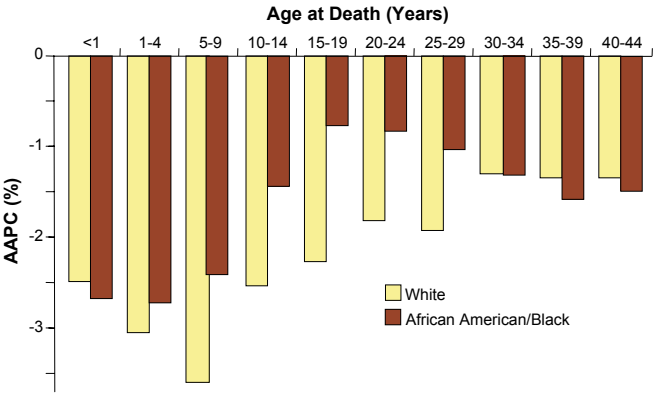

Figure 1.22: Average Annual Percent Change (AAPC) in National Mortality for All Invasive Cancer by Race, U.S., 1975-2000

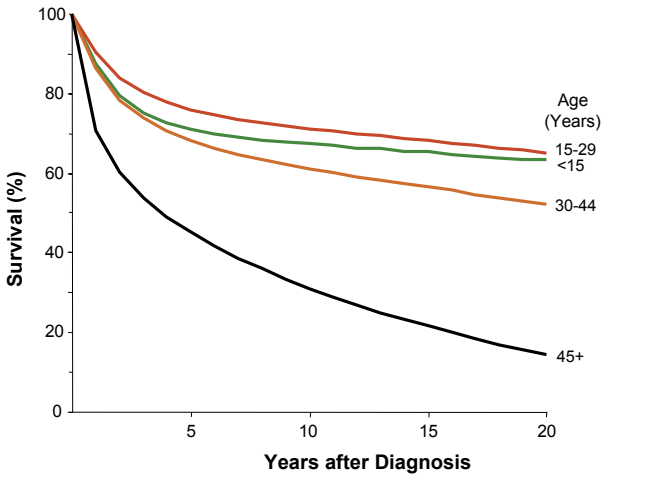

Figure 1.23: Relative Survival for All Invasive Cancer by Age, SEER 1975-1999

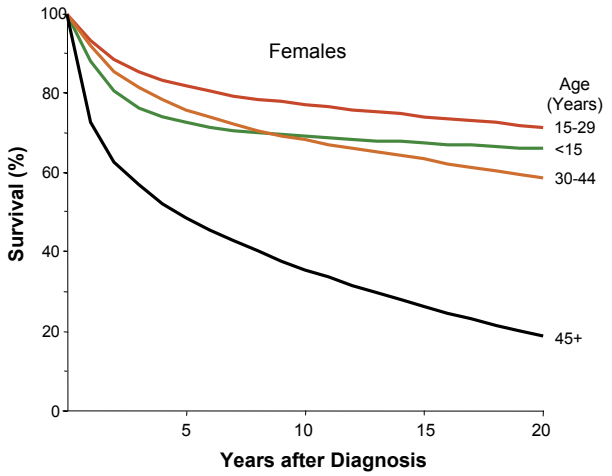

Figure 1.24: Relative Survival for All Invasive Cancer in Females by Age, SEER 1975-1999

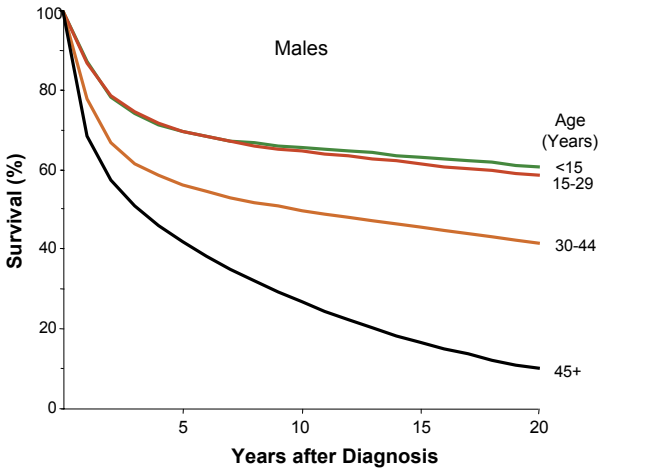

Figure 1.25: Relative Survival for All Invasive Cancer in Males by Age, SEER 1975-1999

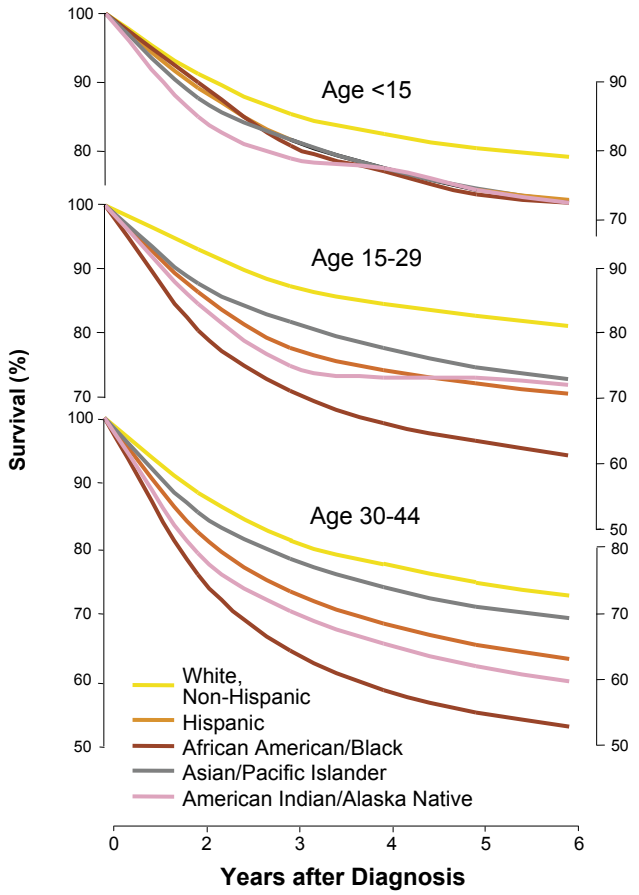

Figure 1.26: Relative Survival for All Invasive Cancer by Race/Ethnicity, SEER 1992-1999

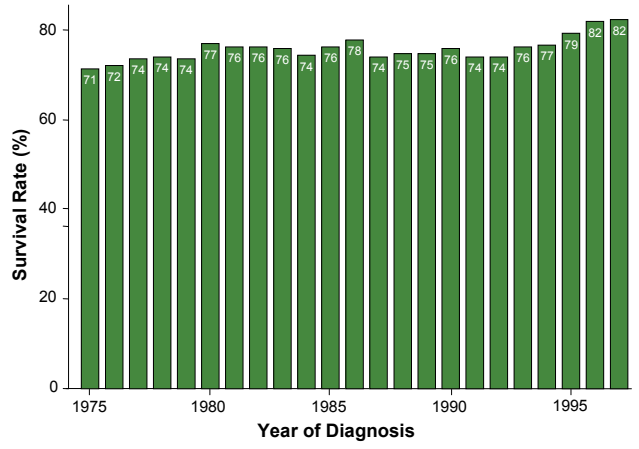

Figure 1.27: 5-Year Relative Survival, Age 15-29, SEER 1975-1997

RISK FACTORS

Etiologic mechanisms and risk factors of the most common cancers that occur in the 15- to 29-year age group are considered in the disease-specific chapters. In general, there are relatively scant data to support either an environmental causation or an inherited predisposition to cancer in this age group. The vast majority of cases of cancer diagnosed before age 30 appear to be spontaneous and unrelated to either carcinogens in the environment or family cancer syndromes. There are exceptions, covered in each disease chapter, but the exceptions are rare. Clear cell adenocarcinoma of the vagina or cervix in adolescent females has in most cases been 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. Melanoma, cervical carcinoma, Kaposi sarcoma and non-Hodgkin lymphoma, and Hodgkin and Burkitt lymphomas account for the majority of environmentally induced malignancies (due to ultraviolet light, human papillomavirus, human immunodeficiency virus, and Epstein-Barr virus, respectively). Ultimately, a larger proportion of cases may be attributable to specific factors or genomic predisposition but, at present, most cancers in this age group appear to be sporadic and random. Overall, family cancer syndromes appear to account for less than 5% of the cases of cancer in the 15- to 29-year age group.

SUMMARY

A cancer diagnosis between the ages of 15 and 30 years is 2.7 times more common than such a diagnosis during the first 15 years of life, and yet is rare—accounting for just 2% of all invasive cancers—relative to cancer occurring at older ages. Malignant disease in persons 15 to 29 years of age is unique in the distribution of 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 non-gonadal germ cell tumors accounting for 95% of the cancers in this

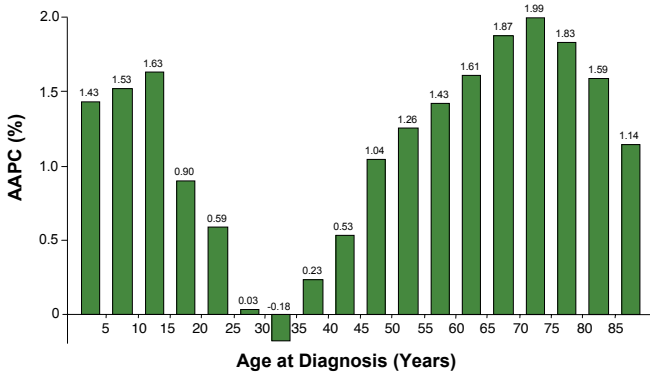

Figure 1.28: Average Annual Percent Change (AAPC) in 5-Year Relative Survival for All Invasive Cancer, SEER 1975-1997

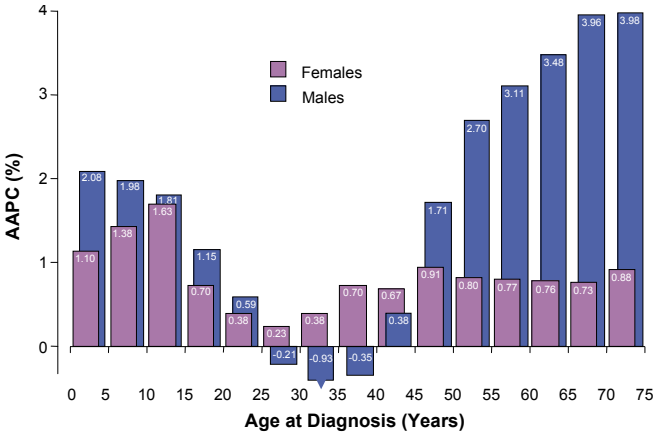

Figure 1.29: Average Annual % Change (AAPC) in 5-Year Relative Survival for All Invasive Cancer by Gender, SEER 1975-1997

age group. In the brief period from 15 to 30 years of age, the frequency distribution of cancer types changes dramatically, such that the pattern at age 15 does not resemble that at age 30.

A failure to improve length of survival and reduce mortality has occurred in this age group relative to other age groups. Fortunately, the incidence increase observed during the past quarter century is declining, and for those at the older end of the age range appears to be returning to the incidence of the 1970s.

Males in the 15- to 29-year age group have been at higher risk of developing cancer, with the risk directly proportional to age. White non-Hispanics have had the highest risk of developing cancer during this phase of life, and Asians/Pacific Islanders, American Indians and Alaska Natives the lowest. Males have had a worse prognosis, as have African Americans/blacks, American Indians, and Alaska Natives among the races/ethnicities evaluated.

The most disturbing finding is the lack of progress in survival improvement among older adolescents and young adults in contrast to all other ages. Whereas the diagnosis of cancer in this age group used to carry a more favorable prognosis relative to cancer at other ages, current survival improvement trends portend a worse prognosis for today's young adults diagnosed with cancer.

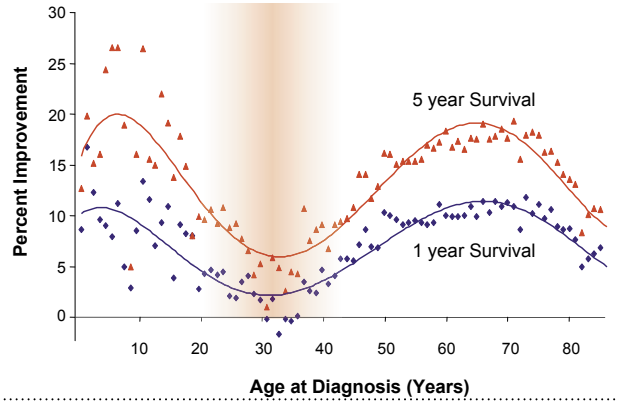

Figure 1.30: Change in Relative Survival Proportion, 1995-1999 versus 1975-1979, for All Invasive Cancer, SEER

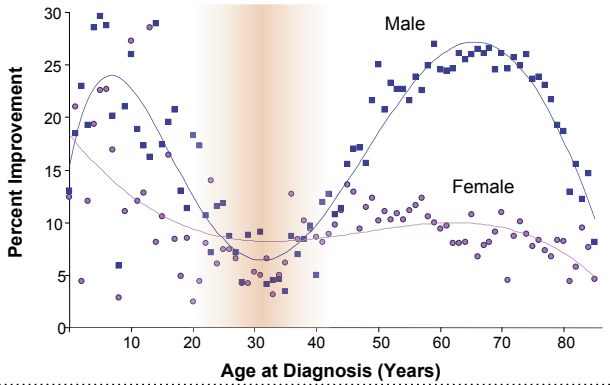

Figure 1. 31: Change in Relative 5-Year Survival Proportion, 1995-1999 versus 1975-1979, for All Invasive Cancer by Gender, SEER

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Chapter 2

Methods

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HIGHLIGHTS

Surveillance, Epidemiology and End Results (SEER)

- The SEER Program of the United States National Cancer Institute was the source of data for determination of estimates of cancer incidence and survival rates and trends for the United States.
- The nine original sites or expanded 12 geographic areas of the SEER program were used for all of the estimates of rates, trends and frequencies in this monograph.
- This database represents about 13% of the population that was specifically chosen for geographic and racial/ethnic representation of the country as a whole.

National Center for Health Statistics (NCHS)

- The United States NCHS was the source of data for mortality analyses.

United States Bureau of Census

- The United States Census Bureau was the source of data for most population estimates from which incidence and death rates and trends were determined.

Classification System

- International Classification of Diseases for Oncology was used for definitions of primary sites and histology. This forms the basis for two different classification systems: the SEER site recode based primarily on site, and the International Classification of Childhood Cancer (ICCC), based primarily on histology.
- Ideally, a hybrid classification system for older adolescents and young adults, such as has been proposed by Birch and her colleagues, should be adopted for future analyses.

Incidence

- Cancer incidence rates were obtained from data collected by SEER from a population-based subset of the United States.

Mortality

- The mortality data included all deaths in the U.S. and were obtained from public use files provided by the National Center for Health Statistics (NCHS). All death rates were based on the underlying cause of death.

Survival

- As derived and explained in the prior monograph, cancer survival rates were obtained from data collected by SEER.

Average Annual Percent Change

- As derived and explained in the prior monograph, trends in cancer incidence, mortality and survival rates were expressed as *average annual percent change* rates obtained from data collected by SEER.

Risk Factors

- Information regarding etiologic and risk factors were obtained from published peer-reviewed literature. Interpretation of the reviewed data represents the opinion of the authors of the chapters, with general concurrence by the editors.

INTRODUCTION

A prior monograph from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI) of the United States reported on cancer in children younger than 20 years of age.[1] The methods and materials used for that treatise are fundamentally those applied to this monograph for 15- to 29-year-olds, inclusive, with updated databases and census information

added in the interim. Calculations of rates and trends have been refined and more powerful statistical methods have been employed.

For every cancer reviewed, 5-year age intervals were used for incidence (age at diagnosis), death rate (age at death) and survival (age at diagnosis). For many of the analyses in the current report, data are presented for 15- to 29-year-olds, with comparisons to the age groups 0 to 15 years and 30 to 44+ years; for some analyses the entire age range from birth to 85+ years are included. All of the common cancers that occur in 15- to 29-year-olds are covered. For those cancers that occur primarily in adolescents, young adults and older adults, comparisons with the older age groups are emphasized. For those malignancies that occur primarily in children, adolescents and young adults, comparison with children and young teenagers (< 15 year-olds, 0- to 4-, 5- to 9- and 10- to 14-year-olds) are emphasized. The U.S. Bureau of Census provided SEER with individual year of age data just before this monograph went to publication, thus only one chapter—the *Introduction*, which reviews all invasive cancer in aggregate—contains data on individual year of age.

The SEER incidence data included in this monograph were collected mainly between 1975 and 2001. Some chapters however, depending on when the analyses were performed, include data for which 1999 or 2000 was the final year of data collection. Rates based on too few subjects or events to provide a reasonably reliable estimate were excluded. Interpretation of the data varies from chapter to chapter depending upon availability of data for specific age categories and racial/ethnic groups in each disease entity. For definitions and additional details, see the *Technical Appendix* at the conclusion of this chapter.

This monograph is also available from the SEER home page under publications (http://seer.cancer.gov).

CLASSIFICATION SYSTEM, PRIMARY SITE, AND HISTOLOGY CODING

Invasive cancer refers to any malignancy except non-melanoma skin cancer (squamous and basal cell carcinoma), *in situ* cancers, or ovarian cancers of borderline significance. It includes low-grade brain tumors with little metastatic potential (e.g., juvenile pilocytic astrocytoma), since these neoplasms can be fatal due to local growth. Information on *in situ* cancers except cervix uteri were collected but are not reported in this monograph.

The International Classification of Diseases for Oncology (ICD-O) was used for definitions of primary sites and histology.[2] This forms the basis for two different classification systems: the SEER site recode,[3] based primarily on site, and the International Classification of Childhood Cancers (ICCC),[4] based primarily on histology. Originally, data for site and histologic type were coded by the different versions of ICD-O (ICD-O-1: 1975-1991; ICD-O-2: 1992-2000; ICD-O-3: 2001+).[2,5,6] SEER areas began using ICD-O-2 for cases diagnosed in 1992 and ICD-O-3 for 2001 and forward, and machine converted all previous data to ICD-O-3. Most data for non-Hodgkin Lymphoma (NHL) can be classified by the Working Formulation (WF) based on ICD-O-2.

At the time the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) published their first monograph on childhood cancer in 1988,[7] Dr. R. Marsden published an annex giving a classification scheme for childhood cancer that consisted of 12 groups based chiefly on histologic type. The classification by Marsden has been modified and is now called the ICCC.[4]

The ICCC was developed to better characterize pediatric cancers than the SEER site recode. The SEER site recode is 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 part because cancer in a majority of adults is localized to the organ of origin with or without regional lymph node involvement at the time of diagnosis. In contrast, many childhood cancers tend to be of cell types that occur widely throughout the body, such as lymphohematopoietic, connective tissue, peripheral nervous system, and blood vessel neoplasms, as opposed to occurring in discrete organs. This tissue- and organ-based nature of the childhood cancers was the basis for the ICCC.

The SEER site recode is therefore primarily topographic and the ICCC is primarily histology—and tissue—based.[8] For certain chapters such as those for leukemia, lymphoma, and sarcomas, the ICCC is more appropriate and for others, such as breast, male genital tract, and colon cancers, the SEER site recode is more useful. A few require more detailed information than provided by either classification, such as the chapter on female genital tract cancers, which is divided by histology. The classification section of each chapter specifies which system was used.

Since ICD-O-3 was only used for cases diagnosed in 2001+, the ICCC classification based on ICD-O-2 was used for these analyses. All of the topographic codes and many of the morphologic codes are the same between versions. Any case originally coded in ICD-O-3 was converted to ICD-O-2 before the ICCC classification was applied. In some chapters, there is a notation of new morphology codes in ICD-O-3 to explain where they fit into the classification. A new revised ICCC classification based on ICD-O-3[9] includes an extended classification table which expands the categories presented in the original ICCC, especially for solid tumors.

Further refinements have been proposed for use with adolescents and young adults, to allow for categorization of the epithelial tumors (carcinomas) that are much more common in this age group than in children.[10,11] This approach is discussed in the *Introduction* and *Highlights and Challenges* chapters, but is not used per se in the disease-specific chapters.

SOURCES AND ANALYSIS OF DATA

Surveillance, Epidemiology and End Results (SEER) Program

The Surveillance, Epidemiology and End Results (SEER) Program is a cancer data-collection program started in 1973 as an outgrowth of the Third National Cancer Survey of the National Cancer Institute (NCI). The NCI contracts out with various medically oriented non-profit organizations, local city or state Health Departments, or Universities for collection of these data. Contracts for collecting these data are with the entire states of Connecticut, Iowa, New Mexico, Utah and Hawaii, and with certain metropolitan areas. These organizations collect data on all malignancies and *in situ* cancers except basal and squamous cell skin and cervix *in situ* cancers. Only residents of specific geographic areas are included so that the base populations can be properly determined.

The population-based data used in this monograph for incidence and survival are from the NCI SEER Program.[12] Data back to 1975 are from SEER 9, which included the five states cited above and four metropolitan areas (Detroit, Michigan; Atlanta, Georgia; Seattle-Puget Sound, Washington; and San Francisco-Oakland, California) and comprised about 9% of the United States population. Some analyses also included the SEER 9 areas plus four additional areas (SEER 13): Los Angeles, California; San Jose-Monterey, California; rural Georgia, and the Alaska Native Cancer Registry.

Altogether, this monograph includes information on incidence and survival of 60,824 persons 15 to 29 years of age who resided in SEER areas between 1975 and 2000, and were diagnosed to have cancer. This group was compared with a total of 20,010 persons in the same era and SEER areas who were diagnosed before the age of 15, a total of 223,916 comparable patients aged 30 to 44 years, and 2,563,155 such persons 45 years of age or older at diagnosis.

The mortality data are presented for the same time period but cover all cancer deaths among adolescents and young adults in the entire United States. Data based on underlying cause of death were provided by the National Center for Health Statistics (NCHS), of the Centers for Disease Control and Prevention (CDC).

In order to calculate rates, population estimates were obtained from the Bureau of the Census. In 2000 there were 5.6 million persons residing in the SEER areas who were 15 to 29 years of age, and nearly 59 million people in the entire United States in this age group. Twenty-one percent of the U.S. population was in the 15- to 29-year age group, with 7.2% in the 15- to 19-year group, 6.8% in the 20- to 24-year group, and 6.8% in the 25- to 29-year group. Enumeration of the population at risk by single year of age was available only for the census years 1990

and 2000. Recently, however, the U.S. Census Bureau provided intercensal population estimates by single year of age for each year. Since most of the analyses for the disease-specific chapters were completed before the year-by-year, single year of age data became available, only the *Introduction* chapter contains data based on the individual year-of-age data.

In order to establish reasonably reliable estimates of rates, a minimum number of persons had to be available for analysis. For most purposes, this threshold was 16. If fewer persons were in this 'numerator,' the rate was not calculated and associated graphs were constructed without a datapoint for this value. In most charts therefore, absence of a datapoint means that the value was not evaluable and *not* that the rate was zero.

- *SEER*Stat*
  SEER*Stat is a software program that allows access to the SEER databases and downloading of data and calculations. Data available via SEER*Stat include the number of persons with specific types of cancer, incidence and death rates, and survival estimates. Most of these parameters can be assessed according to gender, race/ethnicity (see *Terminology* Section below), year of diagnosis, age at diagnosis or death, type of cancer according to either ICD-O or ICCC (or modifications) (see *Classification System* above), primary site, stage, and a number of other variables. SEER*Stat is available for public use (http://seer.cancer.gov/seerstat/).

- *Population Census*
  Most population data were obtained from the U.S. Census Bureau. For the year 2000, the data were accessed on 11/18/05.[13]

- *Calculation of rates* (See *Terminology* Section below)
  The incidence and death rates are the annual rates per million persons. Rates for interval of age exceeding 5 years are age-adjusted to the 2000 U.S. standard population. Survival rates are expressed as percents, and they are calculated and provided by SEER if there are a sufficient number of persons at risk for an event to warrant a calculation. In general, the latter requires at least 16 persons. When other criteria are used, the limitations are specified. If the minimum number of values required is not met, estimates are not provided.

- *SEER Modification to ICCC*
  As described above, the SEER program classifies all cases by cancer site and histologic type using the ICD-O (various editions).[2,5,6] In contrast to most cancer groupings, which are usually categorized by the site of the cancer, the pediatric classification is determined mostly by histologic type. The SEER data have been grouped according to ICCC specifications[4,8] with some exceptions for brain cancer.[8] Please refer to Appendix II for the distribution by ICCC groupings.

- *Histologic confirmation*
  In the SEER program, most of the cancers (95%) are histologically confirmed. This is important because most adolescent cancer classifications are based on histologic types: leukemia, lymphoma, connective tissue (sarcomas), etc. The percentage of histologically confirmed cases, however, does vary by ICCC category, ranging from a low of 90 percent for the nervous system (CNS) (ICCC group III) to a high of 99 percent for leukemia (ICCC group I).

- *Trends in incidence and mortality*
  Average annual percent changes (AAPC, APC; see *Terminology* section below) in incidence and mortality are provided by SEER when there are a sufficient number of persons at risk, as described in the *Calculation of Rates* section above. AAPCs achieving statistical significance are flagged by SEER and p-values provided within general ranges (< 0.05, < 0.001, etc.).

ORGANIZATIONAL STRUCTURE OF MONOGRAPH

This monograph consists of a chapter for each of the principal types of cancer that occur in the 15- to 29-year age group in the U.S. Each of the disease-specific chapters discusses incidence, mortality, and survival rates of the patients, as well as trends in these measures by demographic characteristics. Risk factors are also reported with—where possible—a description of the strength of

the evidence that the factor is associated with the disease (cf. *Etiology and Risk Factors* section below).

The estimates are presented for each five-year age group (15 to 19, inclusive; 20 to 24, inclusive; 25 to 29, inclusive) and, where appropriate, for 15-year age intervals (0 to 14, inclusive; 15 to 29, inclusive; 30 to 44, inclusive). Data on the 45-year and older age group is included when comparison with the oldest age group appears helpful. For each type of cancer reviewed in this monograph, the number of cases in the U.S. for the year 2000 is estimated, as projected from the trend in incidence from 1975 to 2000 and the estimated population in 2000 for the age group, as derived from the U.S. Census Bureau.

TERMINOLOGY

Age-adjusted rate

An age-adjusted rate is a weighted average of the age-specific incidence or death rate, where the weights are the proportions of persons in the corresponding age groups of a standard population. The potential confounding effect of age is reduced when comparing age-adjusted rates computed using the same standard population. For this report, the 2000 U.S. standard population was used to compute all age-adjusted rates. Since rates of cancer vary widely by 5-year age group, age-adjustment was used for any age group representing more than one 5-year grouping. Age-adjustment was performed by 5-year age group and weighted by the 2000 U.S. standard population.

Age-specific rate

Age-specific rates are usually presented as a rate per million. The numerator of the rate is the number of cancer cases found in a particular 5-year age group in a defined population; it is divided by the number of individuals in the same 5-year age group in that population. In this publication, there are some rates by single year of age. Population estimates by single year of age, race, gender, and geographic region were not previously available for intercensal years.

Case-control study

A case-control study is an epidemiologic study in which a group of individuals with a disease (the cases) are compared to a group of individuals without the disease (the controls). Exposures or characteristics that are more common in the cases than in the controls may be causes of the disease. Exposures or characteristics that are equally common in the cases and controls are highly unlikely to be causes of the disease. The majority of epidemiologic studies of cancer are case-control studies due to relative efficiency in studying relatively uncommon diseases.

Cohort study

A cohort study is an epidemiologic study in which the incidence of disease is compared between a group of individuals with an exposure or characteristic and a group without that exposure or characteristic. For example, smokers and nonsmokers are observed over time and the incidence of heart disease is compared between the two groups. Or, the incidence of breast cancer is compared in women with and without a BRCA1 gene mutation. This type of study is rarely feasible in investigating the etiology of cancer. Since cancer in adolescents and young adults is uncommon relative to its incidence in older adults, especially if we consider that each cancer should be studied separately, huge numbers of young people (tens of thousands) would have to be observed over a relatively long period of time to determine which would develop cancer.

Average annual percent change (APC, AAPC)

The Average Annual Percent Change (AAPC) was calculated in one of two ways. The most common method, and the one officially used by SEER, fits a linear regression line to the natural logarithm of rates using calendar year as a regressor variable, i.e. $Y = mX + b$, where $Y = \ln(r)$ and X = calendar year. The AAPC = $100 \times (e^m - 1)$. A modified method was used when the SEER database (accessed via SEER*Stat; see above) did not provide AAPC values. In this case, the linear regression was applied to the original values and not to their logarithms. Comparison of the two methods has demonstrated qualitatively equivalent results and generally insignificant quantitative differences.

Testing the hypothesis that the AAPC is equal to zero is equivalent to testing the hypothesis that the slope of the line in the above equation is equal to zero. The latter hypothesis is tested using the t distribution of m/SE_m with the number of degrees of freedom equal to the number of calendar years minus two. The standard error of m, i.e. SE_m, is obtained from the fit of the regression.[14] This

calculation assumes that the rates increased/decreased at a constant rate over the entire calendar year interval. The validity of this assumption has not been assessed. In those few instances where at least one of the rates was equal to zero, the linear regression was not calculated.

Follow-up

SEER areas attempt to follow all patients until death. Although the overall proportion of cancer patients of all ages who are lost to follow-up is only about 5%, it is larger—about 11%—for adolescent and young adult patients. Survival rates are relatively high for this age group, making long-term follow-up a challenge due to factors such as patient interest and name and address changes.

Incidence

In this monograph, incidence is the rate of all new cancers, or of a specific cancer site/type, occurring in a specified population over a specific interval, expressed as the number of cancers per year per one million people. The numerator of incidence can include multiple primary cancers occurring in one individual. For age intervals that exceed 5 years (e.g. 15-year intervals described in *Structure of Monograph* above), the rates are age-adjusted to the 2000 U.S. standard population. Age adjustments were not applied to 5-year age intervals (e.g. 15 to 19 years). Rates are for invasive cancer only, unless otherwise specified.

Mortality data

Death rates were derived from public use files provided by the National Center for Health Statistics (NCHS), and as such cover all deaths in the U.S. Death rates were based on the underlying cause of death. The rates presented for 1975 to 1978 were coded to the ICD 8th revision,[15] those for 1979 to 1998 to the ICD 9th revision.[16] and those for 1999+ to the ICD 10th revision.[17] Unfortunately, mortality of all specific groups of the ICCC pediatric classification are not available from U.S. mortality files for several reasons. Although certain groups can be identified as specific entities on death certifications (Leukemias, Lymphomas, Bone Cancers, Brain and other CNS tumors, and Hodgkin and Non-Hodgkin Lymphomas), other types of cancer cannot (e.g., germ cell tumors and certain carcinomas). To compare data over time, deaths coded to the sympathetic nervous system in the ICD-8 were combined with deaths coded to the adrenals in the ICD-9.

Death rates

The cancer death rate refers to the number of deaths to all cancers or to specific cancer site/type occurring in a specified population during a specific interval, expressed as the number of deaths due to cancer per year per one million people. Death rates were age-adjusted to the 2000 U.S. standard population, as described for incidence in the *Incidence* section above.

Relative survival rate

The relative survival rate is calculated using a procedure described by Ederer, Axtell, and Cutler,[18] whereby the observed survival rate is adjusted for expected mortality. The relative survival rate represents the likelihood that a patient will not die from causes associated specifically with cancer at some specified time after diagnosis. It is always larger than the observed survival rate for the same group of patients.

Expected rate tables were used for white, African American/black, and other races combined. Ideally, expected rate tables for each of the races/ethnicities are used to calculate relative survival rates for Hispanics, white non-Hispanics, Asians/Pacific Islanders, and Native Americans/Alaska Natives. For younger ages, the expected survival rates are very high among all of the racial/ethnic groups and it is suspected that not using race/ethnicity-specific expected rate tables for ages 15 to 29 years of age would have minimal impact on the relative survival rates.

Population data

Population estimates are obtained each year from the U.S. Census Bureau by five-year age groups (0 to 4 years, inclusive; 5 to 9 years inclusive, etc., to 85 and over), gender, race/ethnicity, and single year of age.

Race/ethnicity

Demographic data for racial/ethnic groups were obtained from the U.S. Census Bureau. Since each person could report multiple races in the 2000 Census, race-specific counts and percentages are based on persons reporting only one race. The following designations, based on U.S. Census data, are used throughout this monograph:

white non-Hispanic, African American/black, Hispanic, Asian, Native Hawaii/Pacific Islander, and American Indian/Alaska Native. In the monograph, Hispanic refers to Latinos, with Hispanics/Latinos being able to declare themselves as such in the national census surveys conducted in 1990 and 2000. Hispanic ethnicity is tabulated independently of race, thus Hispanic persons may be of any race. SEER currently codes the following Asian groups: Chinese, Japanese, Korean, Asian Indian/Pakistani, Vietnamese, Hmong, Kampuchean, Thai, and *other* Asian. SEER currently codes the following Pacific Islander groups: Hawaiian, Chamorran, Guamanian, Tahitian, Samoan, Tongan, Fiji Islander, New Guinean, other Melanesian, other Micronesian, other Polynesian, and *other* Pacific Islander. Data for Asian and Native Hawaii/Pacific Islander groups were combined into the Asian/Pacific Islander group in this monograph. Alaska Natives include Aleutian Islanders and Eskimos.

The Census Bureau estimates for Hawaii were altered according to independent estimates developed from sample survey data collected by the Health Surveillance Program (HSP) of the Hawaii Department of Health. For Hawaii, the *all races* and *black* populations are the same as those obtained from the Census Bureau. Proportions of the population by different racial groups from the HSP were used to generate estimates for whites, etc.

Risk factor

A risk factor is a characteristic or exposure that increases the risk of disease. A risk factor might be exposure to high levels of radon, having a diet low in vitamin A, having a family history of colon cancer, or having a high cholesterol level.

ETIOLOGY AND RISK FACTORS

Throughout this monograph, potential causes and risk factors for individual cancers are included. In many chapters, the evidence for risk association is categorized into levels of certainty, as indicated below.

Known risk factors
Most epidemiologists consider these characteristics or exposures to be 'causes' of the particular cancer.

Probable risk factors
Factors that are considered by most epidemiologists as 'causative' but not universally accepted.

Conflicting evidence
Factors associated with higher risk in some studies but not in others.

Limited evidence
Single case reports or investigations of a superficial manner or with methodologic issues that render the results difficult to interpret.

Multifactorial etiology
It is unlikely that a single exposure, behavior, or genetic trait completely explains any of the common cancers that occur in adolescents and young adults. Rather, multiple causation or multifactorial etiology is likely to explain most if not all the common cancers in the age group. Characteristics of the individual and the biologic, social, or physical environment may all play a role in the development of cancer. Such characteristics might include genetic, immune, dietary, occupational, hormonal, viral, socioeconomic, and lifestyle factors.

Associations versus causes
How do epidemiologists decide whether an association between an exposure and a disease is one of cause and effect? The methods and processes of epidemiology and their limitations make it nearly impossible for a single study to prove that an exposure causes a disease. There must be a number of studies that epidemiologists can evaluate using a set of criteria.

1. Epidemiologists consider the **strength** of the association, that is, the relative risk. An exposure associated with a ten-fold increase in risk is more likely to be a true cause than an exposure associated with a two-fold increase.
2. The **consistency** of an association is considered. An association observed in many different studies in different populations using different study methods is likely to be true.

3. Demonstration of a **dose-response relationship** between the exposure and the disease increases confidence that the exposure is really related to the disease.
4. The association must be **temporally consistent,** with the exposure preceding development of the disease.
5. A **biologically plausible** association is more likely to be true than one without other supporting evidence.
6. **Other possible explanations** of the observed association must be ruled out.

All or most of these six criteria must be met before an association between a disease and an exposure is considered a causal association.

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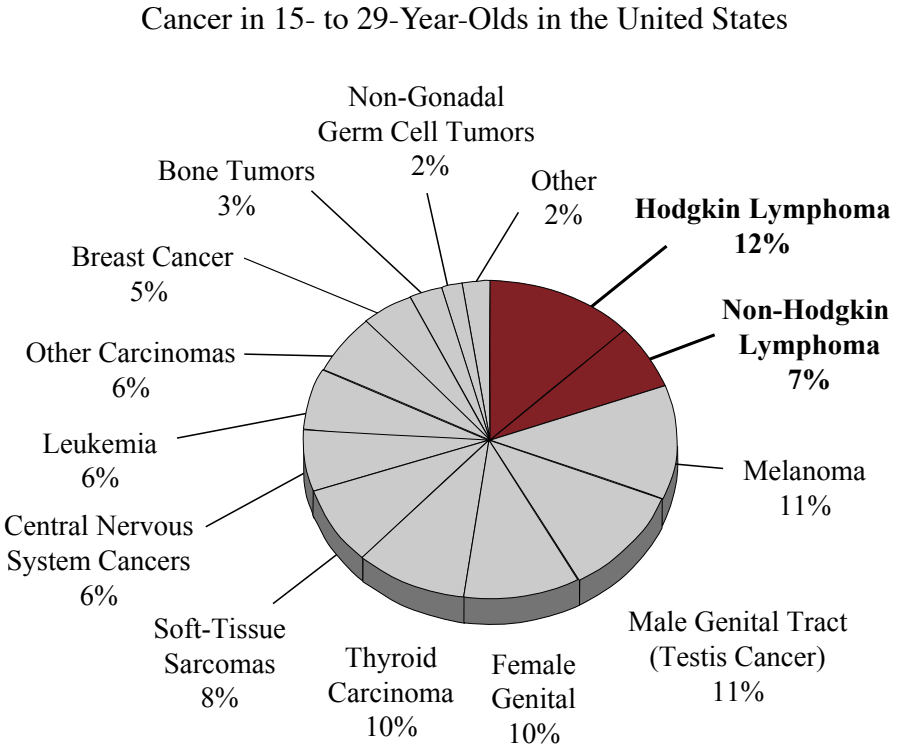
Chapter 3

Lymphomas and Reticuloendothelial Neoplasms



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HIGHLIGHTS

Incidence

- Lymphomas now represent 4-5% of all new malignancies diagnosed in the United States and are the most common hematologic malignancy.
- Lymphomas accounted for 19% of all cancers in 15- to 29-year-olds in the United States during the time period 1975 to 1999.
- In the adolescent and young adult population, the incidence of all lymphomas relative to other cancers decreased with age during this period—from 26% in 15- to 19-year-olds to 15.8% in 25- to 29-year-olds.
- Females had a higher incidence of Hodgkin lymphoma in the 15- to 19-year age group. Males had a higher incidence of all lymphomas in all other age groups.
- Incidence of Hodgkin lymphoma in the adolescent and young adult age group was highest in white non-Hispanics.
- The incidence of Hodgkin lymphoma as a function of age is bimodal, with a peak between 20 and 25 years of age and a second peak between 75 and 80 years of age.
- The incidence of non-Hodgkin lymphoma was highest in white non-Hispanics in the 15- to 19-year age group but highest in African Americans/blacks in the 20- to 29-year age group.

Mortality & Survival

- Males had higher mortality from lymphomas than females at all ages.
- Mortality for all lymphomas was comparable for 15- to 19-year-old whites and African Americans/blacks, but was higher for African Americans/blacks at all ages ≥ 20 years.
- Although little change in lymphoma survival for the 15- to 29-year age group has been observed, there has been marked improvement in survival in the < 15-year age group.
- Five-year survival for lymphomas in the 15- to 29-year age group was similar for all racial/ethnic groups.

Risk Factors

- Factors associated with a high standard of living may contribute to delayed exposure to childhood infections and subsequent delay in maturation of cell immunity. EBV infection acquired in adolescence, with subsequent development of infectious mononucleosis, may increase the risk of Hodgkin lymphoma in adolescents and young adults.
- A history of autoimmune disorder, family history of malignancy/hematopoietic disorder, and Jewish ethnicity are all risk factors for Hodgkin lymphoma.
- HIV infection predisposes to both Hodgkin and non-Hodgkin lymphoma.
- EBV infection has been linked to non-Hodgkin lymphoma.
- Autoimmune disorders, Helicobacter pylori infection, genetic susceptibility, male gender, tobacco use, and chemical exposure have been linked to an increased risk of non-Hodgkin lymphoma.

INTRODUCTION

In the time period 1975 to 1999, lymphomas accounted for 19% of cancers in 15- to 29-year-olds in the United States. In 2004 they represented 4-5% of all new malignancies diagnosed in the United States and were the most common hematologic malignancy.[1,2] Cancer was the second leading cause of death for all ages combined. In males between the ages of 20 and 40, non–Hodgkin lymphoma was the fourth most common malignancy and the fifth leading cause of cancer death. In the adolescent and young adult population, the incidence of all lymphomas relative to

other cancers decreased with age during the time period 1975 to 1999—from 26% in 15- to 19-year-olds to 15.8% in 25- to 29-year-olds (Figure 3.1).

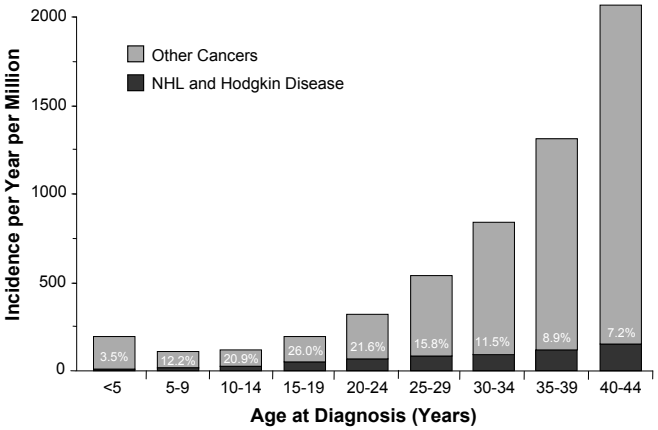

Figure 3.1: Incidence of All Lymphoma Relative to All Cancer, SEER 1975-1999

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), Lymphomas and Reticuloendothelial Neoplasms are in category II. Since many of the morphology codes used to designate ICCC category II changed between ICD-O-2 and ICD-O-3, the following discussion on specific histologies will only use the ICD-O-2 classification. Not included in ICCC is Letterer-Siwe disease (9722).

In the ICCC, category II is divided into: II(a) *Hodgkin lymphoma*; II(b) *Non-Hodgkin Lymphoma*; II(c) *Burkitt Lymphoma*; II(d) *Miscellaneous Lymphoreticular Neoplasms*; and II(e) *Unspecified Lymphomas*. Hodgkin lymphoma spans codes 9650-9667 and includes specific types of Hodgkin lymphoma [mixed cellularity (9652), lymphocytic depletion (9653-9655), lymphocytic predominance (9657-9659), nodular sclerosis (9663-9664), and mixed types (9665-9667)], Hodgkin lymphoma not otherwise specified (9650), Hodgkin paragranuloma (9660), Hodgkin granuloma (9661), and Hodgkin sarcoma (9662). The ICCC *Non-Hodgkin lymphoma* category II(b) is constituted by specific types of non-Hodgkin lymphoma (9670-9686, 9688, 9690-9717), non-Hodgkin malignant lymphoma (9591), lymphosarcoma (9592), reticulosarcoma (9593), microglioma (9594), true histiocytic lymphoma (9723), and diffuse malignant lymphoma (9595). The ICCC *Burkitt Lymphoma* II(c) category is Burkitt lymphoma (9687). The ICCC *Miscellaneous Lymphoreticular Neoplasm* category—II(d)—includes malignant histiocytosis (9720), plasmacytoma (9731), multiple myeloma (9732), mast cell tumors (9740-9741), immunoproliferative disease NOS (9760), Waldenstrom macroglobulinemia (9761), alpha heavy chain disease (9762), gamma heavy chain disease (9763), and immunoproliferative small intestinal disease (9764). ICCC *Unspecified Lymphoma* category II(e) is limited to malignant lymphoma, NOS (9590) in the ICD-O-2.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

Non-Hodgkin lymphoma (NHL) can be defined as only II(b) or as multiple subgroups of II. For example, ICCC categories II(b,c,e) constitute non-Hodgkin lymphoma in the SEER site recode and in the mortality data and II(d) is reported under *Miscellaneous* neoplasms for both. Since medical terminology used to describe the subtypes of NHL has undergone change, the specific subtypes have not been emphasized. When lymphoma occurs among 15- to 29-year-old patients, it represents a transition from pediatric to adult disease.

INCIDENCE

Age-Specific Incidence

Table 3.1 depicts the incidence of all lymphomas in the pediatric and adolescent/young adult age group. Average incidence in the U.S. increased with age for all lymphomas per million people. When observing the incidence trend and the average annual percent increase in incidence, the greatest increase was within the

non-Hodgkin lymphoma group, consistent with the adult experience.[3]

In Figure 3.2, the incidence of lymphoma by ICCC type from 1975 to 2000 is further delineated by age. A progressive increase was seen in non-Hodgkin lymphoma II(b) from birth to age 80. Burkitt lymphoma occurred at all ages, with three peaks in incidence: between the ages of 5 and 10 years, 35 and 45 years, and after 70 years. Over all age groups, the lowest rate of Burkitt lymphoma was in 20- to 24-year-olds. The incidence of Hodgkin lymphoma peaked twice, during the 20- to 24-year age interval and again in late adulthood as described further below.

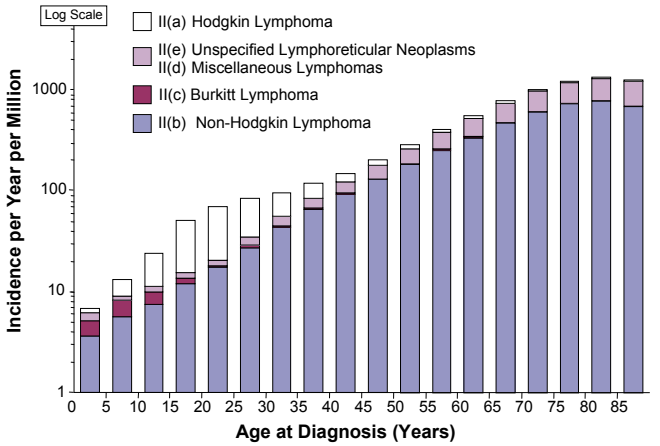

Figure 3.2: Incidence of Lymphoma by ICCC Group, SEER 1975-2000

Gender-Specific Incidence

Figure 3.3 depicts overall incidence per year per million for all lymphomas, by gender. Male incidence was predominant in all age groups, particularly in very young children and those over 30 years of age. If one observes incidence by gender for Hodgkin lymphoma, male predominance was not as striking as in lymphoma overall (Figure 3.4).

Female incidence of Hodgkin lymphoma was higher than the male incidence in the 15- to 19-year age group, but male incidence was slightly higher in 20- to 24- and 25- to 29-year-olds (Figure 3.4). In Non-Hodgkin lymphoma, male incidence was higher for all age groups (Figure 3.5). This held true when the numbers were age-adjusted to the 2000 U.S standard.

McMahon first noted the bimodal incidence of Hodgkin lymphoma in 1957.[4,5] Between 1975 and 2000, the first peak occurred between 20 and 25 years of age (Figure 3.5).

Table 3.1 *Incidence of Lymphoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
HODGKIN LYMPHOMA*						
Average incidence per million, 1975-2000, SEER	0.5	4.1	13.3	36.6	49.9	49.8
Average annual % change in incidence, 1975-2000, SEER	na	-2.3%	-0.6%	-0.4%	0.2%	1.0%
Estimated incidence per million, year 2000, U.S.	na	2.5	12.2	34.7	51.3	55.3
Estimated number of persons diagnosed, year 2000, U.S.	10	84	273	702	973	1,072
NON-HODGKIN LYMPHOMA**						
Average incidence per million, 1975-2000, SEER	3.4	5.4	7.1	11.7	16.5	27.3
Average annual % change in incidence, 1975-2000, SEER	na	0.2%	2.2%	2.3%	3.6%	6.2%
Estimated incidence per million, year 2000, U.S.	2.8	5.5	8.8	14.3	21.8	39.3
Estimated number of persons diagnosed, year 2000, U.S.	66	110	147	290	413	762
OTHER LYMPHOMA***						
Average incidence per million, 1975-2000, SEER	2.0	3.7	3.9	3.1	3.6	7.5
Average annual % change in incidence, 1975-2000, SEER	na	-1.0%	-0.7%	1.6%	9.8%	18.5%
Estimated incidence per million, year 2000, U.S.	1.9	3.	3.6	3.5	5.6	12.5
Estimated number of persons diagnosed, year 2000, U.S.	54	76	81	72	108	243

*ICCC II(a) **ICCC II(b) ***ICCC II(c,d,e)

The second peak—among older persons—occurred between 75 and 80 years of age, and was not as high as the initial incidence peak. As shown in Figure 3.4, more males than females were diagnosed in older patients.

Non-Hodgkin lymphoma was more common in males than females for all ages up to 45, with the male:female ratio increasing over this age interval to nearly 2-fold greater in males (Figure 3.6).

In Burkitt lymphoma, the male predominance was striking, with male:female ratios approaching 6 for the 5- to 14- and 25- to 44-year age groups (Figure 3.7). Females in the 15- to 24-year age group had a higher incidence of Burkitt lymphoma relative to males than in younger or older age groups, with a male:female ratio at a nadir of 2.6 to 3.2.

When analyzed according to histologic type diagnosed between 1975 and 2000, the greatest change in non-Hodgkin lymphoma over the 15- to 29-year age span was the appearance of follicular (nodular) lymphoma, which was virtually non-existent before age 15 and increased in relative proportion to 11% among 25- to 29-year-olds (Figure 3.8). Diffuse small-cell lymphoma also increased, and mantle cell lymphoma made its appearance in 15- to 29-year olds. Significant decreases as a function of age were noted for lymphoblastic lymphoma and Burkitt lymphoma, with cases decreasing from 12% to 4% and 10% to 4%, respectively, from the 15- to 19-year

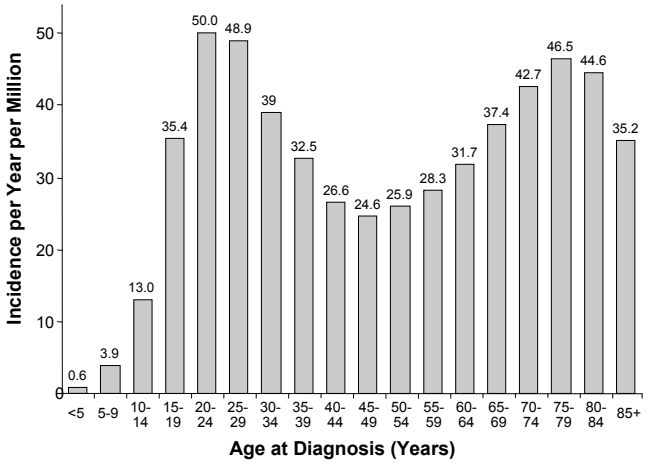

Figure 3.5: Incidence of Hodgkin Lymphoma, SEER 1975-2000

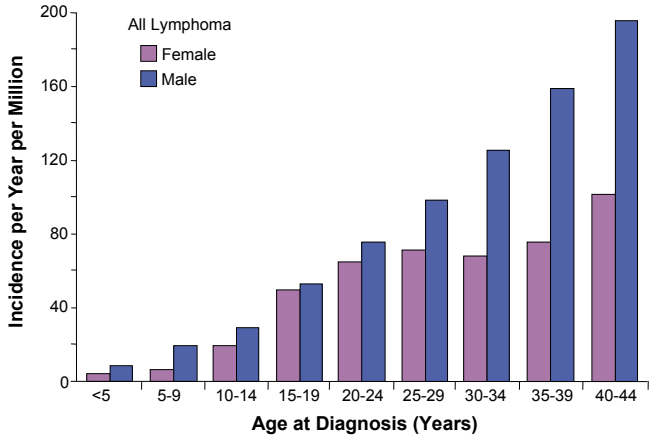

Figure 3.3: Incidence of All Lymphoma (ICCC II) by Gender, SEER 1975-1999

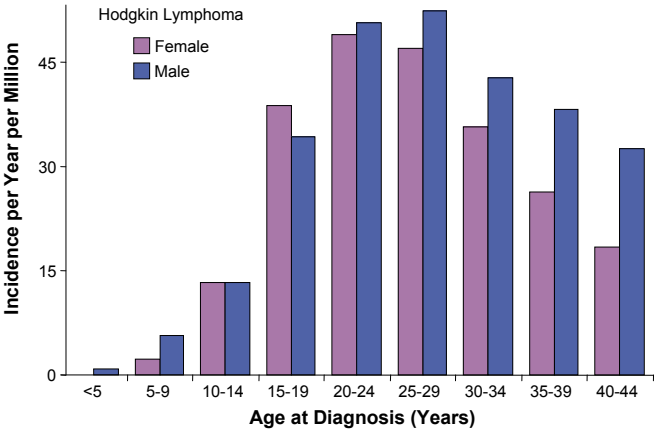

Figure 3.4: Incidence of Hodgkin Lymphoma (ICCC IIa) by Gender, SEER 1975-1999

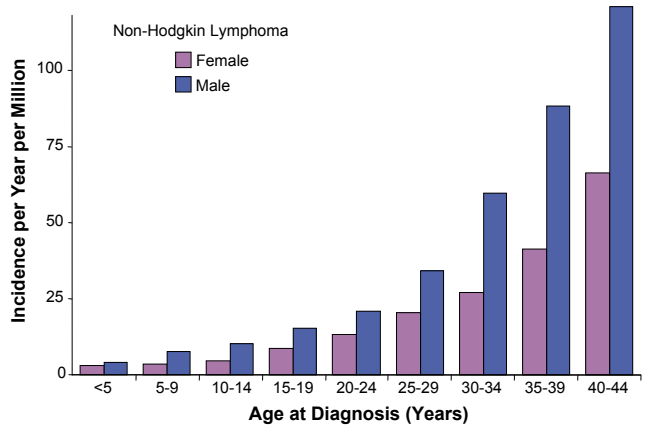

Figure 3.6: Incidence of Non-Hodgkin Lymphoma (ICCC IIb) by Gender, SEER 1975-2000

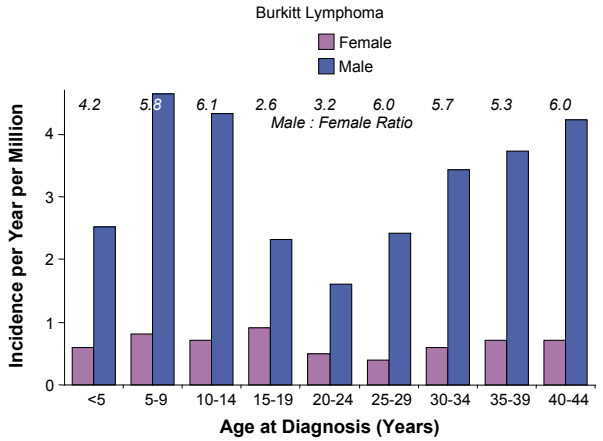

Figure 3.7: Incidence of Burkitt Lymphoma (ICCC IIc) by Gender, SEER 1975-2000

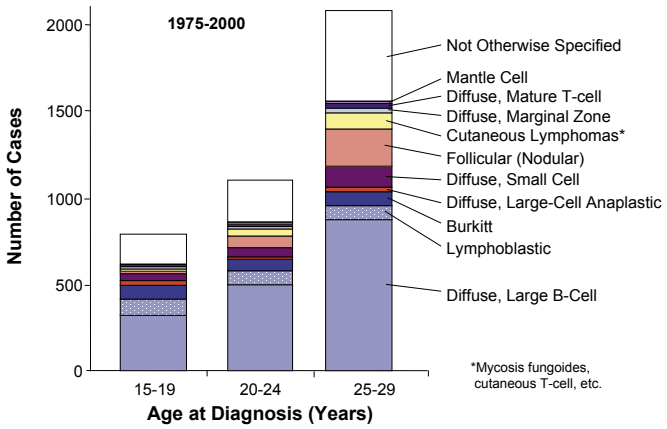

Figure 3.8: Histologic Types of Non-Hodgkin Lymphoma, SEER 1975-2000

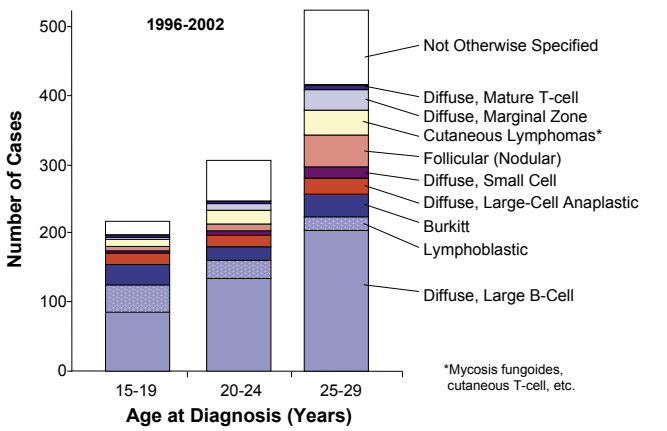

Figure 3.9: Histologic Types of Non-Hodgkin Lymphoma, SEER 1996-2002

age interval to the 25- to 29-year interval. When a more recent interval—1996 to 2002—was assessed according to histologic type, four types were more prominent than in the earlier era, particularly in 25- to 29-year-olds: Burkitt lymphoma, diffuse anaplastic large-cell lymphoma, cutaneous lymphomas, and diffuse marginal zone lymphoma (Figure 3.9 versus. Figure 3.8). There was a commensurate decrease in diffuse, small-cell lymphoma. This was probably due to pathologists being more specific about subtypes during recent years rather than to a real change in the incidence of the subtypes.

Correlative studies on the subtypes of non-Hodgkin lymphoma have shown that the incidence has risen, but that when the pathology of the subtypes were reviewed by a central reference, the subtype assignment varied from 5-100% correlation and 77% of unclassified lymphomas were placed into a subtype classification.[6] The SEER database does not reflect a centrally-reviewed population.

Racial/Ethnic Differences in Incidence

Figure 3.10 displays incidence by race/ethnicity for all lymphomas. In the 15- to 29-year age group, incidence was highest in white non-Hispanics while American Indians/Alaska Natives had the lowest incidence. A shift occurred in the next age group (30 to 44 years), where incidence was highest in the African American/black population.

Figure 3.11 shows the racial/ethnic differences in the incidence of Hodgkin lymphoma among the young. Non-

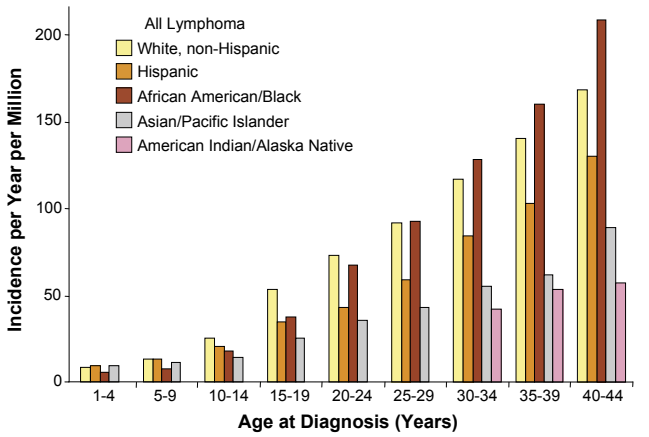

Figure 3.10: Incidence of All Lymphoma by Race/Ethnicity, SEER 1992-2000

Hispanic whites had by far the greatest incidence in 15- to 29-year-olds, followed by African Americans/blacks, Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives. The range in incidence of Hodgkin lymphoma according to race/ethnicity varied nearly 10-fold in the 15- to 29-year age group. Above age 30, the incidence of Hodgkin lymphoma among whites and African Americans/blacks converged, but both races/ethnicities remained 2-fold or higher above the others. The higher incidence in white non-Hispanics in the adolescent and young adult group has been attributed to higher socioeconomic status.[7]

Figure 3.12 displays the incidence of all non-Hodgkin lymphoma by race/ethnicity. Incidence increased for all groups as a function of age. Although white non-Hispanics or Asians/Pacific Islanders had the highest incidence in the younger age groups, African Americans/blacks had the highest incidence at 20 years of age and older.

Trends in Incidence

Malignant lymphoma increased in incidence during the past quarter century among all age groups younger than age 45. The change in incidence for all lymphomas in the SEER registry from 1975 to 1999 was statistically significant in all age groups over 19 years (Figure 3.13).

Average annual percent change (AAPC) from 1975 to 1999 is shown in Figure 3.14 for Hodgkin and non-Hodgkin lymphoma. In all age groups, there was a greater increase in the incidence of non-Hodgkin lymphoma than in Hodgkin lymphoma. In non-Hodgkin lymphoma, the increase in incidence for all age groups over 15 years was statistically significant. In Hodgkin lymphoma there was less of an increase for those over 45 years of age.

In Hodgkin lymphoma, only those 30- to 44-years of age demonstrated a statistically significant increase in incidence; in patients over 45 years of age, a statistically significant decrease in incidence was seen (Figure 3.14; yellow bars). As seen in Figures 3.15 and 3.16, the increase in Hodgkin lymphoma occurred in females (Figure 3.15), whereas in non-Hodgkin lymphoma, the increase was in males (Figure 3.16)

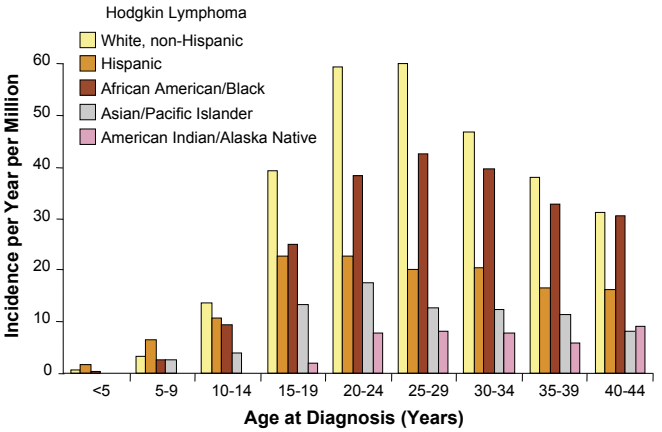

Figure 3.11: Incidence of Hodgkin Lymphoma by Race/Ethnicity, SEER 1992-2000

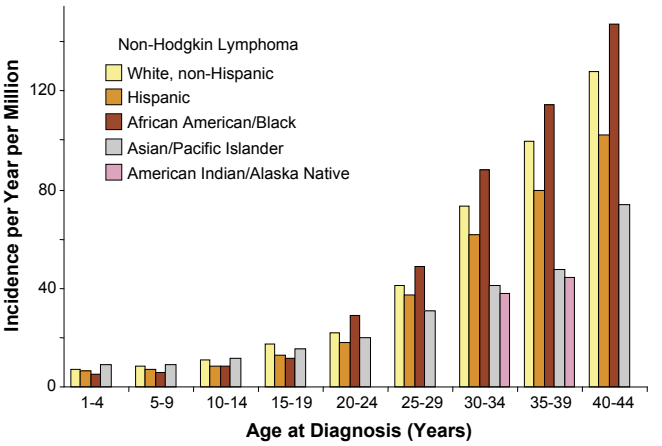

Figure 3.12: Incidence of Non-Hodgkin Lymphoma by Race/Ethnicity, SEER 1992-2000

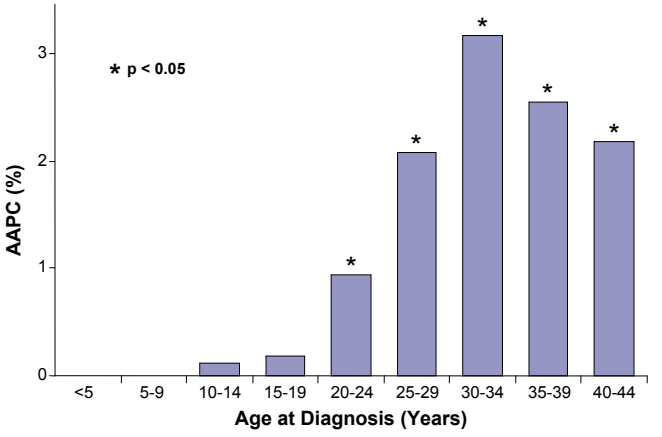

Figure 3.13: Average Annual Percent Change (AAPC) in Incidence for All Lymphoma, SEER 1975-1999

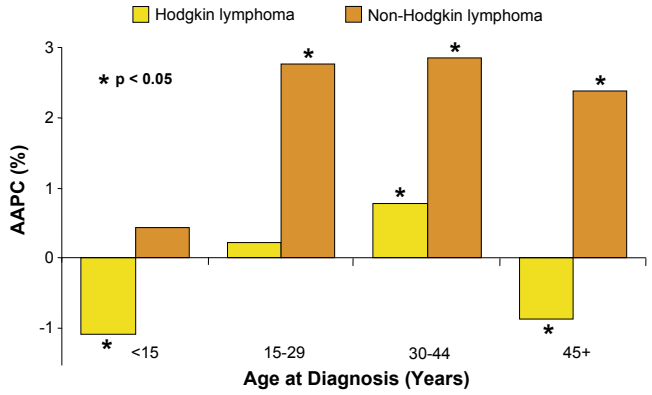

Figure 3.14: Average Annual Percent Change (AAPC) in Incidence for Non-Hodgkin Lymphoma and Hodgkin Lymphoma, SEER 1975-1999

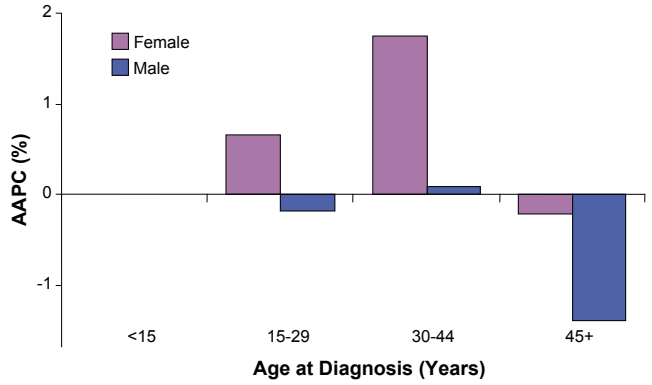

Figure 3.15: Average Annual Percent Change (AAPC) in Incidence for Hodgkin Lymphoma by Gender, SEER 1975-1999

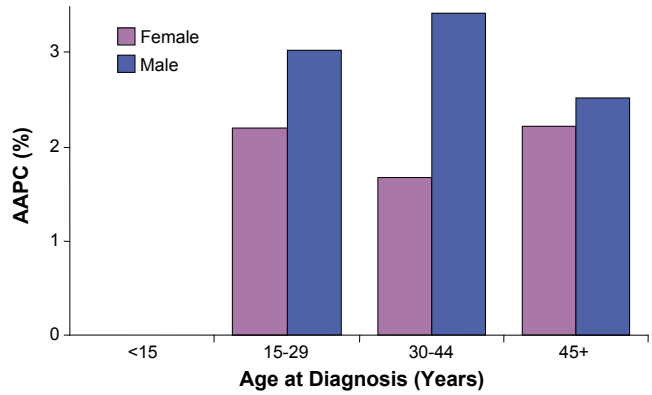

Figure 3.16: Average Annual Percent Change (AAPC) in Incidence for Non-Hodgkin Lymphoma by Gender, SEER 1975-1999

OUTCOME

Mortality

Mortality in 15- to 29-year-olds with Hodgkin lymphoma during the time period 1975 to 1999 was 4.82 deaths per year per million (Figure 3.17; inset). The death rate doubled for 20- to 24 year-olds when compared to 15- to 19-year-olds; rates for 25- to 29-year-olds reached nearly the maximum, as seen in Figure 3.17.

Mortality for adolescents and young adults with non-Hodgkin lymphoma over a similar time period was 59 deaths per year per million (Figure 3.18; inset). Mortality for non-Hodgkin lymphoma increased slowly as a function of age, with the highest rate in the over 45-year age group (Figure 3.18; inset).

Figure 3.19 displays mortality from 1975 to 1999 for those younger than 45 years of age for all lymphomas by gender. In all age groups, males had a higher mortality. This male predominance increased as a function of age, with nearly two times as many deaths among 25- to 44-year-old males as among females. Most of this gender difference was due to the higher incidence in males (Figure 3.3).

For Hodgkin lymphoma, the male excess occurred only over age 10 (Figure 3.20), and the comparison with incidence showed that there were more males than females dying of the disease between 15 and 40 years of age than expected from the incidence pattern (Figure 3.21). This analysis suggests that male gender was an

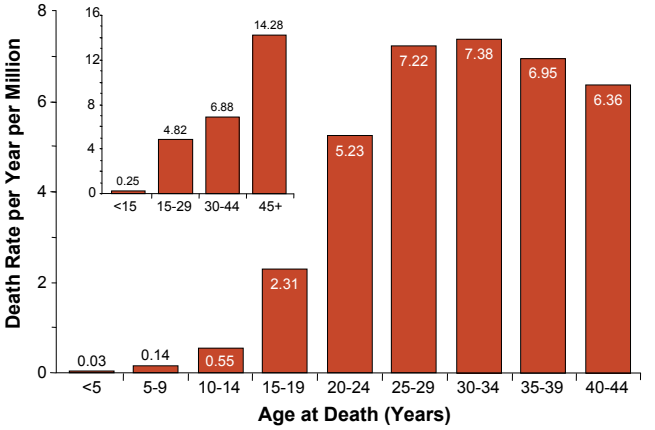

Figure 3.17: National Mortality for Hodgkin Lymphoma, U.S.,1975-1999

adverse prognostic factor in patients between 15 and 40 years of age. Females are known to present with more favorable histology and lesser stage disease.[7]

For non-Hodgkin lymphoma, the male excess in mortality occurred at all ages (Figure 3.22), and the comparison with incidence revealed that under age 30 (Figure 3.6), the excess was not accounted for by differences in incidence. This analysis suggests that male gender was an adverse prognostic factor in patients younger than 30 years of age.

Similar analyses of mortality by race/ethnicity as function of age are shown in Figures 3.23 to 3.25. For all lymphoma, African Americans/blacks had the highest death rate for those over 20 years of age (Figure 3.23). The African American/black excess occurred for both Hodgkin lymphoma (Figure 3.24) and non-Hodgkin lymphoma (Figure 3.25). When compared with incidence patterns (Figures 3.10 and 3.11, the excess death rate among African Americans/blacks was not explained by differences in incidence, either in Hodgkin or non-Hodgkin lymphoma.

Survival

Figure 3.26 depicts the 5-year survival rate for all lymphomas as function of age at diagnosis, by 15-year intervals until age 45, and as a single group in older patients. There was no progress in improving the 5-year survival rate among 15- to 44-year-old patients with lymphoma during the past quarter century, in contrast to steady gains in this outcome measurement among younger and older patients. Hodgkin and non-Hodgkin lymphoma showed little to no significant gain in 5-year survival rates over the years 1975 to 1998.

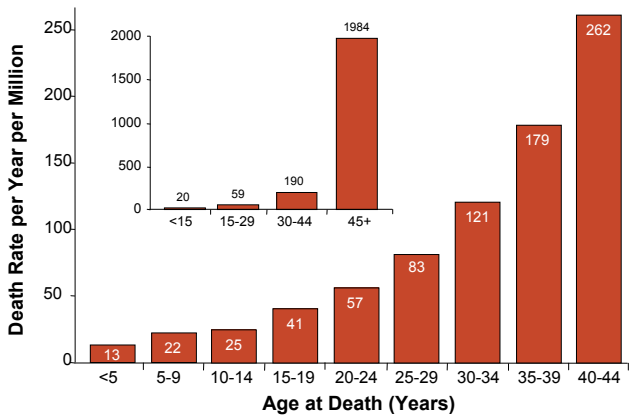

Figure 3.18: National Mortality for Non-Hodgkin Lymphoma, U.S.,1975-2000

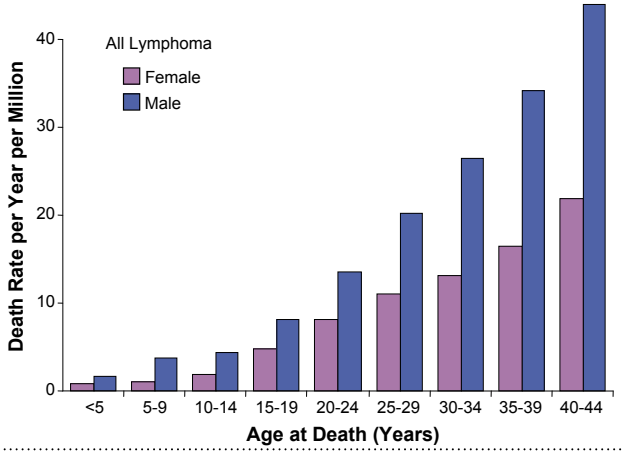

Figure 3.19: National Mortality for All Lymphoma by Gender, U.S.,1975-1999

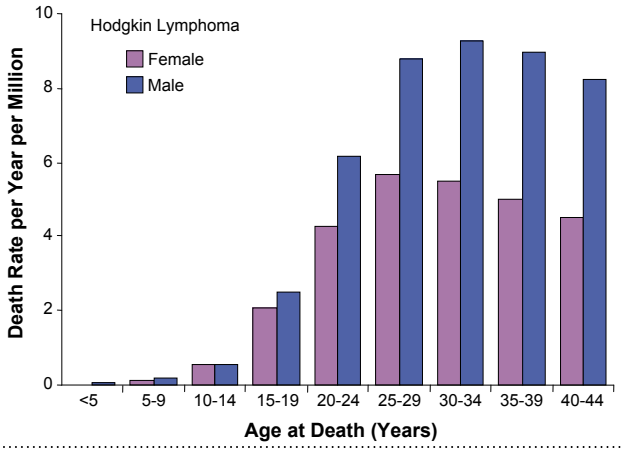

Figure 3.20: National Mortality for Hodgkin Lymphoma by Gender, U.S.,1975-1999

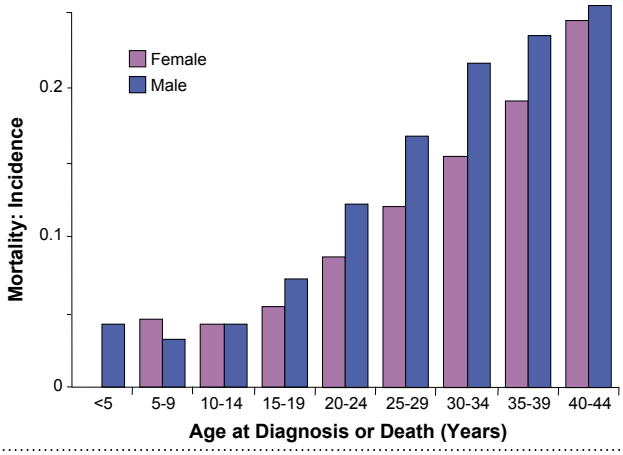

Figure 3.21: Ratio of National Mortality to SEER Incidence for Hodgkin Lymphoma by Gender, U.S.,1975-1999

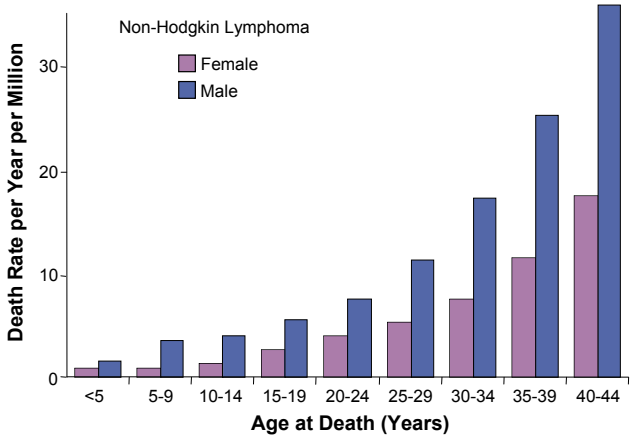

Figure 3.22: National Mortality for Non-Hodgkin Lymphoma by Gender, U.S.,1975-1999

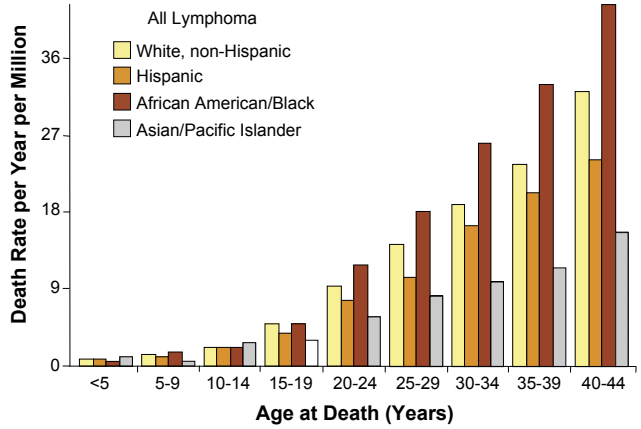

Figure 3.23: National Mortality for All Lymphoma by Race/Ethnicity, U.S.,1990-2000

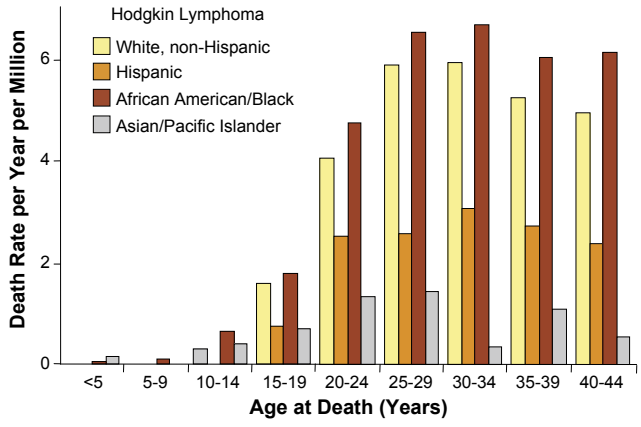

Figure 3.24: National Mortality for Hodgkin Lymphoma by Race/Ethnicity, U.S.,1990-2000

Since 1990, there have been no significant differences in 5-year survival rates among whites of either Hispanic or non-Hispanic ethnicity, African Americans/blacks, or Asians/Pacific Islanders with Hodgkin (Figure 3.27) or non-Hodgkin lymphoma (Figure 3.28). The suggestion from comparisons of death rates to incidence that show a deficit among African Americans/blacks applies to the period 1975 to 1998. It appears that this racial inequity may have been overcome by 1990.

Survival curves as a function of age are shown in Figures 3.29 to 3.31 for patients followed by SEER from 1975 to 1998. For all lymphomas, 15- to-29-year-old patients had an outcome similar to those younger than age 15 when diagnosed, with the exception that there was less evidence for a plateau in the survival curve for 15- to 29-year-old patients (Figure 3.29).

For Hodgkin lymphoma, 15- to-29-year-old patients did not fare as well as younger patients, with a continued fall-off in Hodgkin lymphoma survival and no evidence for a plateau in the survival curve (Figure 3.30). For non-Hodgkin lymphoma, a progressive decline in survival was apparent when observed by 5-year age intervals (Figure 3.31).

The AAPC in 5-year survival rates from 1975 to 1997 for Hodgkin and non-Hodgkin lymphoma are shown in Figures 3.32 and 3.33. As suggested by the mortality versus incidence comparisons above, the least amount of progress occurred in 15- to 50-year-olds with Hodgkin lymphoma (Figure 3.32) and in 25- to 45-year-olds with non-Hodgkin lymphoma (Figure 3.33). The lack of progress was

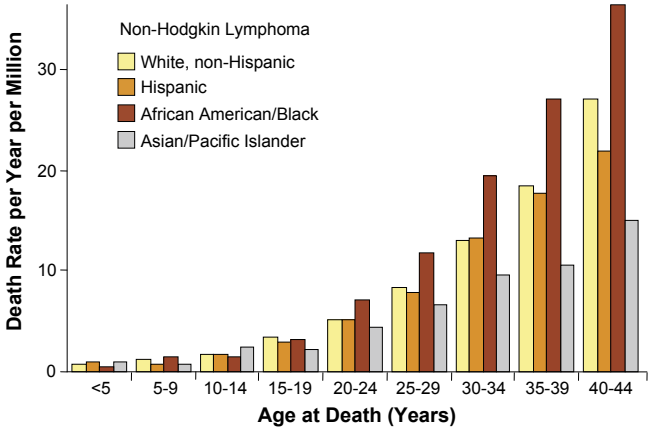

Figure 3.25: National Mortality for Non-Hodgkin Lymphoma by Race/Ethnicity, U.S.,1990-2000

particularly obvious for non-Hodgkin lymphoma. Both non-Burkitt, non-Hodgkin lymphoma and Burkitt lymphoma had little to no evidence for survival improvement when the 5-year survival rates were averaged out over the past quarter century (Figure 3.33). Some of the latter non-Burkitt, non-Hodgkin lymphoma survival improvement deficit may be due to lymphomas with a particularly poor prognosis that occurred during the human immunodeficiency virus (HIV) epidemic of the 1980s.

RISK FACTORS

Hodgkin Lymphoma

Evidence suggests that Hodgkin lymphoma may represent several disease entities over the age spectrum, with different etiological factors for different age groups. In developing countries, children acquire Hodgkin lymphoma at an earlier age than in developed countries, and commonly show Epstein-Barr virus (EBV) genomic sequences in the Reed-Sternberg cells.[8,9] Incidence of Hodgkin lymphoma in developed countries peaks in the adolescent and young adult years, and again in older adults.[10] This reflects the bimodal peak first noted by McMahon.[4] An increased risk of developing Hodgkin lymphoma in the early age group has been linked to a higher socioeconomic status and standard of living during childhood that includes low housing density, high maternal education, and few older siblings. These conditions may contribute to a delay in exposure to common childhood infections and a subsequent delay in

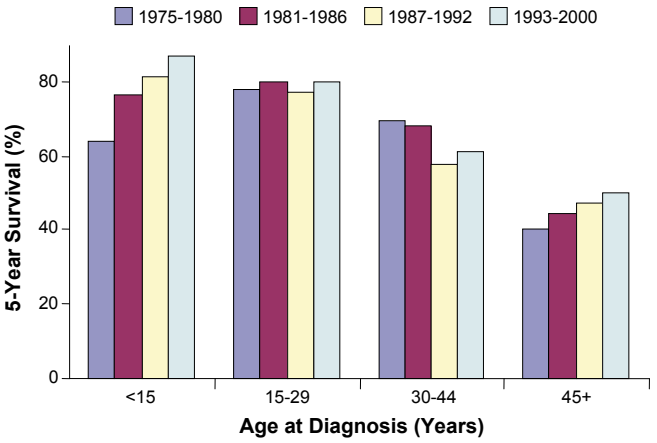

Figure 3.26: 5-Year Survival for All Lymphoma by Era, SEER

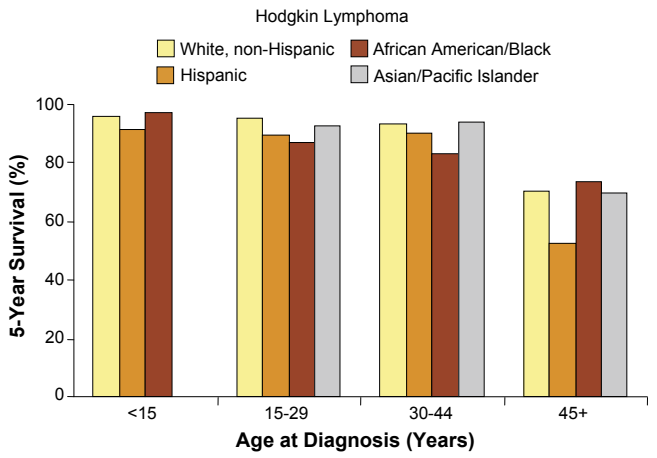

Figure 3.27: 5-Year Survival for Hodgkin Lymphoma by Race/Ethnicity, SEER 1990-1998

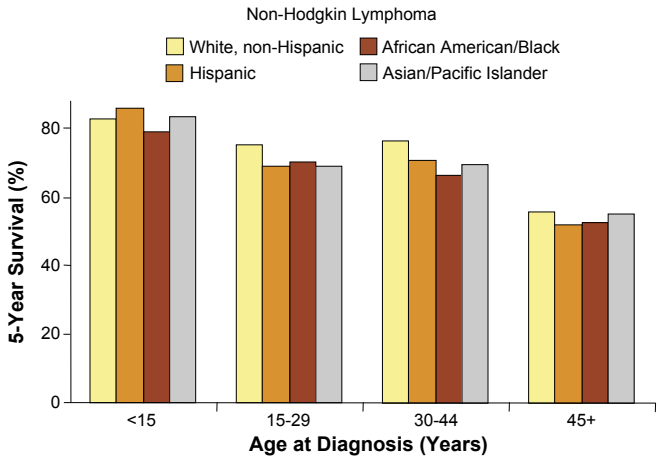

Figure 3.28: 5-Year Survival for Non-Hodgkin Lymphoma by Race/Ethnicity, SEER 1990-1998

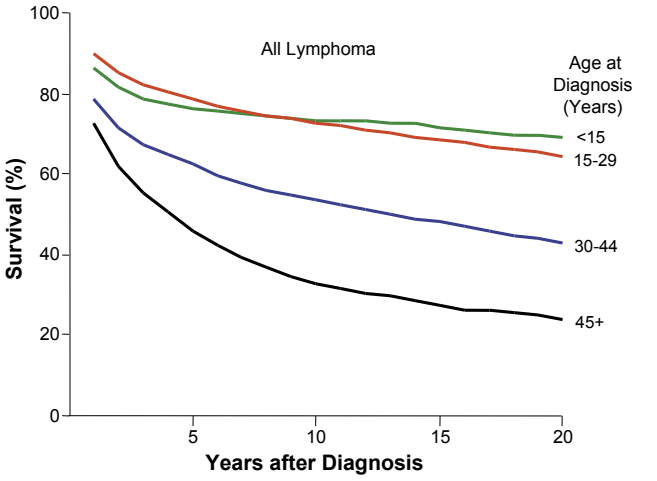

Figure 3.29: Survival Rates for All Lymphoma, SEER 1975-1998

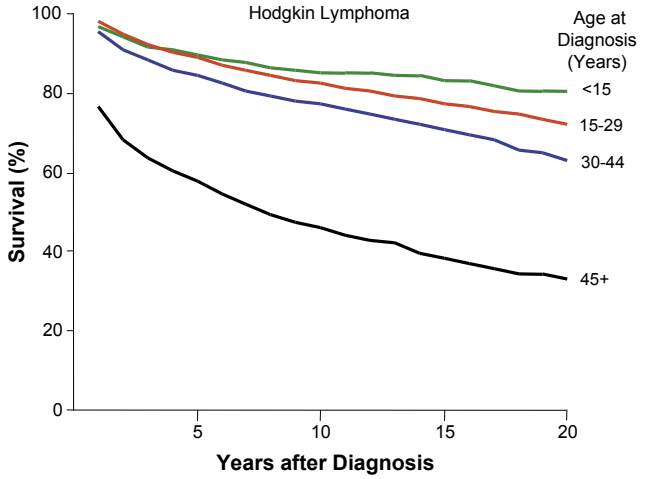

Figure 3.30: Survival Rates for Hodgkin Lymphoma, SEER 1975-1998

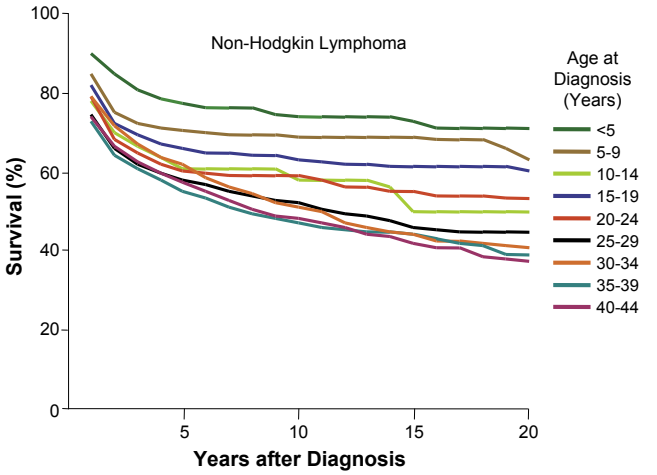

Figure 3.31: Survival Rates for Non-Hodgkin Lymphoma, SEER 1975-1998

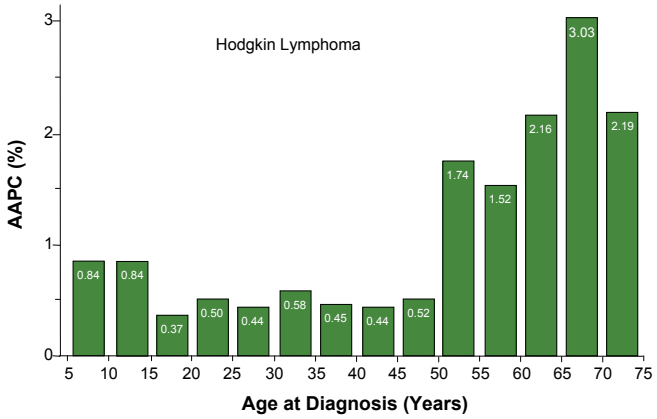

Figure 3.32: Average Annual Percent Change (AAPC) in 5-Year Survival for Hodgkin Lymphoma, SEER, 1975-1997

maturation of cell immunity.[11] Yet in the younger (< 10 years) and older (> 45 years) age groups, the association with higher socioeconomic status is reversed.[12] Among the histologic subtypes of Hodgkin lymphoma, the nodular sclerosing subtype has a more favorable prognosis.[13]

Epstein Barr virus (EBV) is considered a primary etiologic agent for Hodgkin lymphoma.[14] While the evidence points to EBV as a cofactor in the development of Hodgkin lymphoma, the exact relationship of the infection to the subsequent development of tumor is not completely delineated.[12] The presence of the EBV genome in Reed-Sternberg cells is associated with the mixed cellularity sub-type.[7]

Genetic susceptibility is also a factor for adolescents and young adults. The risk of developing Hodgkin lymphoma is significantly higher for those with relatives with the disease; the risk is higher for males than females, and for siblings than for parents or offspring.[15] Adults with Hodgkin lymphoma are more likely to have children who develop the disease at a younger age, that is, in adolescence and young adulthood.[16]

In patients with HIV infection, there is an increase in both Hodgkin and non-Hodkgin lymphoma.[17,18] Other risks associated with the development of Hodgkin lymphoma in this age group are a history of autoimmune disorder, a family history of cancer/hematopoietic disorder, and Jewish ethnicity.[11,15,16]

Non-Hodgkin Lymphoma

The etiology of non-Hodkgin lymphoma in adolescents and young adults is complex. Several risk factors have been identified, including HIV infection, immunodeficiency syndromes, immunosuppressive therapies, EBV or helicobacter pylori infection, genetic susceptibility, tobacco, chemical or other environmental exposure.[2,19-23] Incidence is twice as high in males than females, and is higher in whites than African Americans/blacks.[24]

Recent studies indicate that the incidence of non-Hodkgin lymphoma has increased nearly 80% since the 1970s.[1,24] In underdeveloped countries, there is a documented link between EBV and Burkitt lymphoma,[19] while in the developed world EBV is also associated with other subtypes of non-Hodgkin lymphoma.[12]

Secondary neoplasms are well documented sequelae of HIV infection, and account for an increase in non-Hodgkin lymphoma incidence, particularly in males.[18,25] The increase in non-Hodgkin lymphoma has persisted in the face of a stabilization of the incidence of new cases of HIV and with improved treatments for the infection.

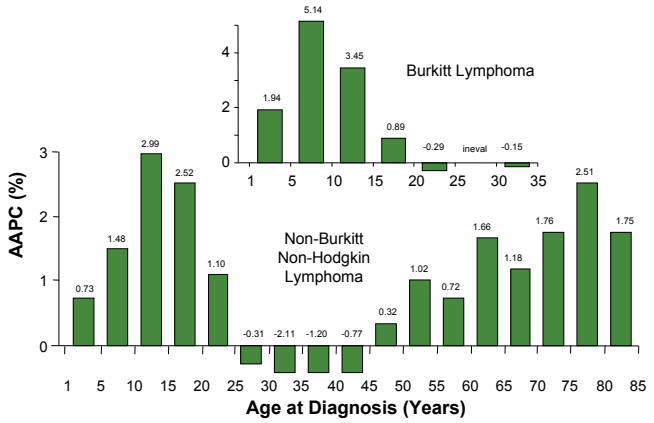

Figure 3.33: Average Annual Percent Change (AAPC) in 5-Year Survival Rate, SEER 1975-1997

SUMMARY

Lymphomas are common cancers in the 15- to 29-year age group. Hodgkin and non-Hodgkin lymphomas, while distinct entities, share some common risk factors such as EBV and HIV infection, overall male predominance and an association with immunodeficiency syndromes. There is no apparent racial/ethnic influence over the entire age spectrum. While there has been an improvement in survival in the pediatric non-Hodgkin lymphoma group under 15 years of age, no such improvement has been noted in the older adolescent and young adult age group. With the advent of monoclonal antibody biologic treatments, an improvement in survival is anticipated for both Hodgkin and non-Hodgkin lymphoma. Follicular lymphoma and mantle cell lymphoma, both subsets of non-Hodgkin lymphoma, have shown durable responses to combination therapy with anti CD20 antibody and aggressive chemotherapy.[26-28]

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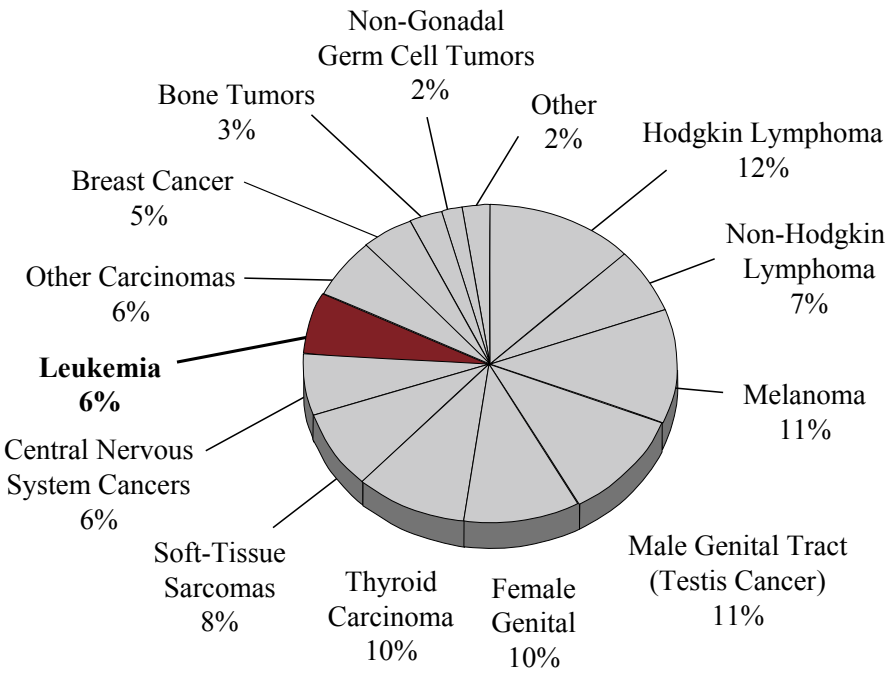
Chapter 4

Leukemias



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HIGHLIGHTS

Incidence

- The leukemias represented 6% of all cancers that occurred in 15- to 29-year-olds in the United States over the time period 1975 to 1999.
- Approximately 24 persons per million patients 15 to 29 years of age were diagnosed with leukemia in the U.S. during the year 2000.
- The incidence of leukemia was lower in the 15- to 29-year cohort than in any other age group.
- In the years between adolescence and older adulthood, the incidence of acute lymphoblastic leukemia (ALL) gradually decreased as the incidence of acute and chronic myeloid leukemias (AML and CML) increased.
- In the 15- to 19-year age group, ALL occurred at a rate twice that of AML; in the 20- to 24-year age group, both types of leukemia occurred at approximately equal rates; but in the 25- to 29-year age group, AML occurred at a rate 1.5 times that of ALL.
- Between 1975 and 1999, leukemia increased in incidence in 15- to 29-year-olds, with those in the 20- to 24-year age group experiencing the greatest increment, at an average rate of 1.2% per year.

Mortality & Survival

- During the period 1975 to 1999, the death rate for leukemias was higher for males than females in all age categories.
- Hispanics experienced the highest mortality for leukemias in those younger than 25 years, while African Americans/blacks had the highest mortality in those 25 years and older.
- Five-year survival rates for leukemia declined with advancing age.
- Survival rates for leukemia declined significantly as a function of age for those older than 15 years of age, and remained below 20% at 20 years for all age groups 20 years of age or older.
- An improvement in survival has occurred since 1975 in each category of leukemia, although the decrease in mortality among adolescent and young adult patients with ALL lags behind that of younger patients.
- Despite being a "chronic" leukemia, the ultimate survival of patients with CML was poor in all age groups, with a 20-year survival less than 20% regardless of age at diagnosis—including chronic myelogenous leukemias of childhood (juvenile myelomonocytic leukemia, etc.).

Risk Factors

- Risk factors for ALL include male gender, young age (2 to 5 years), Caucasian race/ethnicity, pre- and post-natal radiation exposure, and constitutional syndromes including trisomy 21, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, and ataxia-telangiectasia.
- Risk factors for AML include Hispanic race/ethnicity, chemotherapeutic exposure to alkylating agents or topoisomerase II inhibitors, and constitutional syndromes including trisomy 21, Fanconi anemia, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, familial monosomy 7, and Kostmann granuocytopenia.

INTRODUCTION

Leukemias represented approximately 6% of the cancers that occurred in adolescents and young adults over the time period 1975 to 2000. In the transition between childhood and older adulthood, the incidence of acute myeloid leukemia (AML) slowly rose while that of acute lymphoblastic leukemia (ALL) steadily decreased. In the 15- to 19-year age group, ALL occurred with an incidence approximately twice that of AML, whereas in the 25- to 29-year age group the incidence of AML was approximately 1.5 times that of ALL.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), leukemia is category I and in the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) it spans categories 9800 to 9941. Leukemias coded under ICD-O-3 were converted to ICD-O-2 codes for inclusion in this chapter.

The ICCC leukemia class excludes the following ICD-O-3 histologies: myelodysplastic syndromes (refractory anemias with preleukemic manifestations) (9980-9989), and some chronic myeloproliferative disorders (9950, 9960-9962). The ICD-O-3 histologies of hypereosinophilic syndrome (9964) and chronic neutrophilic leukemia (9963) were included with I(e) unspecified leukemia. ICD-O-3 histologies of chronic myelomonocytic leukemia, NOS (9945) and juvenile myelomonocytic leukemia (9946) are reported under chronic myelomonocytic leukemia (ICD-O-2 9868) and ICCC I(c) and aggressive NK-cell leukemia (9948) is reported under ICD-O-2 code 9801 and ICCC I(e).

The ICCC I(a) has two subcategories of *lymphoid leukemia*, ALL and non-ALL lymphoid leukemia. ALL corresponds to ICD-O-2 9821, which has been expanded in ICD-O-3 as follows: precursor cell lymphoblastic leukemia, NOS (9835), precursor B-cell lymphoblastic leukemia (9836), and precursor T-cell lymphoblastic leukemia (9837). The "non-ALL" lymphoid leukemias are constituted by "lymphoid leukemia" (9820), acute, subacute, chronic, and aleukemic lymphocytic leukemia (9822-9824), prolymphocytic leukemia (9825), Burkitt cell leukemia (9826), and adult T-cell leukemia (9827).

ICCC I(b) includes acute myeloid leukemias. ICCC I(b) has two subcategories: AML (9861) and non-AML acute leukemia [erythroleukemia (9840), acute erythemia (9841), aleukemic myeloid leukemia (9864), acute promyelocytic leukemia (9866), acute myelomonocytic leukemia (9867), acute monocytic leukemia (9891), aleukemic monocytic leukemia (9894), and acute megakaryocytic leukemia (9910). Included in AML are the following ICD-O-3 categories: acute myeloid leukemia with abnormal marrow eosinophils (9871), acute myeloid leukemia, minimal differentiation (9872), acute myeloid leukemia without maturation (9873), and acute myeloid leukemia with maturation (9874).

Chronic Myeloid Leukemia is category I(c) in the ICCC and applies to chronic myeloid leukemia (9863) and chronic myelomonocytic leukemia (9868) in the ICD-O-2. Additional ICD-O-3 groups included in I(c) are chronic myelogenous leukemia, BCR/ABL positive (9875) and atypical chronic myeloid leukemia, BCR/ABL negative (9876).

ICCC designates *Other Specified Leukemias* and *Unspecified Leukemias* in category I(d) and I(e), respectively. These two categories in ICCC apply to miscellaneous and unspecified types of leukemia (9800-9804, 9830, 9842, 9860, 9862, 9870-9890, 9892, 9893, 9900, 9930-9941).

For cases diagnosed in 2001 and forward, ICD-O-3 divides AML and CML into several different subtypes, but previous versions of the ICD-O did not. ICD-O-3 includes, in addition, data for lymphoproliferative syndromes, which are not included in this chapter.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

ALL in the 15- to 19-year age group is characterized by a higher proportion of T-cell immunophenotype, higher hemoglobin levels at diagnosis, and a lower frequency of lymphomatous features compared to younger children.[1] Cytogenetically, ALL in this age group is associated with a lower ratio of favorable features than is seen in younger children, including t(12;21) and hyperdyploidy (chromosome number > 51), and a higher incidence of Philadelphia-positive ALL,[1,2] although still low by comparison with older adults.

Adolescents with leukemia may receive care from either pediatric or medical oncologists. Four recent studies have suggested that young adult patients with ALL entered on

Table 4.1: *Incidence of Leukemia in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
ALL LEUKEMIA						
Average annual incidence per million, 1975-2000, SEER	68.2	35.2	24.2	22.7	20.7	22.7
Average annual % change in incidence, 1975-2000, SEER	0.8%	2.2%	2.1%	1.5%	22.9%	0.2%
Estimated incidence per million, year 2000, U.S.	74.1	39.3	26.3	23.5	23.5	22.8
Estimated number of persons diagnosed, year 2000, U.S.	1,308	723	541	475	446	442
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)						
Average annual incidence per million, 1975-2000, SEER	55.3	28.4	15.9	11.5	6.4	4.9
Average annual % change in incidence, 1975-2000, SEER	0.9%	3.3%	3.8%	2.8%	71.1%	17.6%
Estimated incidence of ALL per million, year 2000, U.S.	60.6	32.8	18.3	12.4	8.5	6.2
Estimated number of persons diagnosed, year 2000, U.S.	1.060	584	375	251	162	120.4
ACUTE MYELOGENOUS LEUKEMIA (AML)						
Average annual incidence per million, 1975-2000, SEER	5.4	3.4	4.2	5.8	6.7	7.5
Average annual % change in incidence, 1975-2000, SEER	1.7%	-9.4%	51.1%	8.5%	22.2%	38.5%
Estimated incidence of AML per million, year 2000, U.S.	6.3	3.0	3.4	5.3	5.9	4.8
Estimated number of persons diagnosed, year 2000, U.S.	103	69	70	108	112	94
CHRONIC MYELOID LEUKEMIA (CML)						
Average annual incidence per million, 1975-2000, SEER	1.0	0.6	1.0	2.1	3.1	5.2
Average annual % change in incidence, 1975-2000, SEER	na	na	na	-22.3%	29.1%	-13.6%
Estimated incidence per million, year 2000, U.S.	0.0	0.0	1.4	1.7	2.7	5.5
Estimated number of persons diagnosed, year 2000, U.S.	19	12	28	34	51	106

pediatric clinical trials have a significantly better event-free survival (EFS) and overall survival compared to adolescents treated on adult clinical trials.[3-6] The recently completed Children's Cancer Group study CCG-1961 for newly diagnosed patients with high-risk ALL had a 5-year EFS of 69.5% and a 5-year survival rate of 77%.[7] No difference in outcome has been observed for adolescents with AML treated on adult versus pediatric protocols.

INCIDENCE

Age-Specific Incidence

Table 4.1 shows age-adjusted incidence for ICCC sub-categories, and Figures 4.1 and 4.2 illustrate the strong dependence on age of all leukemia and the individual subtypes. During the last quarter century, the incidence of leukemia peaked in early childhood and reached a nadir in late adolescence, and it was lower in the 15- to 29-year cohort than in any other younger or older age group except infants younger than 1 year of age.

The incidence of leukemia as a percentage of all cancers was inversely proportional to age, reflecting the rise in incidence of other cancers beginning at about 10 years of age (Figure 4.1). Within 5-year age groups there was a decrease in incidence from 11.5% in 15- to 19-year-olds to 6.4% and then to 4.2% in 20- to 24-year-olds and 25- to 29-year-olds, respectively. Leukemia represented 35.2% of all cancers in those younger than 5 years of age and 20.8% in those 10 to 14 years of age. In adults over 30 years the percentage was low, and gradually declined to just 2.3% of all cancers by age 40.

As shown in Figure 4.2 and Table 4.1, the incidence of different types of leukemia varied with age. Overall, ALL

decreased in incidence across all age groups, while AML and chronic myelogenous leukemia (CML) increased in incidence beyond age 5 years. ALL was the most common type in the 15- to 19-year group, occurring at an annual rate of 11.5 per million, twice that of AML. However, over the subsequent two 5-year age groups, ALL and AML incidence curves crossed: they were approximately equal in the 20- to 24-year age group, at about 6.6 per million; in the 25- to 29-year age group AML occurred at a rate of 7.5 per million, compared with a rate of 4.9 per million for ALL. The incidence of CML was 1.7 per million in children under 15 years of age and gradually increased over the 15- to 29-year age range, reaching a rate of 5.2 per million in those 25 to 29 years old, at which point it was more common than ALL.

Gender-Specific Incidence

Leukemia occurred with greater frequency in males of all ages, as shown in Figure 4.3. The male:female (M:F) ratio was relatively stable from birth through 44 years (M:F = 1.2 to 1.5) (Table 4.2). When examining gender incidence ratios in adolescents and young adults, differences emerge within the types of leukemia (Figures 4.4A-C; Table 4.2). ALL showed a male preponderance (1.9 to 2.1), whereas gender differences were marginal in AML, with M:F ratios of 1.0 in the 15- to 19- and 20- to 24-year groups, and 1.2 in the 25- to 29-year group. CML showed a male preponderance in all groups; as the overall incidence rose steadily with advancing age, the gender discrepancy widened to 2.1.

Racial/Ethnic Differences in Incidence

The incidence of leukemia in the 15- to 29-year age group varied by race/ethnicity (Figure 4.5; inset). Hispanics experienced the highest rate of leukemia—32.2 per million population—which was 1.3- to 1.7-fold higher than that of other racial/ethnic groups. The incidence in African Americans/blacks was lower, at 19.0 per million. The same ordering of incidence was seen in the 15- to 19- and 20- to 24-year age groups. In the 25- to 29-year age group, the incidence among African Americans/blacks increased to 25.7 per million, similar to the other racial/ethnic groups.

For ALL, the incidence order by race/ethnicity in 15- to 29-year-olds was similar to that of leukemias in general, with a slightly higher incidence in white non-Hispanics

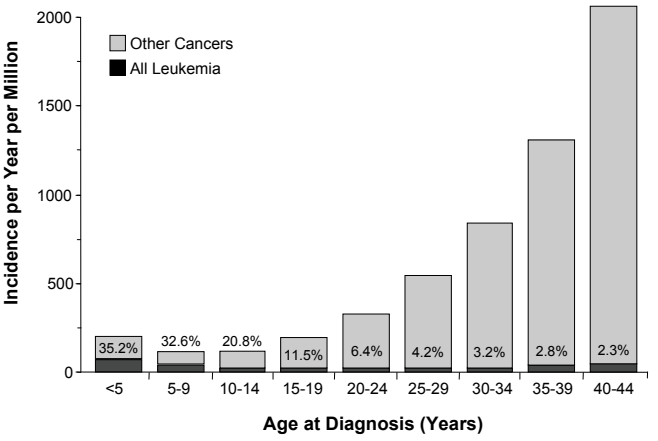

Figure 4.1: Incidence of Leukemia Relative to All Cancer, SEER, 1975-1999

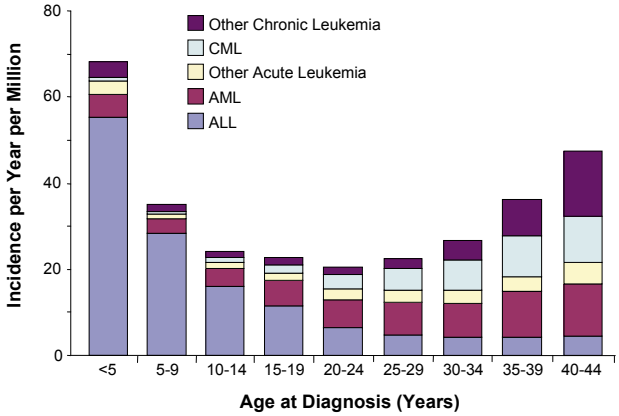

Figure 4.2: Incidence of Leukemia by Type, SEER 1975-1999

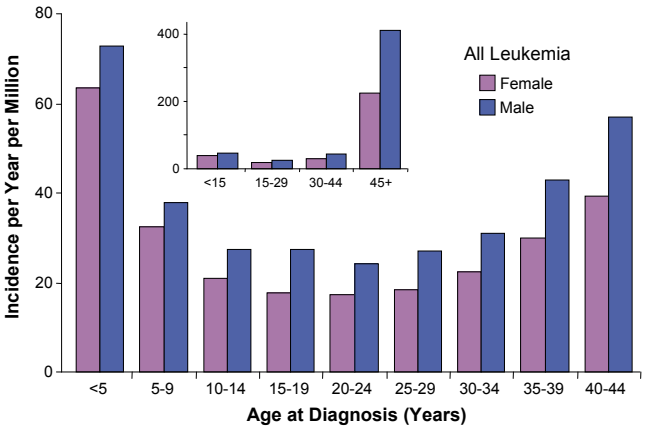

Figure 4.3: Incidence of All Leukemia by Gender, SEER 1975-1999

Table 4.2: *Investigated Risk Factors for ALL and AML*[8; modified]

DEGREE OF CERTAINTY	ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	ACUTE MYELOID LEUKEMIA (AML)
GENERALLY ACCEPTED RISK FACTORS	Males	Race (Hispanic)
	Age (2-5 years)	Chemotherapeutic agents (alkylating agents, topoisomerase II inhibitors)
	High socioeconomic status	Down syndrome
	Race (whites>blacks)	Fanconi anemia
	In utero x-ray exposure	Neurofibromatosis type 1
	Postnatal radiation (therapeutic)	Bloom syndrome
	Down syndrome	Shwachman syndrome
	Neurofibromatosis type 1	Familial monosomy 7
	Bloom syndrome	Kostmann agranulocytosis
	Shwachman syndrome	
	Ataxia-telangiectasia	
SUGGESTIVE OF INCREASED RISK	Increased birth weight	Maternal alcohol consumption during pregnancy
	Maternal history of fetal loss	Parental and child exposure to pesticides Parental solvent exposure
LIMITED EVIDENCE	Parental smoking prior to or during pregnancy	Maternal marijuana use during pregnancy
	Parental occupational exposures	Indoor radon
	Postnatal infections	Postnatal use of chloramphenicol
	Diet	
	Vitamin K prophylaxis in newborns	
	Maternal alcohol consumption during pregnancy	
	Electric and magnetic fields	
	Postnatal use of chloramphenicol	
PROBABLY NOT ASSOCIATED	Ultrasound	
	Indoor radon	

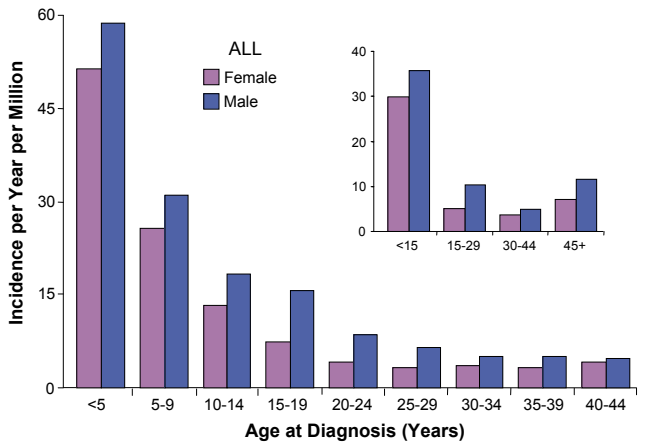

Figure 4.4A: Incidence of ALL by Gender, SEER, 1975-1999

as compared to Asians/Pacific Islanders and with a 2.1-fold excess incidence among Hispanics as compared to African Americans/blacks (Figure 4.6; inset).

The incidence of AML (Figure 4.7) was highest in Asians/Pacific Islanders, but the racial/ethnic variation was modest (range 5.9 to 7.7 per million). Due to the low incidence of CML among those 15 to 24 years of age, more comprehensive racial/ethnicity data were available for the 25- to 29-year age group, in which the incidence was highest for Asians/Pacific Islanders (6.7 per million), with lower—and virtually equivalent—incidence for the remaining racial/ethnic groups (approximately 5.3 per million) (Figure 4.8).

Incidence Trends

Between 1975 and 1999, the incidence of leukemia in children younger than 15 years of age increased annually at a statistically-significant average of 0.8% per year (Figure 4.9). In 15- to 29-year-olds the annual rate of increase was 0.6%. The highest rate of increase occurred in 20- to 24-year-olds, at an average of 1.2% per year. Adults 30 years and older experienced a modest decrease in annual incidence, which was statistically significant in those over 45 years of age when diagnosed.

From 1975 to 1999, the incidence of leukemias in females 15 to 29 years old increased annually at an average rate two-fold that of males (0.8 versus 0.4%) (Figure 4.10). For children younger than 15 years of age the rate of increase was similar for both genders. In older age groups the annual incidence of leukemia decreased for both genders, with the greatest decrease among women in the 30- to 44-year subset and among men 45 years old and older.

The annual incidence of ALL has increased for all age groups (Figure 4.11). Between 1975 and 1999, the incidence of ALL increased by an average of 1.5% per year for those 15 to 29 years of age and by 1.0% per year for those younger than 15 years and for those 30 years of age and older. AML has shown an annual decline in incidence in all age groups 15 years of age or younger—on average, a decrease of 1.4% per year for 15- to 29-year-olds, 1.9% for those 30- to 44 years, and 0.5% for those 45 years of age and older. Trend data for AML are not

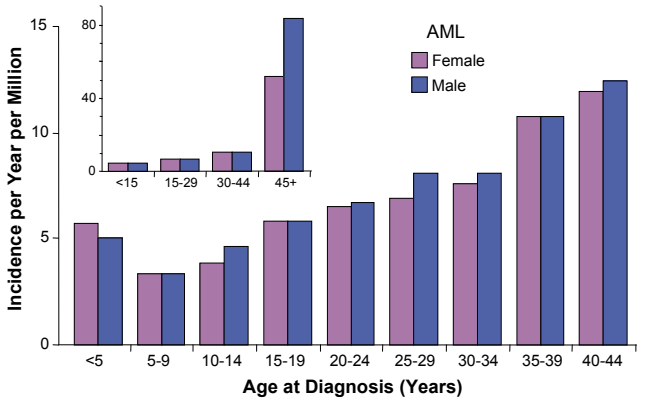

Figure 4.4B: Incidence of AML by Gender, SEER 1975-1999

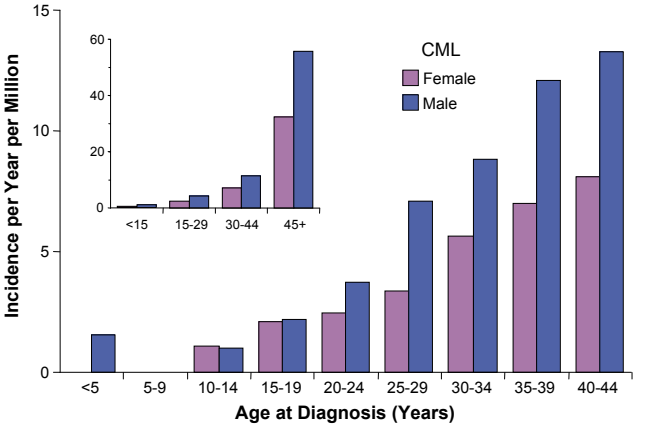

Figure 4.4C: Incidence of CML by Gender, SEER 1975-1999

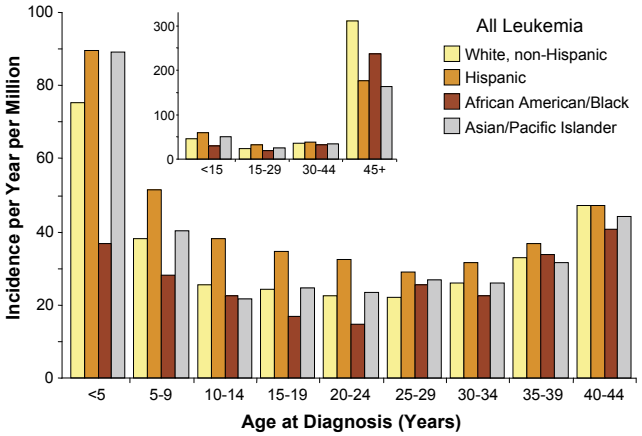

Figure 4.5: Incidence of All Leukemia by Race/Ethnicity, SEER 1990-1999

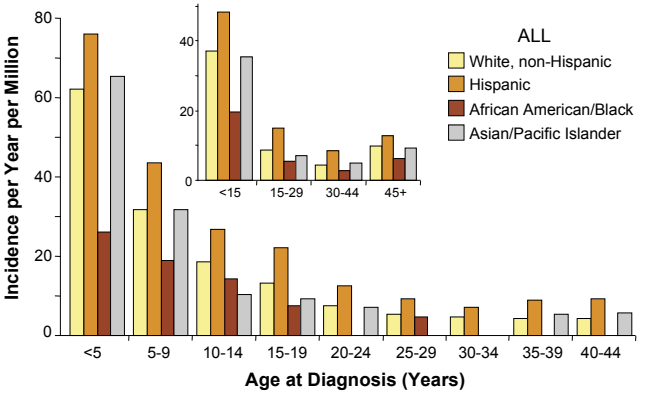

Figure 4.6: Incidence of ALL by Race/Ethnicity, SEER 1990-1999

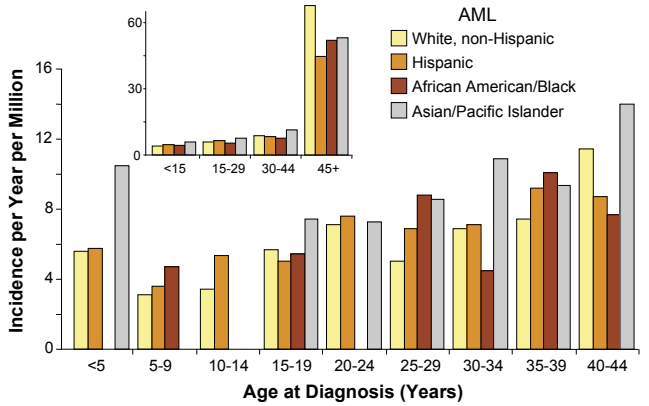

Figure 4.7: Incidence of AML by Race/Ethnicity, SEER 1990-1999

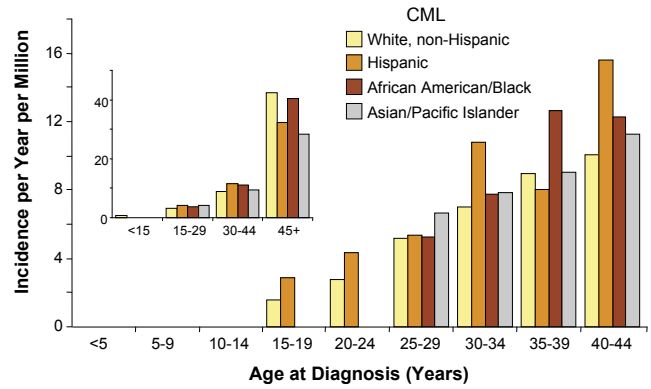

Figure 4.8: Incidence of CML by Race/Ethnicity, SEER 1990-1999

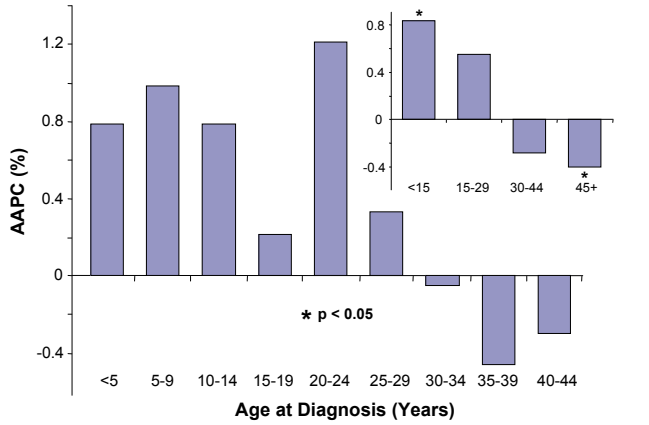

Figure 4.9: Average Annual Percent Change (AAPC) in Incidence of All Leukemia, SEER 1975-1999

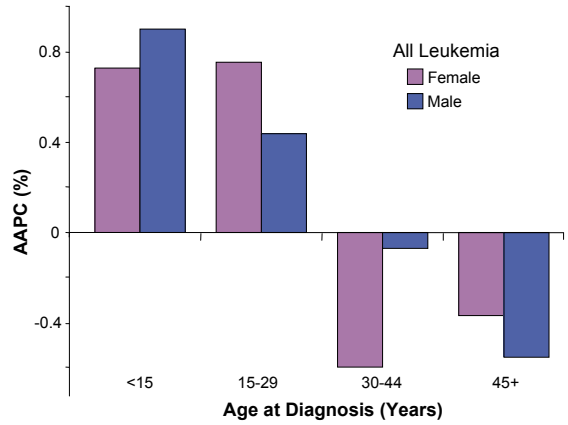

Figure 4.10: Average Annual Percent Change (AAPC) in Incidence for all Leukemia by Gender, SEER 1975-1999

available for those younger than 15 years of age due to the low baseline incidence.

OUTCOME

Mortality

During the period 1975 to 1999, mortality (deaths per year per million) for leukemias was higher for males than females in all age categories (Figure 4.12). The discrepancy was smallest for those younger than 5 years of age, with a M:F mortality ratio of 1.1, and remained in the 1.3 to 1.6 range through age 44; thereafter mortality for males was 1.8-fold that of females. Figure 4.13 shows mortality as a function of SEER incidence, thus normalized for the higher incidence of leukemias in males. These data reveal equivalent death rates for males and females in those younger than 5 and those 10 to 34 years old. The death rate was slightly higher for males in the 5- to 14-year age range, and was slightly higher for females 35 years and older.

Race/ethnicity data from 1990 to 1999 (Figure 4.14) reveal that Hispanics experienced the highest mortality in those younger than 25 years of age with leukemia, while African Americans/blacks had the highest mortality of those 25 years and older. The lowest mortality was consistently seen among American Indians/Alaska Natives in all age groups except those 20 to 24 years old; Asians/Pacific Islanders had a slightly lower mortality in this age group (9.2 versus 9.7 per million per year).

Survival

For the population in general and for both genders, 5-year survival rates for all leukemia declined with advancing age. For the 1975 to 1998 era, the 20-year survival rates were highest among those younger than 10 years of age, at 62% and 59% for the 0- to 5-year-olds and the 5- to 9-year-olds, respectively (Figure 4.15). The 20-year rates decreased dramatically for the next two age groups (10 to 14 years, 42%; 15 to 19 years, 30%, and remained below 22% for all groups 20 years of age and older.

As shown in Figures 4.16 and 4.17, long-term survival rates for each gender were twice as high among those younger than 15 years than in those 15 to 29 years, and even lower for those 30 years of age and older.

The same inverse relationship between survival and age at diagnosis was observed for ALL (Figures 4.18, 4.19, and 4.20), with the 15- to 29-year age groups having 20-year survival rates that were 5% to 10% better than for all leukemia (Figure 4.15).

Among those with AML (Figure 4.21), the 5- to 9-year age group had the highest 20-year survival rate (39%), followed by those under 5 years (30%). Individuals 15 to 29 years of age had 20-year survival rates between 20% and 27%, while survival for those 30 years and older was below 20%. Patients over 45 years of age had only a 5% 20-year survival.

Figure 4.22 shows 20-year survival rates for CML patients over the period 1975 to 1998. Despite being a "chronic"

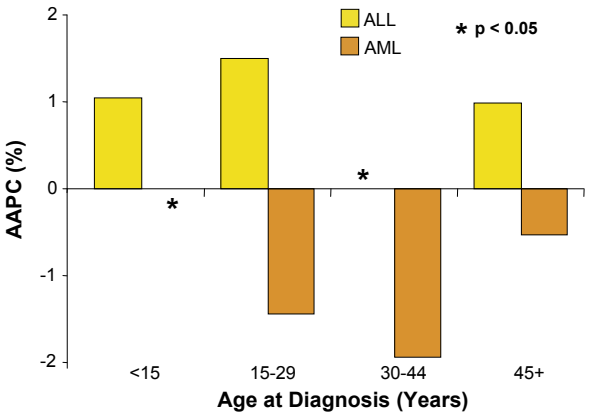

Figure 4.11: Average Annual Percent Change (AAPC) in Incidence for AML and ALL, SEER 1975-1999

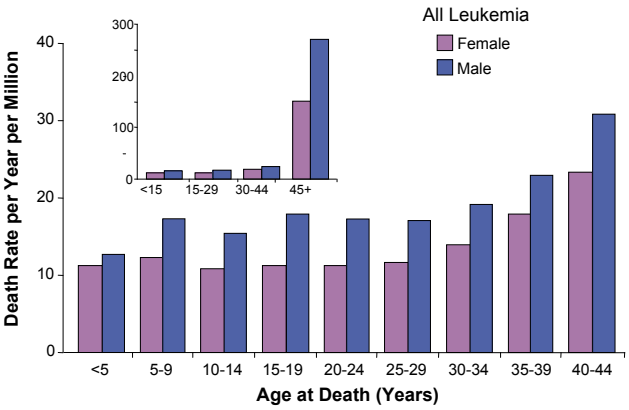

Figure 4.12: National Mortality for All Leukemia by Gender, 1975-1999

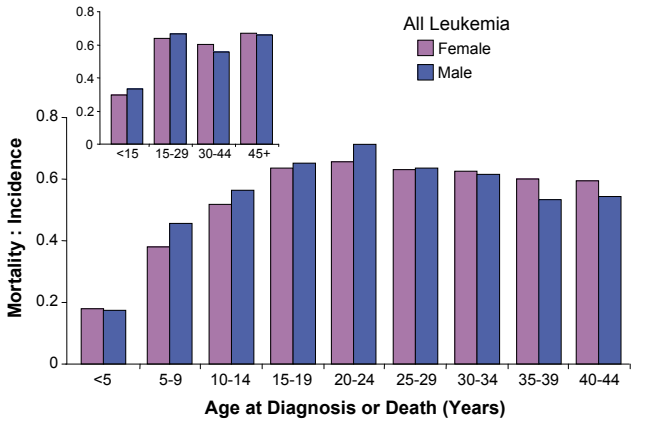

Figure 4.13: Ratio of National Mortality to SEER Incidence for All Leukemia, 1975-1999

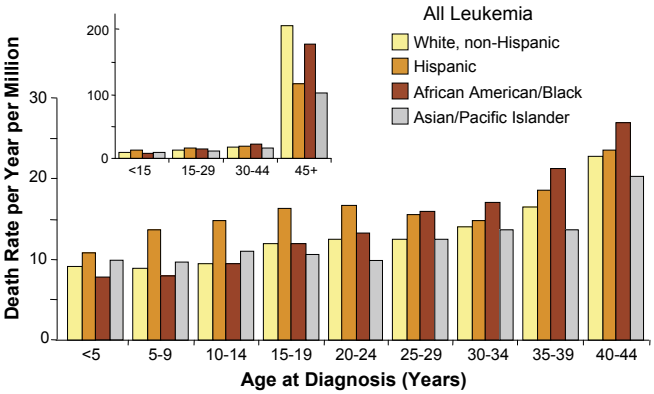

Figure 4.14: National Mortality by Race/Ethnicity for All Leukemia, 1990-1999

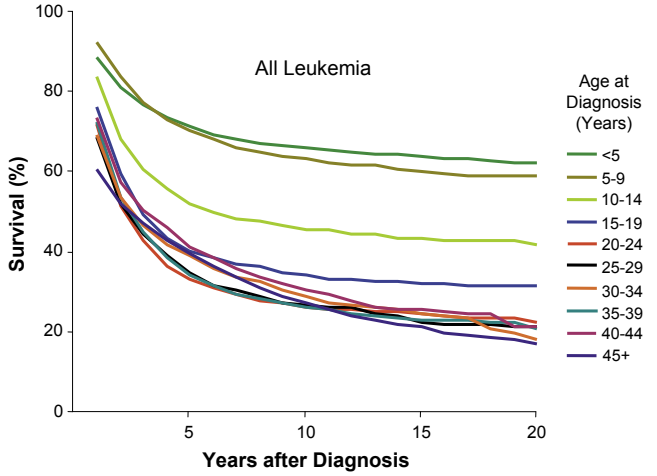

Figure 4.15: Survival Rates for All Leukemia by Age, SEER 1975-1998

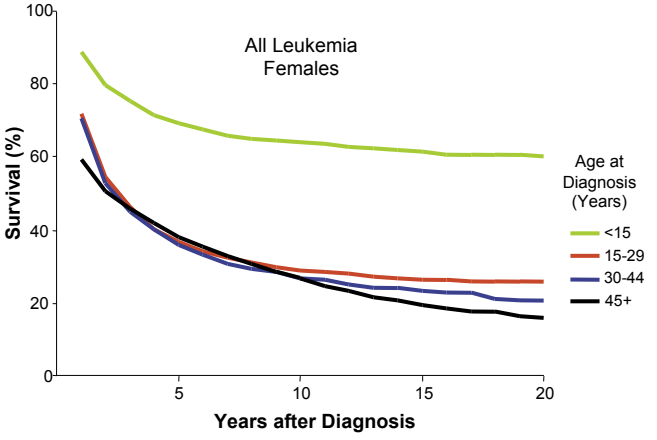

Figure 4.16: Survival Rates for All Leukemia in Females by Age, SEER 1975-1998

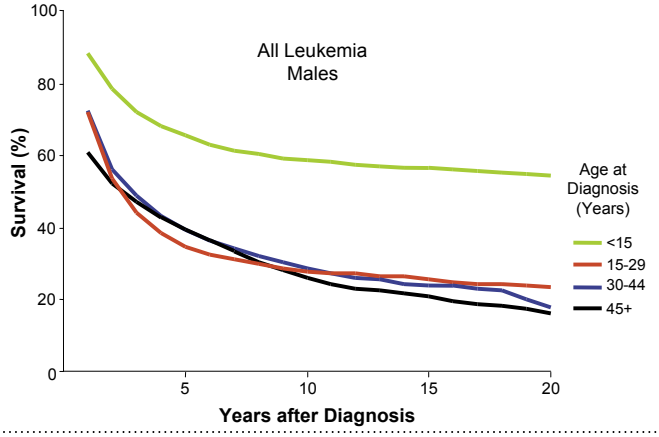

Figure 4.17: Survival Rates for All Leukemia in Males, by Age, SEER 1975-1998

leukemia, the ultimate survival was poor in all age groups, with 12-year survival rates less than 20% in all patients older than 15 years when diagnosed. The best survival was in the <5 and 15- to 19-year age groups (about 30 % at 15 years) and the worst survival occurred in those older than 45, of whom 85% died within two years.

Figures 4.23, 4.24, and 4.25 illustrate the 5-year survival rates for all leukemia, for ALL, and for AML by age according to era (four equal 6-year intervals from 1975 to 1998). While improvements in survival in each disease and age category occurred during this period, survival for the acute leukemias remained inversely correlated with age (Figs. 4.24 and 4.25). There was less of an age-dependent difference for all leukemia in those older than 15 years (Fig. 4.23), in large part due to an increasing proportion of chronic leukemias across this age span. In ALL, steady progress was made across the eras in all age groups. During the late 1980s and 1990s, progress in AML therapy in those under 30 years of age was negligible and considerably less than in older patients.

RISK FACTORS

Numerous risk factors have been investigated as to their potential association with the development of leukemia in children and adolescents, although little is known about such factors for older adolescents and young adults. These have been summarized recently into categories, based on the degree of certainty of the association, and include demographic, environmental, genetic, and exposure-related factors (Table 4.2). Age, gender, race/ethni-

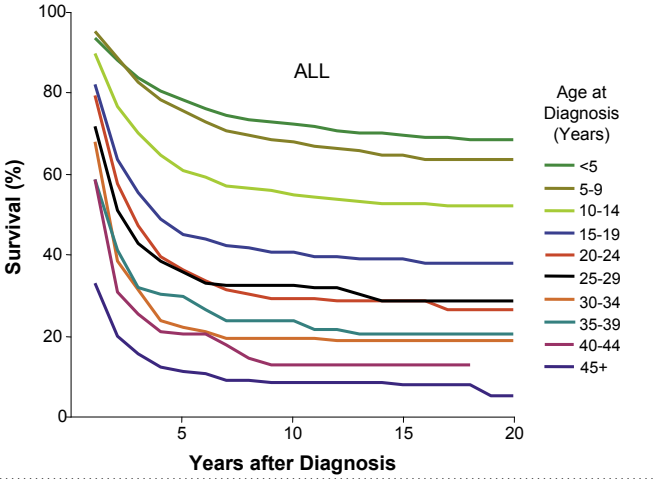

Figure 4.18: Survival Rates for ALL by Age, SEER 1975-1998

city, socioeconomic status, genetic syndromes, and radiation exposure (in-utero and/or therapeutic) are known risk factors for leukemias in younger age groups.[8]

Genetic syndromes have been reported in an estimated 2.6% of British children diagnosed with leukemia, 90% of these attributable to Down syndrome (DS, constitutional trisomy 21).[9] Whereas the pathogenic basis for the 10- to 20-fold increased risk of ALL in individuals with DS has not been elucidated, somatic mutations of the GATA1 gene are seen in virtually all cases of DS-associated AML and may be implicated in the 500-fold increased risk of megakaryoblastic AML seen in these patients.[10,11] Such mutations may also confer enhanced leukemic sensitivity to cytarabine via dysregulation of cytidine deaminase gene expression.[12]

Among individuals with neurofibromatosis type 1, homozygous mutations in the neurofibromin tumor-suppressor gene are associated with myeloid leukemias.[13] Characteristic to the chromosome breakage syndromes is DNA instability resulting in aberrant pathways of DNA repair. Mutations associated with leukemic and lymphomatous malignancy have been identified in genes associated with ataxia-telangiectasia (ATM, ATR), Fanconi anemia (FANC family), and Bloom syndrome (BLM).[14,15] Causative factors in the development of leukemias in those with congenital neutropenia (Kostmann agranulocytosis, Shwachman syndrome) have not been identified. The autosomal dominant form of severe congenital neutropenia is associated with heterozygous mutations in the neutrophil elastase gene (ELA2) and consequent alterations in the

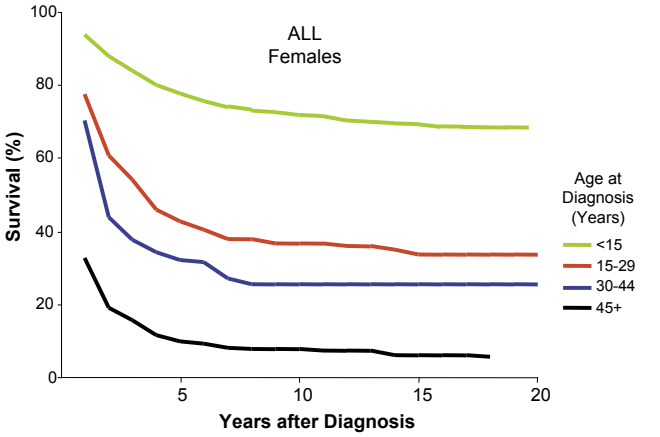

Figure 4.19: Survival Rates for ALL in Females by Age, SEER 1975-1998

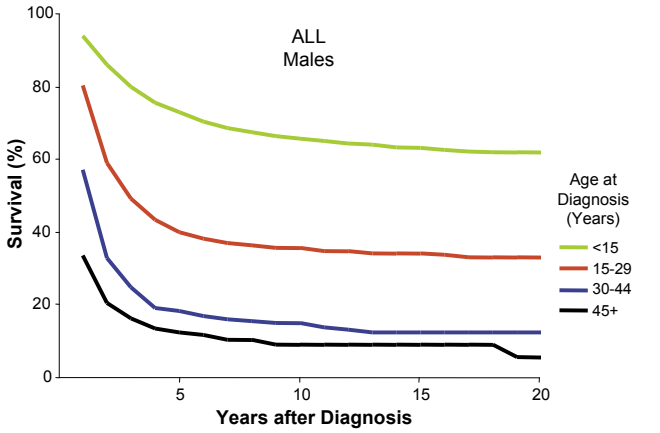

Figure 4.20: Survival Rates for ALL in Males by Age, SEER 1975-1998

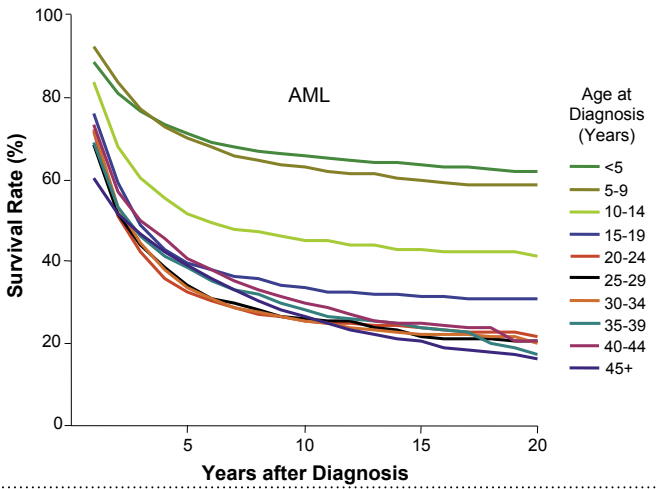

Figure 4.21: Survival Rates for AML by Age, SEER 1975-1998

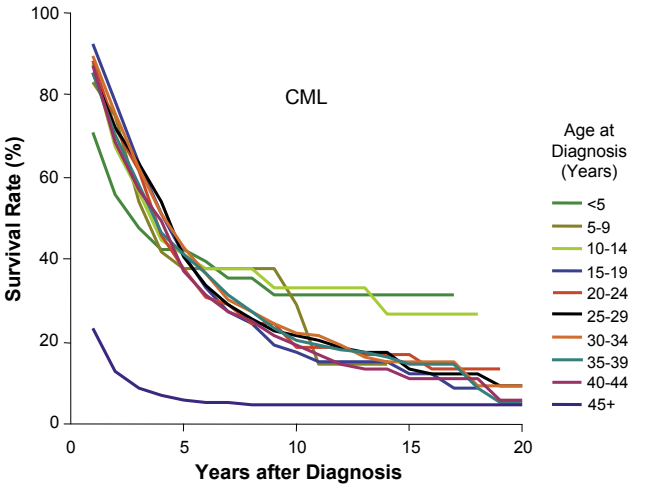

Figure 4.22: Survival Rates for CML by Age, SEER 1975-1998

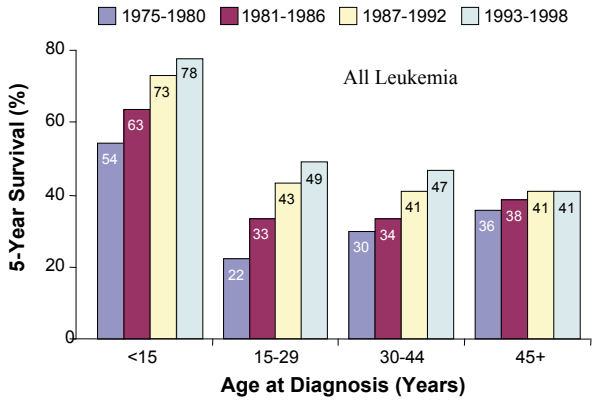

Figure 4.23: 5-Year Survival Rate for All Leukemia by Era, SEER

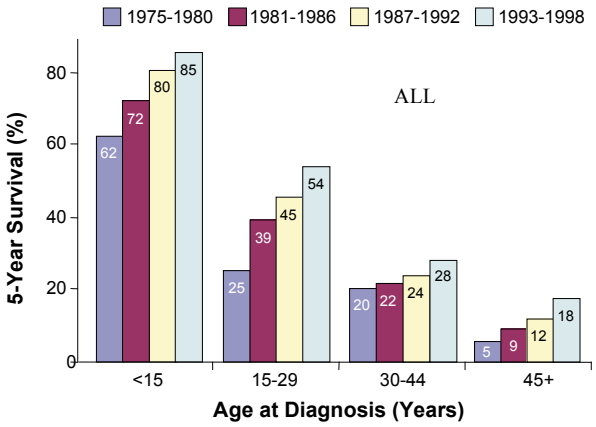

Figure 4.24: 5-Year Survival Rate for ALL by Era, SEER

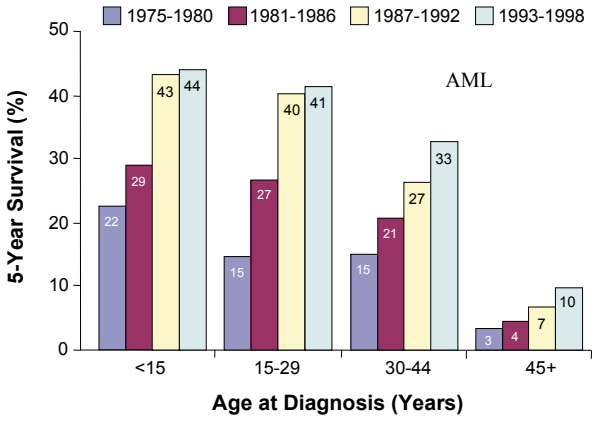

Figure 4.25: 5-Year Survival Rate for AML by Era, SEER

serine protease neutrophil elastase. Proteolytic regulation of hematopoiesis may be affected.[16]

Originally proposed in 1988, the so-called Greaves' hypothesis has attempted to correlate patterns of infection during infancy with the development of B-precursor ALL in early childhood.[17] Specifically, reduced exposure to infection during the first year of life purportedly results in immunologic naiveté, a biologically abnormal response to later infection and, rarely, leukemic transformation of a susceptible clone.[18,19] Support for the hypothesis has been derived mainly from proxy measures of delayed infectious exposure during infancy, including higher socioeconomic status (improved hygiene), social isolation (avoidance of daycare), breast-feeding (passive immunity), and birth order (higher rank equated with reduced exposure).[20,21] Studies assessing history of infections during infancy have drawn conflicting conclusions.[21,22]

SUMMARY

Leukemias in the AYA cohort reflect a transition from a childhood pattern, represented by a preponderance of ALL with favorable prognostic features, to an adult pattern, dominated by AML and a rising incidence of CML. Between 1975 and 1999, leukemia increased in incidence in 15- to 29-year-olds, with those in the 20- to 24-year age group experiencing the greatest increment at an average rate of 1.2% per year. Risk factors for ALL include male gender, young age (2 to 5 years), Caucasian race/ethnicity, pre- and post-natal radiation exposure, and constitutional syndromes including trisomy 21, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, and ataxia-telangiectasia. Risk factors for AML include Hispanic race/ethnicity, chemotherapeutic exposure to alkylating agents or topoisomerase II inhibitors, and constitutional syndromes including trisomy 21, Fanconi anemia, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, familial monosomy 7, and Kostmann granuocytopenia.

An improvement in survival has occurred since 1975 in each category of leukemia, although the decrease in mortality among adolescent and young adult patients with ALL lags behind that of younger patients. Despite being a "chronic" leukemia, the ultimate survival of patients with CML was poor in all age groups, with a 15-year survival

less than 20% regardless of age at diagnosis. During the period 1975 to 1999, the death rate for leukemias was higher for males than females in all age categories. Hispanics experienced the highest mortality for leukemias in those younger than 25 years, while African Americans/blacks had the highest mortality in those 25 years and older.

Broader participation in cooperative clinical group trials by adolescents and young adults is needed to further define the unique features of leukemia in these patients and to better assess and optimize therapies.

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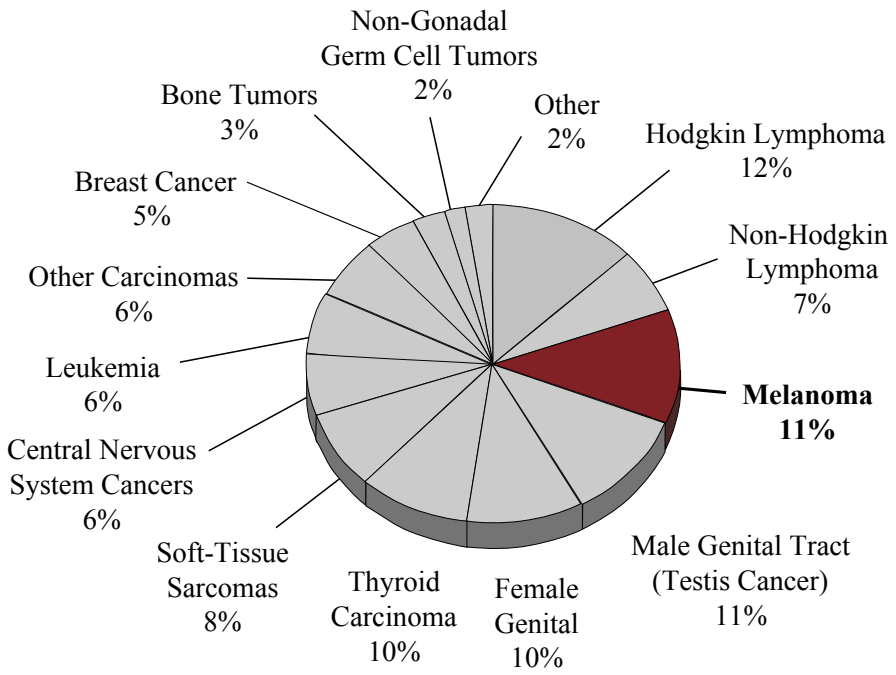
Chapter 5

Malignant Melanoma

Cancer in 15- to 29-year-olds In The United States



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HIGHLIGHTS

Incidence

- Melanoma accounted for 11% of all malignant neoplasms in individuals 15 to 29 years of age in the time period 1975 to 2000, and was the 2nd most common type of cancer in this age group. An estimated 2,600 individuals 15 to 29 years of age were diagnosed with malignant melanoma in the U.S. during the year 2000.
- As a proportion of all cancer, malignant melanoma peaked at 25 to 29 years of age, accounting for 12.8% of all cancers in this age group.
- The incidence of melanoma increased over time in individuals 15 to 29 years of age, but not as rapidly as the dramatic increase observed in older adults.
- Up to age 40, females had a higher incidence of melanoma than males, with a peak ratio of 1.8:1 (female:male) occurring between 20 and 24 years of age.
- After age 40 the gender incidence predominance reverses; older men had twice the incidence of older females.
- White, non-Hispanic individuals at any given age had a far higher incidence of malignant melanoma than any other race or ethnicity, including non-white Hispanic individuals. 90% of all melanomas diagnosed in the U.S occurred in white, non-Hispanic individuals.
- For other races/ethnicities, a greater proportion of melanoma cases occurred at younger ages than at older ages.
- The relative incidence of melanoma among races/ethnicities in the U.S. was inversely correlated with skin pigmentation. The order of incidence, from highest to lowest, was white non-Hispanics, Hispanics, Asians/Pacific Islanders, and African Americans.
- Among 15- to 29-year-olds, the increase in incidence of malignant melanoma occurred primarily in females; the trunk was the most common anatomic location.
- Head and neck melanomas were distinctly uncommon in 15- to 29-year-olds, in contradistinction to older adults.

Mortality and Survival

- As expected from the incidence patterns, the vast majority of deaths from melanoma among adolescents and young adults occurred in white, non-Hispanic patients.
- Mortality for malignant melanoma showed continued improvement over time in all age groups, but particularly in 20- to 29-year-olds.
- Melanoma in 10- to 39-year-olds was highly curable, with 5-year survival rates exceeding 90%.
- Females had a higher survival rate—exceeding 95% at five years among 15- to 29-year-olds—in comparison to males, who had an 88% 5-year survival rate during the past quarter century.
- Males with malignant melanoma of the head and neck had the worst survival rate, determined to be 80% at five years during the past quarter century.
- In the interval from 1975 to 1999, males had a greater survival improvement than females, however—particularly in the 15- to 24-year age group.

Risk Factors

- The etiology of melanoma in 15- to 29-year old individuals is not known.
- Solar/ultraviolet irradiation does not appear to be as important a causative factor in this age group as it is in older individuals.
- An exception may be those melanomas that arise in the skin of the trunk, where most of the increase has occurred, particularly in females. The increase at this body site may be a result of cultural changes that have resulted in more incidental and deliberate skin exposure (sun tanning) to this part of the body.
- Mutations in CDKN2A and CKD4 explain some of the familial melanomas, but the proportion of these mutations that occur in melanomas in 15- to 29-year-olds is not established.

INTRODUCTION

Melanoma was one of the most frequent cancers in adolescents and young adults in the period 1975 to 2000—second in incidence only to lymphoma—and accounted for one in nine patients with cancer in 15- to 29-year-olds. In the year 2000, approximately 2,600 individuals were diagnosed with melanoma in the adolescent and young adult age group (Table 5.1); this number has likely increased in light of population growth and the rising incidence of melanoma (see *Trends in Incidence*).

METHODS, CLASSIFICATION SYSTEM AND BIOLOGICAL IMPLICATIONS

Malignant melanoma is classified in the International Classification of Childhood Cancer (ICCC) in category XI(d) as one of the *Carcinomas and Other Epithelial Neoplasms* (category XI). The ICCC melanoma category specifies that malignant melanoma includes categories 8720-8780 (*Nevi and Melanomas*) in the International Classification of Diseases for Oncology (ICD-O-2). These categories include malignant melanomas (8720-8721, 8722-8723, 8730, 8740, 8742-8745, 8761, 8770-8774), malignant melanoma in Hutchinson melanotic freckle (8742), and malignant melanoma in precancerous melanosis (8741). ICD-O-3 histologies meningeal melanomatosis (8728) and mucosal lentiginous melanoma (8746), were also included.

One biologic implication of the classification is that the ICCC category of "malignant melanoma" does not include benign lesions (nevi and other precancerous histologies), which do occur in this age group. The SEER site recode for melanoma is limited to malignant melanomas of the skin. In the ICCC, malignant melanoma refers to malignant melanoma of all sites in the body (ICD-O Topography codes C00.0-C80.9). ICD-O allows the melanomas to be further classified by the site of origin. For the 25- to 29-year age group, the sites where most melanomas occurred were skin (further subdivided into skin location: head/neck, upper limb/shoulder, trunk, lower limb/hip), genital tract (included with pelvis), and eye (included with head/neck).

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

INCIDENCE

Age-Specific Incidence

The incidence of melanoma increased with age throughout the lifespan (Figure 5.1). Melanoma was exceedingly rare in prepubertal patients, accounting for only 1% of the cancers seen in patients under age 15. Considering males and females together, the incidence of melanoma increased from age 20 to 80 at a remarkably linear rate (data not shown). When males and females are evaluated separately however, the patterns are not linear (see *Gender-Specific Incidence*), with a switch in gender dominance occurring at about age 40. As a proportion of all cancers, the incidence of melanoma peaks between 20 and 40 years of age and then decreases. It accounts for 7.1% of all cancers diagnosed in 15- to 19-year olds, 12.0% of the cancers in the 20- to 24-year age group, and 12.8% of cancer in 25- to 29-year olds (Figure 5.1). From 1975 to 2000 there were about 80,000 cases of melanoma reported in the SEER population base, with 7.6% occurring in patients aged 15 to 29 years. Melanoma accounted for 11.5% of all cancers seen in this age group.

Table 5.1: *Incidence of Melanoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	0.7	0.9	2.8	14.0	38.9	69.4
Average annual % change in incidence, 1975-2000, SEER	na	na	na	0.87	1.23	0.58
Estimated incidence per million, year 2000, U.S.	na	na	4.0	15.5	44.4	73.8
Estimated number of persons diagnosed, year 2000, U.S.	13	19	81	314	841	1431

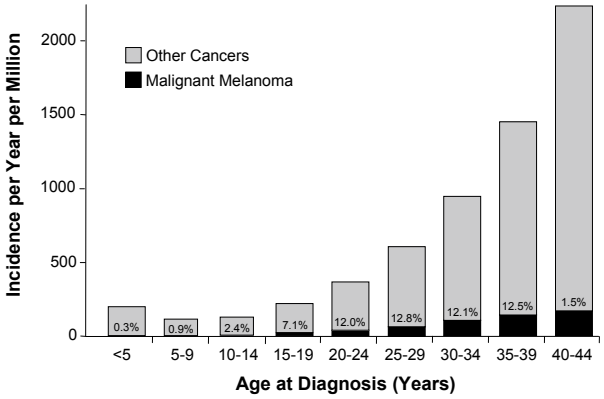

Figure 5.1: Incidence of Malignant Melanoma Relative to All Cancer, SEER 1975-2000

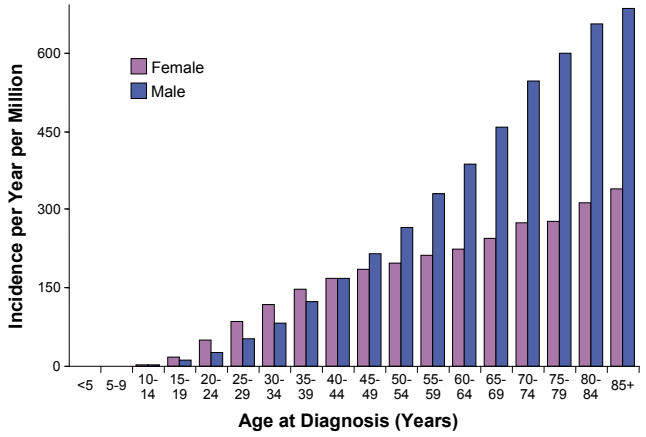

Figure 5.2: Incidence of Malignant Melanoma by Gender, SEER 1975-2000

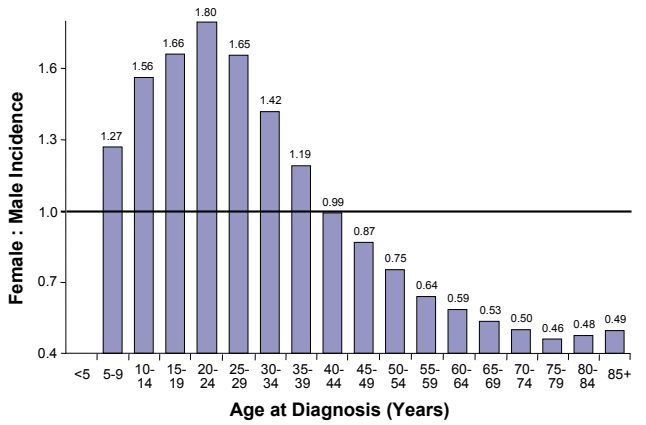

Figure 5.3: Female : Male Incidence Ratio, Malignant Melanoma, SEER 1975-2000

Gender-Specific Incidence

In females, the incidence increase was triphasic, with a rapid increase between 20 and 40 years of age, a slower increase from 40 to 70 years of age, and then an accelerated increase thereafter that was not as rapid as the increase in young adults (Figure 5.2). In males, the temporal pattern was sigmoid, with a slower increase in 20- to 40-year-olds than in females and the most rapid increase between 50 and 80 years of age. Below age 40, the incidence in females was higher in all age subgroups than in males (Figure 5.2). In terms of relative gender incidence, the female predominance peaked sharply between 20 and 25 years of age, at a ratio of 1.8 (Figure 5.3). The gender predilection switched by age 40 years, after which males were at substantially higher risk than females. By age 70, males developed melanoma at twice the rate of females (Figure 5.3).

Site-Specific and Gender Differences in Incidence

In 15- to 29-year olds, melanoma occurred most commonly on the trunk and legs, and least commonly on the head and neck (Figure 5.4). In older persons, the trunk was the least likely site of presentation, whereas head and neck incidence dramatically increased, becoming the most common site (Figures 5.5 and 5.6). In 15- to 29-year-old

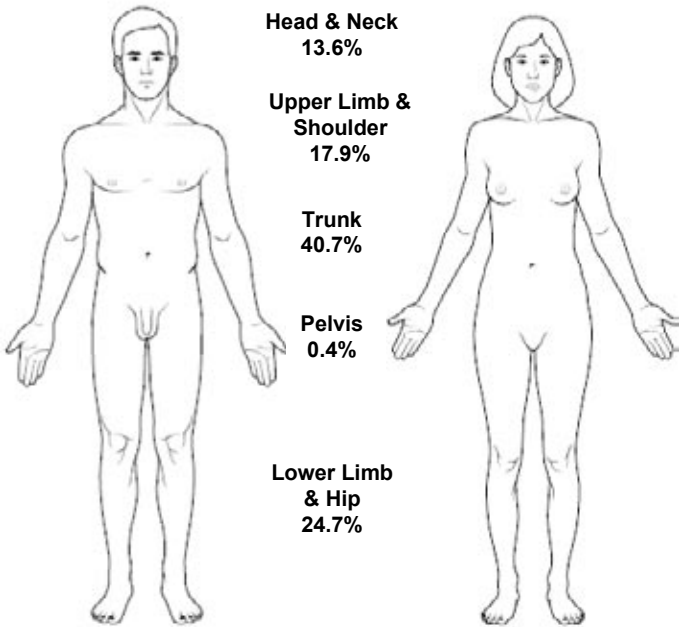

Figure 5.4: Common Sites of Malignant Melanoma in 15- to 29-Year-Olds, SEER 1992-2002. Drawings by Medscape

males, the majority of melanomas occurred on the trunk (Figure 5.5), which remained the most frequent anatomic site until age 80, when—as in females—head and neck sites rapidly increased and became the most common site (Figure 5.6). The extremities were much more likely to be affected in females than in males, and females were more likely to have melanoma arising in the legs than in the arms (Figures 5.5 and 5.6).

Racial/Ethnic Differences in Incidence

In the U.S., as in most countries for which comparable data are available, the incidence of melanoma was highest in fair-skinned persons (Figure 5.7). The proportion of non-white persons developing melanoma was inversely proportional to age throughout the life span, decreasing from 15% during childhood to < 5% by age 70 (Figure 5.8). This complements the age-related increase in the incidence of melanoma among whites. Among 15- to 29-year-olds, 90% of the patients with melanoma were white non-Hispanics. The relative incidence of melanoma among races/ethnicities in the U.S. was proportional to skin pigmentation, with the order of incidence decreasing from white non-Hispanics to Hispanics, Asians/Pacific Islanders, and African Americans/blacks.

Incidence Trends

The increasing incidence of melanoma during the past generation has been well established. However, this increase occurred predominantly in older adults—the older the age group, the greater the increase (Figure 5.9). The increase in 15- to 29-year-olds was insignificant for males and for both males and females younger than age 15 (Figures 5.10 and 5.11). Over age 30, the increase was statistically significant for both males and females, and at all anatomic skin sites (trunk, upper extremity, lower extremity, and head/neck).

Among females 15 to 29 years of age, the increase was statistically significant for the trunk, lower extremities and head/neck, but not for the upper extremities (Figure 5.11). The greatest increase among 15- to 29-year-olds occurred at truncal sites in females.

Among males 15 to 29 years of age, there was no comparable increase at any site (Figure 5.12). Only in men over 30 years of age were there statistically significant

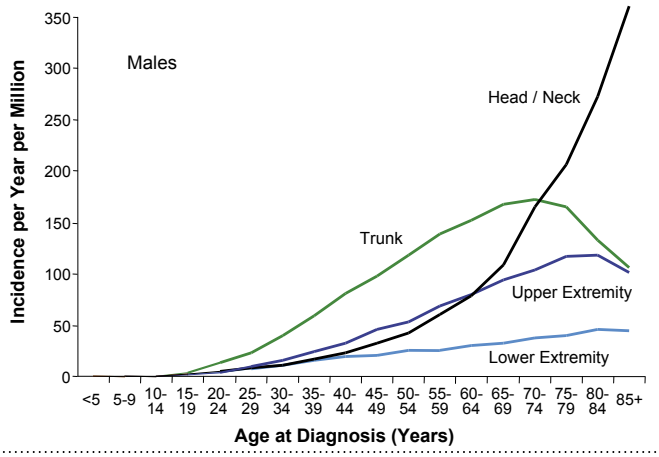

Figure 5.5: Incidence of Malignant Melanoma by Body Site for Males, SEER 1975-2000

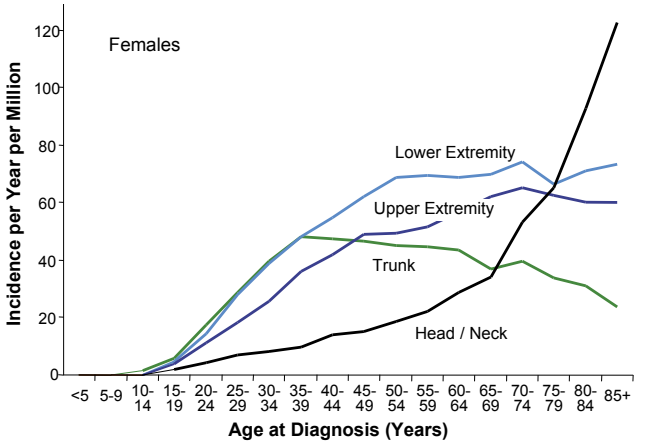

Figure 5.6: Incidence of Malignant Melanoma by Body Site for Females, SEER 1975-2000

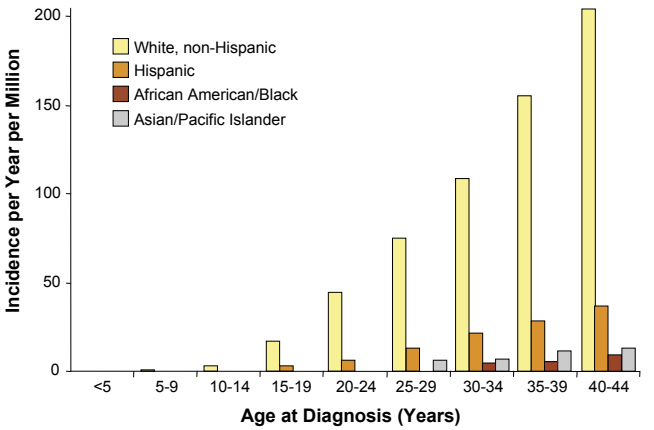

Figure 5.7: Incidence of Malignant Melanoma by Race/Ethnicity, SEER 1990-2000

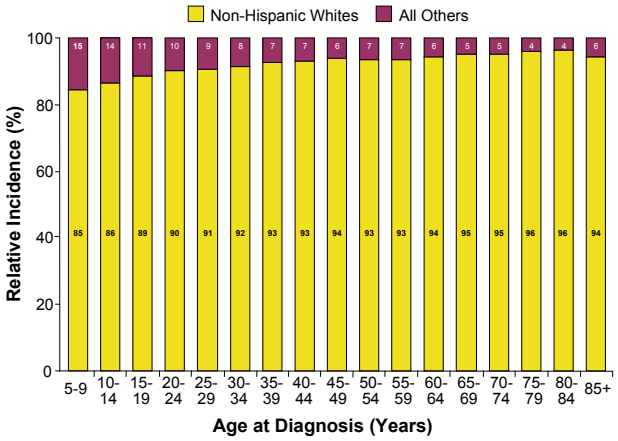

Figure 5.8: Relative Incidence of Melanoma in Non-Hispanic Whites, SEER 1990-2000

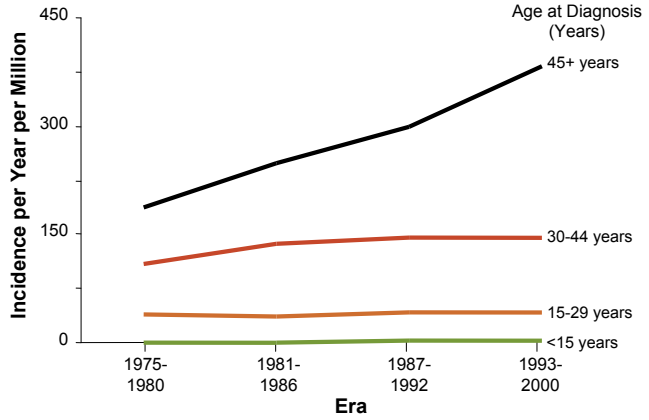

Figure 5.9: Incidence of Malignant Melanoma by Era, All Sites, SEER 1975-2000

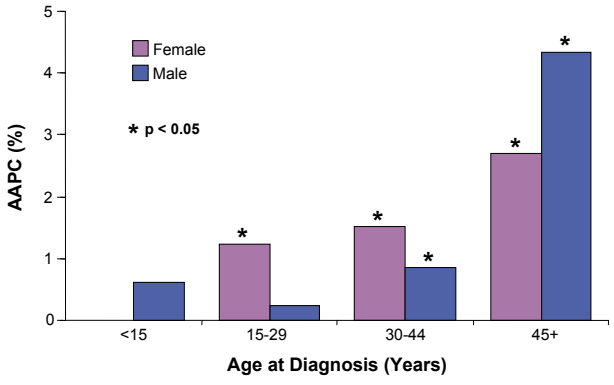

Figure 5.10: Average Annual Percent Change (AAPC) in Incidence for Malignant Melanoma by Gender, SEER 1975-2000

increases in incidence. The greatest increase in 30- to 44-year-old males was in the lower extremities.

In females, the greatest increase occurred at truncal sites, with the increase in 30- to 44 year-olds matching that which occurred above age 45 (Figure 5.13).

OUTCOME

Mortality

The U.S. death rate for melanoma among individuals younger than age 45 decreased steadily from 1975 to 2000 (Figure 5.14).

In patients younger than 45 years of age, males had a higher mortality rate than females, despite the fact that melanoma incidence was higher in females under age 40 (Figure 5.15).

Concordant with the incidence pattern, the vast majority of deaths from melanoma in the U.S. were in white non-Hispanic patients (Figure 5.16).

Those in the 20- to 29-year age group experienced the greatest reduction in mortality during the period 1975 to 2000 (Figure 5.17). Mortality reduction in this age group continued in the most recent decade (1990 to 2000) at a rate similar to that of the past quarter century (1975 to 2000), but was not as dramatic as the reduction in national mortality for melanoma among 30- to 44-year-olds (Figure 5.18).

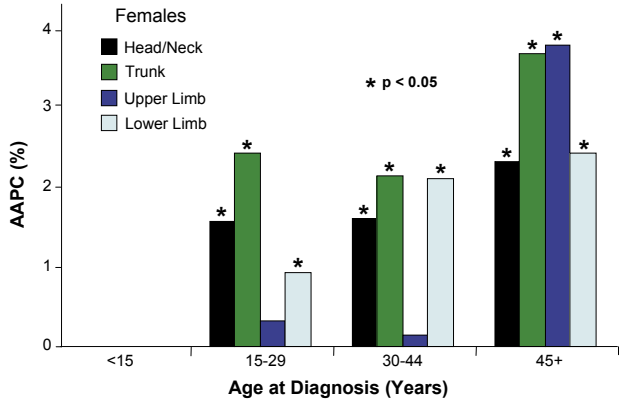

Figure 5.11: Average Annual Percent Change (AAPC) in Incidence for Malignant Melanoma in Females by Body Site, SEER 1975-2000

Survival

During the past quarter century, survival rates averaged 90% among patients diagnosed with melanoma before 45 years of age (Figure 5.19). The youngest (less than 5 years of age) and oldest (40 to 44 years old) in this age range had lower 5-year survival rates than patients in the other age groups (Figure 5.19).

In patients younger than 45 years of age, males had a lower 5-year survival rate than females in all age groups (Figure 5.20). This difference is particularly obvious in patients younger than 30 years of age. Among 15- to 29-year-olds, males with head and neck tumors had a lower 5-year survival rate than males with tumors at other anatomic locations (Figure 5.21).

Survival Trends

Survival rates in patients of all age groups with melanoma improved during the period 1975 to 1999 (Figure 5.22). The improvement was least apparent in children and adolescents younger than 15 years of age, although the low incidence of melanoma in this age group made it difficult to discern such a change.

Young males had a greater rate of survival improvement in the period 1975 to 1999 than females, particularly among 15- to 24-year-olds (Figure 5.23).

RISK FACTORS

The etiology of melanoma is not completely understood, although a variety of epidemiological studies have iden-

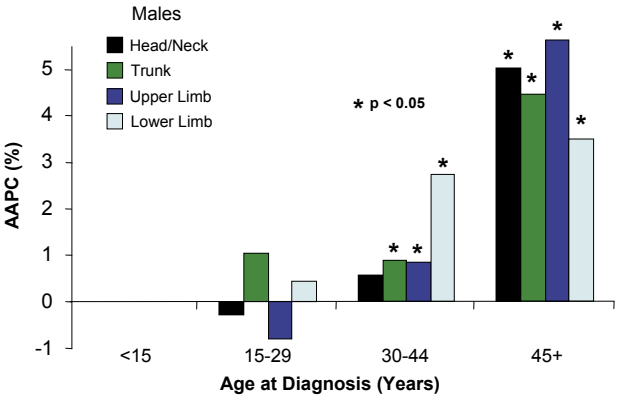

Figure 5.12: Average Annual Percent Change (AAPC) in Incidence for Malignant Melanoma in Males by Body Site, SEER 1975-2000

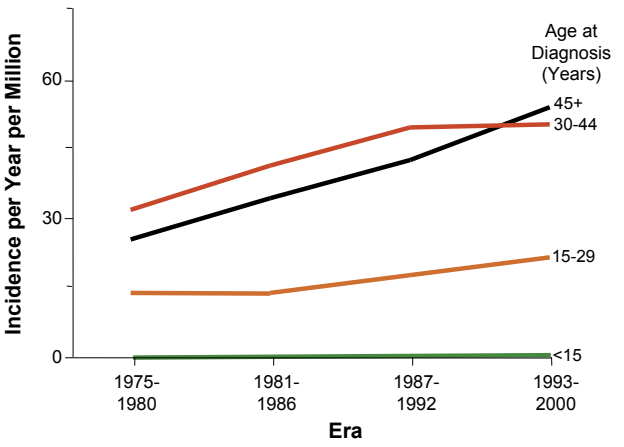

Figure 5.13: Incidence of Truncal Malignant Melanoma in Females by Era, SEER 1975-2000

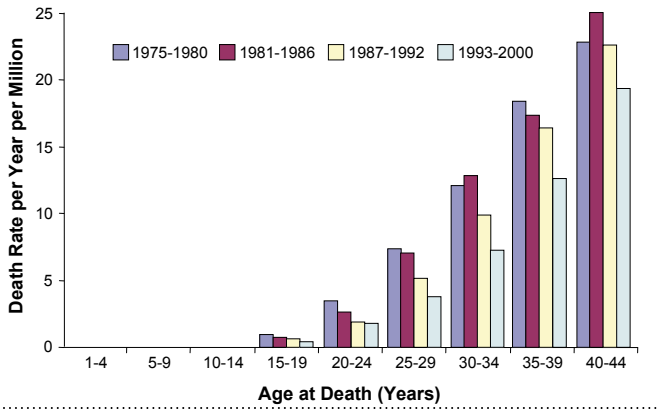

Figure 5.14: National Mortality for Malignant Melanoma by Era, U.S.

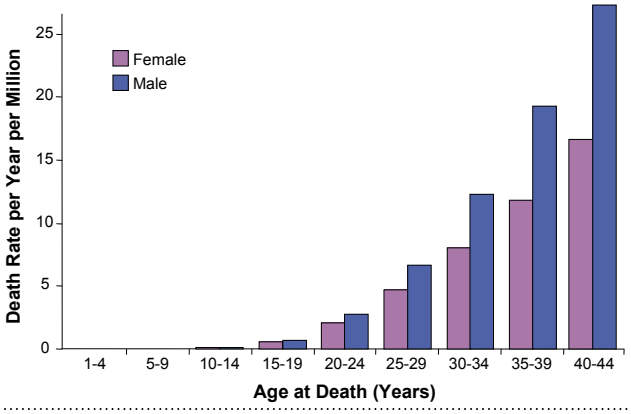

Figure 5.15: National Mortality Rate for Malignant Melanoma by Gender, U.S., 1975-2000

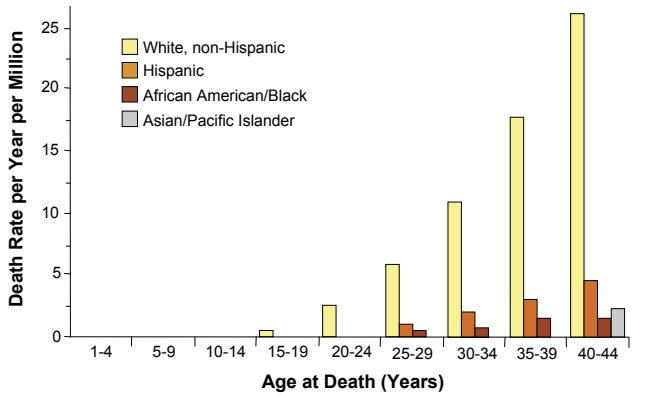

Figure 5.16: Cancer Mortality for Melanoma by Race/Ethnicity, U.S., 1990-2000

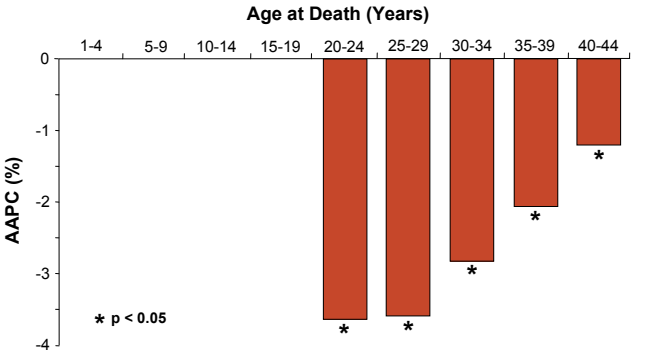

Figure 5.17: Average Annual Percent Change (AAPC) in National Mortality for Malignant Melanoma, 1975-2000

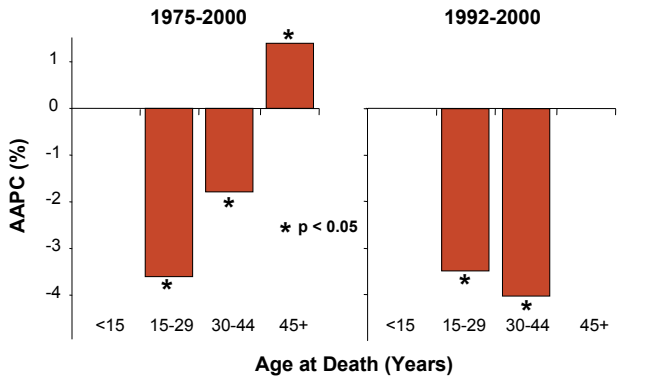

Figure 5.18: Average Annual Percent Change (AAPC) in National Mortality for Malignant Melanoma

tified several factors associated with an increased risk of developing this disease (Table 5.2).[1]

Some melanoma risk factors are age-dependent. For example, rare congenital and infantile melanomas (melanoma seen from birth to one year of age) may be the result of transplacental transmission or originate in a medium- or large/giant-sized congenital nevus.[2] Six cases of transplacental transmission of melanoma affecting a fetus have been reported, and only one of these patients survived long-term.[3] For patients with a large congenital nevus, the estimated lifetime risk of developing melanoma is less than 5%.[4] Over 80% of these patients have nevi located in the head and trunk area, and the melanoma that develops in these lesions usually develops before the age of 10.[4] Curiously, some of the melanomas seen in these patients arise in extracutaneous sites.[4] Other conditions associated with the development of melanoma in the first two decades of life include xeroderma pigmentosum, neurocutaneous melanosis, and immunosuppression.[5]

Females have a higher percentage of melanomas that occur in the upper or lower extremities, and as a result may be diagnosed earlier, with a resultant more favorable stage and prognosis. In males, the predominant site

Table 5.2: *Risk Factors Associated with the Development of Cutaneous Melanoma*[1]

RISK FACTOR	RELATIVE RISK
Immunosuppression	2-8
Excessive sun exposure	3-5
Sun sensitivity	2-3
White race	12
Lentigo maligna	10
Increased number of nevi	2-64
Older age (> 15 years)	88
Clinically atypical moles (with history of familial melanoma)	148
Clinically atypical moles (without a family history of melanoma)	7-70
Previous diagnosis of melanoma	5-9
Cutaneous melanoma in parents, children, siblings	2-8

is the trunk, which may result in a delayed diagnosis since these lesions are least likely to come under scrutiny. These gender-related patterns may explain why males with melanoma have had a lower survival rate than females.

Genetic susceptibility

Family history of melanoma (one or more first-degree relatives affected with melanoma) has been reported to occur in up to 12% of cases of melanoma.[6] Mutations in the CDKN2A and CDK4 genes account for 20%-25% of cases of high-risk melanoma families. The likelihood of finding a mutation in the CDKN2A gene correlates with the number of affected family members, and ranges from 5% in families with two affected individuals to 40% in those with three or more affected members.

Solar Exposure

Approximately half of all cases of melanoma worldwide have been attributed to sun exposure. Table 5.3 shows the results of a review of case-controlled studies that have investigated the relationship between sun exposure and melanoma.[7]

Nevus phenotype

Increased numbers of benign melanocytic nevi have been consistently associated with an increased risk of developing melanoma. In a study from Queensland Australia, the strongest risk factor associated with the development of melanoma in 15- to 19-year-olds was the presence of more than 100 nevi greater than 2 mm in diameter.[8] The presence of dysplastic or clinically atypical nevi confers an increased risk of melanoma. In the familial setting, the majority of melanomas have been reported to arise from dysplastic nevi.[9]

Table 5.3: *Odds Ratio of Developing Melanoma According to Type of Sun Exposure*[7]

TYPE OF EXPOSURE	ODDS RATIO (95% CL)
Intermittent	1.87 (1.67-2.09)
Occupational	0.76 (0.68-0.86)
Total	1.2 (0-1.44)
Sunburn	
Adult/lifetime	1.91 (1.69-2.17)
Adolescence	1.95 (1.6-2.36)
Childhood	1.63 (1.35-1.95)

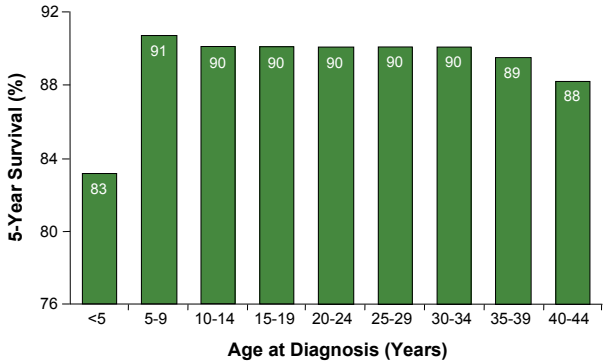

Figure 5.19: 5-year Survival Rate for Malignant Melanoma, SEER 1975-1999

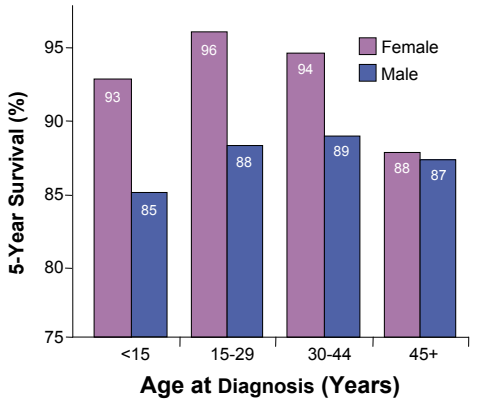

Figure 5.20: 5-year Survival Rate for Malignant Melanoma by Gender, SEER 1975-1999

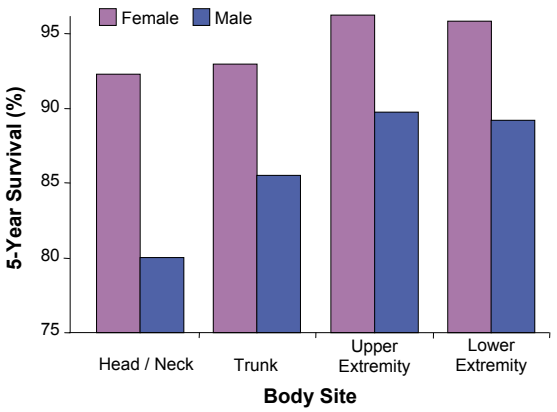

Figure 5.21: 5-year Survival Rate for Malignant Melanoma by Gender and Body Site for 15- to 29-Year-Olds, SEER 1975-1999

SUMMARY

Melanoma is a frequent, generally curable cancer of older adolescents and young adults that peaked in female predominance in the 15- to 29-year age group and shifted to male predominance by age 40. This gender predilection crossover suggests that the etiology and pathogenesis of melanoma is different in females and males, and that it differs for young adults and older adolescents as compared to older adults. Females were more likely to sustain melanoma early in life, while males were twice as likely to develop this neoplasm after age 60. Given the many years that most environmental exposures require to induce cancer, the gender reversal implies that for adolescent and young adult females, the events leading to carcinogenesis began during childhood and were different etiologically than those for males. If solar/ultraviolet exposure was a major cause of melanoma in young adults, the latency would not be expected to lead to a peak incidence during early adult life, or to be shorter in females than in males. Thus, solar radiation as the sole risk factor is not consistent with the age- and gender-specific incidence patterns seen in adolescents and young adults.

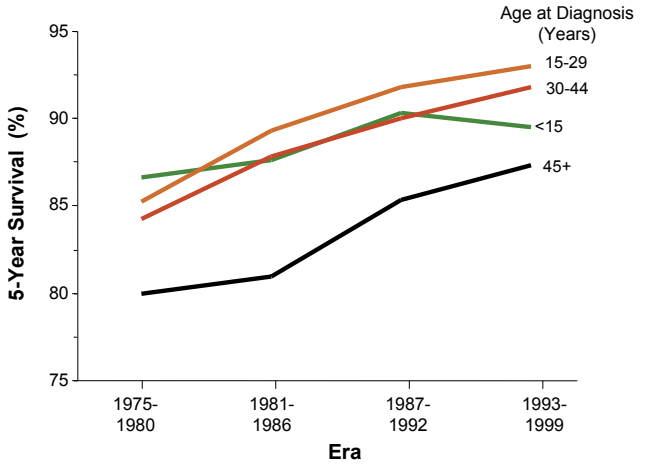

Figure 5.22: 5-Year Survival Rate for Malignant Melanoma by Era, SEER

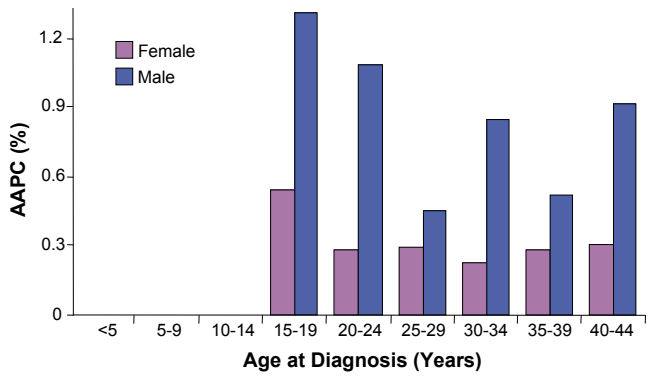

Figure 5.23: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Malignant Melanoma by Gender, SEER 1975-1999

Melanoma in young adults steadily increased in incidence, particularly in females, but at slower rates than observed in older adults. For males and females over the age of 30, this increased incidence over the past quarter century was statistically significant, and occurred at all major sites in the body (head/neck, trunk, arms, legs). For those 15 to 29 years of age, only females showed a significant increase in incidence, which was limited to certain sites—most notably the trunk and lower extremity.

Whereas the increasing incidence in older adults has been strongly correlated with solar and other forms of ultraviolet light exposure, there has been no direct evidence that melanoma in children, adolescents, and young adults is related to these factors. On the contrary, most of the melanomas that occur in young persons arise in dysplastic nevi or in parts of the body that are likely to have been protected from ultraviolet light exposure (e.g. trunk and head/neck).

On the other hand, the observed increased incidence among 15- to 29-year-olds—primarily in females, and specifically on their trunks—is compatible with a solar etiology that manifests skin-related cancer this early in life. The cultural emphasis on suntans and increased skin exposure—particularly that of the trunk in females—may well account for this epidemiologic dynamic (the *bikini effect*). If so, this may be the first evidence that ultraviolet exposure can cause melanoma within a limited number of years, rather than over a decade or more, as previously thought.

The greater susceptibility of fair-skinned individuals to melanoma is a long-standing finding that has been doc-

umented in this report to occur at all ages. That people of non-white race and/or ethnicity have a greater relative incidence of melanoma during childhood, adolescence and early adulthood is compatible with the premise that non-environmental factors are primarily responsible for melanoma development during early life. Solar/ultraviolet exposure either is more causative in later life and/or takes many years of exposure to result in melanoma. The age at which the switchover in the etiologies occurs—from non-environmental to solar exposure—cannot be determined from these data, but it seems reasonable to predict that it occurs between 20 and 40 years of age.

That young adult females are frequently diagnosed with a more favorable stage and prognosis than are men appears to be related to the site of development. In females, the most common site is an extremity, whereas in males the predominant location is the trunk. This gender-related pattern may explain why males with melanoma have had a lower survival rate than females.

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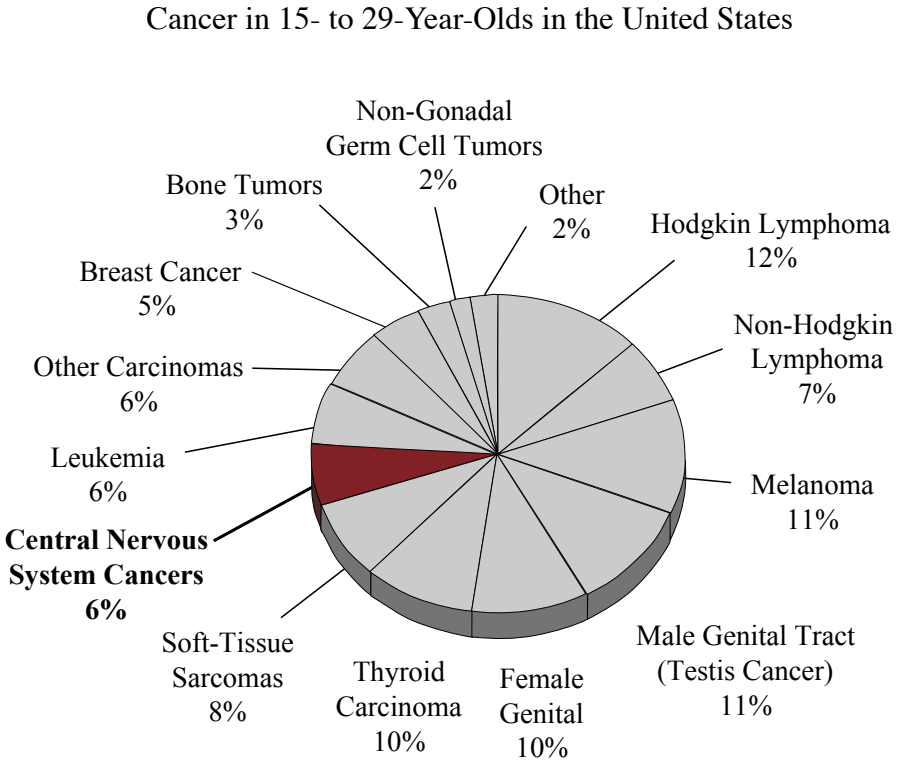
Chapter 6

Central Nervous System Cancer



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HIGHLIGHTS

Incidence

- Central nervous system (CNS) tumors accounted for 6% of all neoplasms in individuals 15 to 29 years of age during the period 1975 to 1998, and were the 7th most common neoplasm in this age group. An estimated 1,500 individuals 15 to 29 years of age were diagnosed with a CNS neoplasm in the U.S. during the year 2000.
- The average incidence of CNS tumors was 22.6 per million per year in the 15- to 29-year age group.
- At all ages, males had a higher incidence of CNS tumors than females.
- White, non-Hispanic individuals at any given age had a higher incidence of CNS tumors compared to African American/black, Hispanic, and Asian/Pacific Islander individuals.
- Between birth and 45 years of age, the incidence of astrocytoma increased and the incidence of ependymoma and PNET decreased with advancing age.
- Astrocytoma accounted for 64% of CNS neoplasms in individuals 15 to 29 years of age, whereas "other gliomas" accounted for 19%, primitive neuroectodermal tumor (PNET) 8%, ependymoma 6%, and miscellaneous CNS tumors 3%.
- The incidence of brain tumors increased slightly since 1975 in individuals 15 to 29 years of age—less so than in younger children, but more so than in 30- to 44-year-olds.
- Adolescents and young adults 15 to 29 years of age—as well as adults 30 to 44 years of age—showed an increasing incidence of "other gliomas" during the period studied (1975 to 1998). "Other gliomas" are defined as malignant glioma not otherwise specified (NOS), mixed oligoastrocytoma, subependymal giant cell astrocytoma, gliosarcoma, oligodendroglioma and monstrocellular sarcoma.

Mortality & Survival

- Mortality for individuals 15 to 29 years of age with CNS tumors showed little variation across racial/ethnic groups and was similar to mortality for children 0 to 14 years of age. Mortality for males at any given age was slightly higher than for females.
- Death rates for CNS tumors improved slightly over time for all age groups.
- The 10-year survival rate for CNS tumors exceeded 50% among patients younger than 20 years of age, but progressively declined with advancing age after age 20 years.
- The age-dependent decline in survival in astrocytoma for those over 20 years of age was dramatic, with a 10-year survival rate of 65% for individuals 15 to 19 years, 40% for those 20 to 24 years and 25% for those 25 to 29 years of age. The 10-year survival rate for 15- to 29-year-olds with PNET was 70%, for those with ependymoma 65%, and for those with "other glioma" 50%.
- Five- and 10-year survival rates for all CNS tumors combined improved slowly but steadily for patients 15 to 29 years of age over the period 1975 to 1998.
- Although the 5- and 10-year survival curves have improved with time, none of the individual age groups or major types of tumors has reached a survival plateau. This suggests that a "cure level" has not been achieved for most CNS neoplasms.
- The improvement in survival rates for CNS tumors in individuals 15 to 29 years of age lags behind that of other age groups.

Risk Factors

- Rare inherited conditions and therapeutic doses of ionizing radiation delivered to the CNS are the only two proven risk factors for CNS tumors, but explain only a small proportion of brain tumors.

INTRODUCTION

Central nervous system (CNS) tumors include both malignant and "benign" neoplasms (see *Classification System*); the latter term is reserved for tumors with a low potential to metastasize. While benign CNS neoplasms are often life-threatening due to local growth in a confined space or invasion/compression of critical structures, data for these tumors were not collected until 2004 and are therefore not included in this chapter. CNS *cancer* is used in the title and throughout the text to refer to malignant tumors of the brain and spinal cord

In the period 1975 to 1998 in the U.S., CNS cancer accounted for 6% of all cancers in adolescents and young adults 15 to 29 years of age, and represented the seventh most common type of cancer in this age group. This is in sharp contrast to individuals 0 to 14 years of age, in whom CNS cancer accounted for 25% of all cancers and were the second most common type of cancer. In the U.S. in the year 2000, 1,500 adolescents and young adults 15 to 29 years of age were diagnosed with a malignant CNS neoplasm (Table 6.1).

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

Malignant CNS neoplasms are histologically diverse and may arise from many different sites in the CNS. They are defined as malignant tumors arising from the brain, meninges, spinal cord, cranial nerves, pituitary gland, pineal gland or the craniopharyngeal duct. The histologic type rather than the site of origin better defines the behavior of CNS tumors, particularly for patients in the first decades of life.

This chapter is limited to primary malignant CNS cancers only; CNS germ cell tumors, CNS lymphoma, and metastases to the CNS from sites outside the CNS are not included. In the International Classification of Childhood Cancer (ICCC), CNS and miscellaneous intracranial and intraspinal neoplasms are divided into five major groups in category III. In the ICCC, astrocytomas appear in category III(b) and other gliomas in III(d). Table 6.2 includes the benign and malignant histologies from the ICCC, but in these analyses only the malignant histologies were used.

The astrocytoma category III(b) includes astrocytomas and glioblastomas regardless of location (categories 9400-9441), gliomatosis cerebri (9381), and malignant glioma of the optic nerve (9380, C72.3). Other gliomas are in category ICCC III(d), including malignant gliomas (9380) of the meninges, acoustic nerve, and other cranial nerves, oligodendroglioma and its variants (9450-9460), mixed gliomas (9382), subependymal giant cell (9384), gliosarcoma (9442), spongioblastoma (9443), and monstrocellular sarcoma (9481).

In the ICCC, primitive neuroectodermal tumors, including medulloblastoma, are in category III(c). These include medulloblastoma (9470), desmoplastic medulloblastoma (9471), primitive neuroectodermal tumor (9473), and medullomyoblastoma (9472). Large cell medulloblastoma (ICD-O-3 9474) is included with III(c).

Table 6.1: *Incidence of Malignant CNS Neoplasms in Persons Younger Than 45 Years of Age, U.S.*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44
U.S. 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 CNS tumors, 1975-2000, per year per million	33.7	29.9	24.1	19.2	21.2	27.0	33.0	39.8	49.3
Average Annual % Change in incidence of CNS tumors, 1975-1998	2.5%	0.8%	2.1%	0.3%	1.1%	1.6%	0.8%	-0.5%	0.2%
Number of persons diagnosed with CNS tumors, year 2000, U.S.	773	693	576	402	469	629	725	827	1154

Ependymoma is assigned a separate major category, III(a), in the ICCC (Table 6.2) and includes for these analyses malignant subependymal glioma (9383) and choroid plexus papilloma, malignant (9390), as well as the classic ependymomas (9391-9394). Ependymomas described as papillary (9393) or myxopapillary (9394) were only included if they were also described as malignant.

The ICCC assigns miscellaneous intracranial and intraspinal tumors to category III(e) and unspecified intracranial and intraspinal neoplasms to category III(f) (Table 6.2). Many histologies in the miscellaneous group, ICCC III(e) (Table 6.2) are not malignant and were not included in this analyses unless stated to be malignant. Malignant tumors in ICCC III(e) include pituitary carcinomas [chromophobe, acidophil, mixed acidophil-basophil, basophil (8270-8281, 8300)], cerebellar sarcoma (9480), and malignant meningiomas (9530-9539) including menigeal sarcomatosis (9539). Included in the analyses of the Unspec ified group are malignant tumors [(NOS (8000), small cell type (8002), giant cell type (8003), fusiform cell type (8004)], malignant tumor cells (8001) and from ICD-O-3 clear cell tumor (8005). In this chapter, these two ICCC

Table 6.2: *ICCC CNS Tumor Subgroups*

III(a) EPENDYMOMA	III(b) ASTROCYTOMA	III(c) PNET	III(d) OTHER GLIOMAS	III(e) MISCELLANEOUS INTRACRANIAL AND INTRASPINAL NEOPLASMS	III(f) UNSPECIFIED INTRACRANIAL AND INTRASPINAL NEOPLASMS
Ependymoma-NOS, anaplastic, papillary, myxopapillary	Astrocytoma-NOS, pilocytic (juvenile and piloid), fibrillary, protoplasmic, gemistocytic, anaplastic	Medulloblastoma-NOS, desmoplastic	Malignant glioma-NOS, mixed glioma	Pituitary adenoma and carcinoma (chromophobe, acidophil, basophil, mixed)	Malignant and benign primary tumors of the brain, spinal cord and cranial nerves NOS
Choroid plexus papilloma-NOS and malignant	Optic tract glioma	Primitive neuroectodermal tumor	Subependymal giant cell astrocytoma	Prolactinoma	
Subependymal glioma	Pleomorphic xanthoastrocytoma	Medullo-myoblastoma	Oligodendroglioma-NOS, anaplastic	Craniopharyngioma	
	Gliomatosis cerebri		Oligodendroblastoma	Pinealoma	
	Glioblastoma-NOS (GBM, giant cell glioblastoma, spongioblastoma multiforme)		Monstrocellular sarcoma	Pineocytoma	
	Spongioblastoma-NOS, polare		Gliosarcoma	Pineoblastoma	
	Astroblastoma		Primative polar spongioblastoma	Cerebellar sarcoma	
				Ganglioglioma	
				Meningioma-NOS, fibroblastic, psammomatous, angiomatous, hemangioblastic, hemangiopericytic, transitional, papillary	
				Meningioma-malignant (leptomeningeal sarcoma, meningeal sarcoma, meningothelial sarcoma)	
				Meningotheliomatous meningioma	
				Meningiomatosis	
				Meningeal sarcomatosis	

categories of miscellaneous (III(e)) and unspecified neoplasms (III(f)) were combined into one category termed "Miscellaneous" and reported only for malignant neoplasms.

In the ICCC, medulloblastoma (9470, 9471), medullomyoblastoma (9472), primitive neuroectodermal tumors (9473) are considered primitive neuroectodermal tumors forming group III(c). In the SEER modification of ICCC neuroblastomas of the CNS only were moved from IV(a) to III(c) and pineoblastoma (9362) was moved from III(e) to III(c). Primary CNS germ cell malignancies are placed in Germ Cell, Trophoblastic and Other Gonadal Malignancies (ICCC X). Primary CNS lymphomas are included under Lymphoma and Reticuloendothelial Neoplasms (ICCC II). The ICCC category of CNS and miscellaneous intracranial and intraspinal neoplasm does not include chordoma (9370), ganglioneuroblastoma (9490), olfactory neuroblastoma (9522), and retinoblastoma (9510-9512), peripheral primitive neuroectodermal tumors (9364) and nerve sheath tumors (9540-9571). Benign CNS neoplasms such as craniopharyngioma, pituitary adenoma, acoustic neuroma, choroid plexus papilloma, and benign neoplasms NOS are included in the CNS neoplasm group (ICCC III) but are not reported in this chapter.

As explained in the Methods chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

A few clarifications need to be made regarding the placement of some CNS tumors within the ICCC (Table 6.2):

- Benign CNS neoplasms such as craniopharyngioma, pituitary adenoma, acoustic neuroma, choroid plexus papilloma, and benign neoplasms NOS are included in the CNS neoplasm group (ICCC III) but are not reported in this chapter.
- Primary CNS germ cell malignancies are placed in Germ Cell, Trophoblastic and Other Gonadal Malignancies (ICCC X)
- Metastatic tumors to the brain are included in the ICCC according to the site of origin.
- Primary CNS lymphomas are included under
- Medulloblastoma, PNET, neuroblastoma and pineoblastoma are considered primitive neuroectodermal tumors. According to the ICCC, however, pineoblastoma is included in Miscellaneous Neoplasms (ICCC IIIe), and CNS neuroblastoma is included in Sympathetic Nervous System Tumors (ICCC IV).

This chapter will utilize the ICD system to assess mortality rates. Unfortunately, this system categorizes CNS neoplasms by site of origin: brain and other nervous system, spine and cranial nerves. Thus, mortality rates for individual histological types cannot be identified using the ICD.

INCIDENCE

SEER incidence data were analyzed from 1975 to 1998. During these years 3,030 primary CNS neoplasms were diagnosed in individuals 15 to 29 years of age who resided in one of the SEER areas. The average incidence of brain tumors in this age group was 22.6 per million. CNS neoplasms accounted for 6% of all malignancies and were the seventh most common type of cancer in this age group.

Spinal cord tumors represented 6-8% of all primary malignant CNS tumors in individuals 15 to 29 years of age, compared to 10-11% in patients < 15 years of age. The proportion of spinal cord tumors decreased progressively as age increased from 0 to 40 years.

Age-Specific Incidence

Figures 6.1 and 6.2 illustrate the relationship between age at diagnosis and incidence of CNS cancer. The proportion of new CNS tumors relative to all new cancer cases declined steadily with advancing age (Figure 6.1). Malignant CNS tumors accounted for more than one in five cases of cancer in children younger than 5 years of age, but accounted for one in 50 cases in adults 40 to 44 years of age. The decline was due more to an increase in other cancers (Figure 6.1) than to a decrease in CNS tumors (Figure 6.2). When five-year age groups are considered, individuals 15 to 29 years of age had the lowest incidence of CNS neoplasms, followed by individuals 20 to 24 years of age. A steady upward climb in incidence

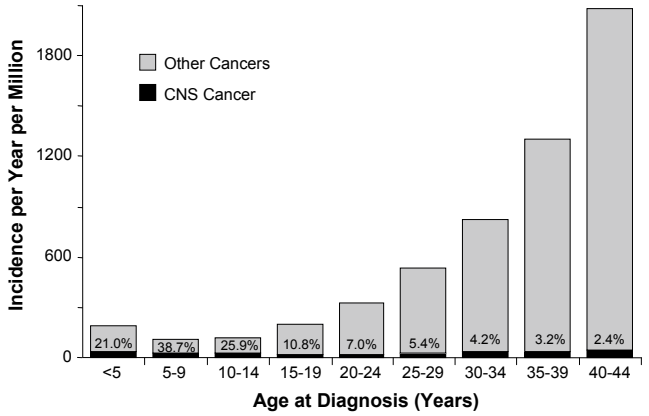

Figure 6.1: Incidence of CNS Tumors Relative to All Cancer, SEER 1975-1998

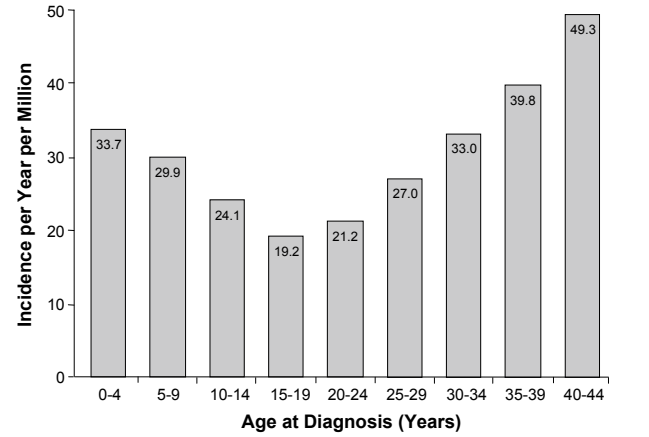

Figure 6.2: U.S. Cancer Incidence: All CNS Cancer, SEER 1975-2000

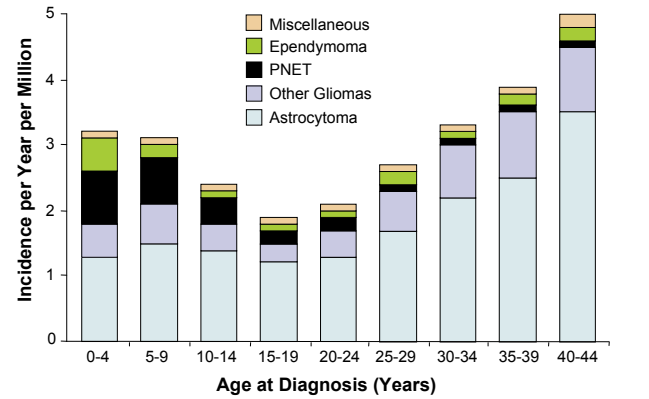

Figure 6.3: Incidence of CNS Tumors by Type (ICCC), U.S. SEER 1975-1998

was seen in those older than 24 years of age, with the rate for 35- to 39-year-olds more than twice that of 15- to 24-year-olds (Figure 6.2).

The incidence of each histological subtype of CNS tumor is displayed in Figure 6.3. In the 15- to 29-year age group, astrocytoma accounted for 64%, "other glioma" 19%, PNET 8%, ependymoma 6%, and miscellaneous 3%. This histologic distribution is more comparable to adults (30 to 44 years of age) than to children (0 to 14 years of age). In children < 15 years of age, astrocytoma accounted for 50%, "other glioma" 15%, PNET 23%, ependymoma 9%, and miscellaneous 3%. The incidence of astrocytoma increased and the incidence of PNET and ependymoma decreased with advancing age (Figure 6.3).

Gender-Specific Incidence

Males at any given age had a higher incidence of CNS tumors compared to females (Figure 6.4), with the male: female incidence ratio never falling below 1.1 (Figure 6.5). The incidence of CNS tumors in males 15 to 29 years of age was 25.1 per million, whereas in females it was 19.3 per million. An average male:female incidence ratio of 1.32 was seen for individuals in this age group. Males had a higher incidence of all histological types of brain tumors as categorized by the ICCC. The male: female incidence ratio for the more common CNS tumors in the 15 to 29 year age group was 1.26 for astrocytoma, 1.32 for ependymoma and "other glioma", and 1.85 for PNET. This male predominance pattern differs from that of all cancers combined, for which the male:female incidence ratio steadily declined with advancing age from age 10 to 45 (Figures 6.5 and 1.3). The gender difference

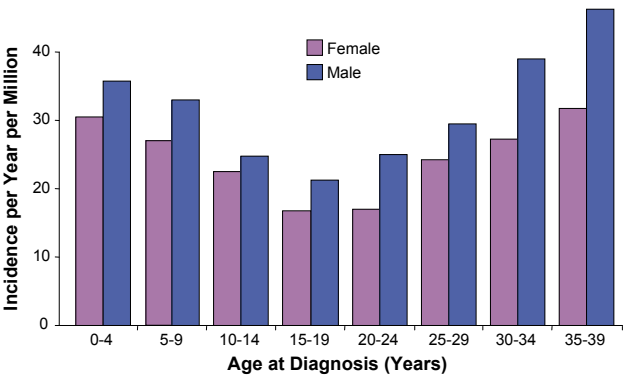

Figure 6.4: Incidence of CNS Tumors (ICCC) by Gender, U.S., SEER 1975-1998

has not been adequately explained. The fact that the male brain is generally larger than the female brain throughout the age span and thereby contains more cells may be a contributing factor.

Racial/Ethnic Differences in Incidence

Figure 6.6 displays CNS tumor incidence from 1990 to 1999 by race/ethnicity. The incidence of CNS neoplasms in all age groups was higher for white non-Hispanic individuals than for African American/black, Hispanic, and Asian/Pacific Islander individuals. In the 15- to 29-year age group, the incidence of CNS neoplasms was 27 per million in white non-Hispanics and 14.4 to 14.8 per million in the other three racial/ethnic groups.

In all racial/ethnic groups, males 15 to 29 years of age had a 20-25% higher incidence of CNS tumors compared to females. The incidence of CNS neoplasms in white non-Hispanic males 15 to 29 years of age was 30.6 per million, compared to 23.2 per million in females. The average incidence of CNS neoplasms for males in the other three racial/ethnic groups was 16 per million, compared to 13 per million for females.

Trends in Incidence

The incidence for all CNS neoplasms based on year of diagnosis (1975 to 1998) is displayed in Figure 6.7. The incidence rate increased for all age groups from 1975 to 1980 and 1987 to 1992. For children 0 to 14 years of age, this data has been rigorously analyzed; this change in incidence did not occur progressively from 1975 to 1994, but, "jumped" to a higher rate after 1985.[1] The timing of the jump was attributed to the wide-scale availability of magnetic resonance imaging (MRI) in the United States—which likely resulted in improved diagnostic sensitivity—rather than an actual increase in incidence.[1] Introduction of MRI may also explain, in part, the increased incidence over time of CNS tumors in individuals older than 15 years of age.

The average annual percent change (AAPC) in incidence of CNS tumors revealed a statistically significant increased incidence of all CNS tumors for children 0 to 14 years of age and for adolescents and young adults 15 to 29 years of age (Figure 6.8; inset). Adults 30 to 44 years of age showed no increase in the incidence of CNS

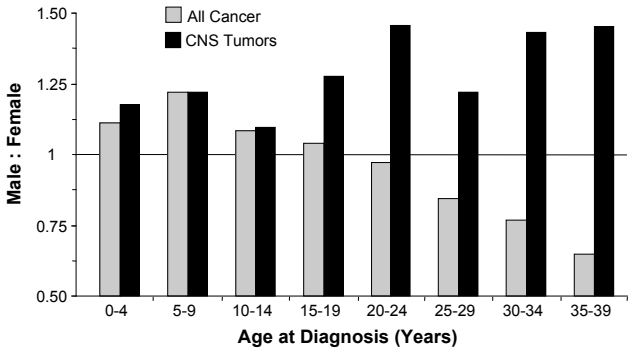

Figure 6.5: Ratio of Male-to-female Incidence for CNS Tumors versus All Cancer, SEER 1975-1998

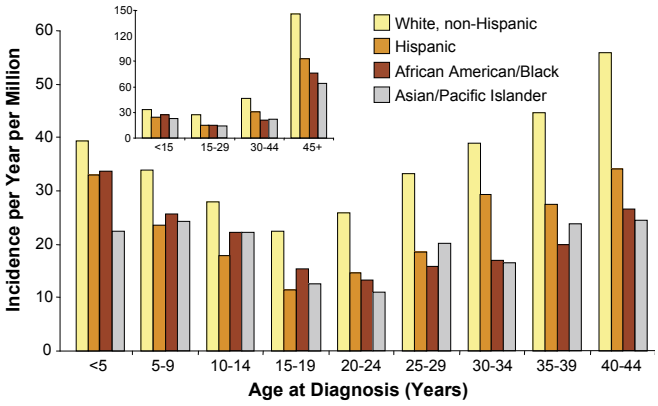

Figure 6.6: Incidence of CNS Tumors by Race/Ethnicity, SEER 1990-1999

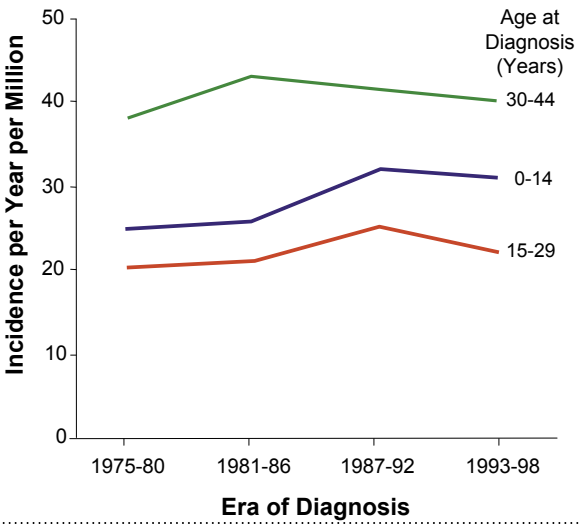

Figure 6.7: Change in Incidence For All CNS Tumors by Era, SEER 1975-1998

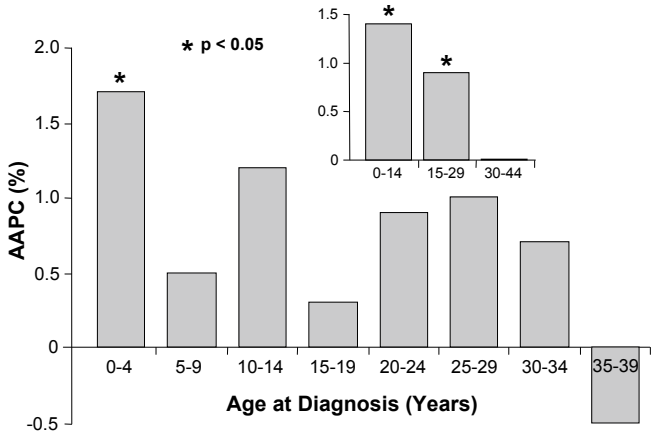

Figure 6.8: Average Annual Percent Change (AAPC) in Incidence for CNS Tumors (ICCC), SEER 1975-1998

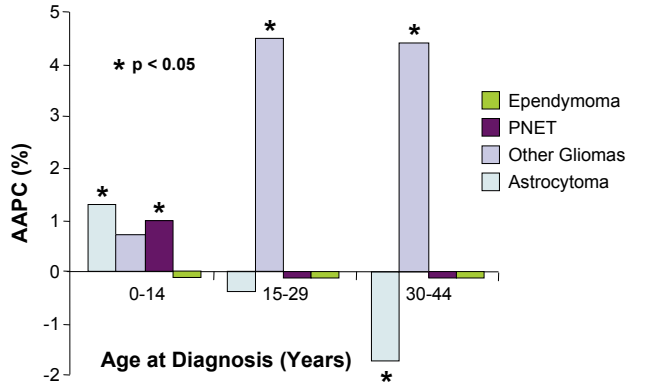

Figure 6.9: Average Annual Percent Change (AAPC) in Incidence by Type of CNS Tumor, SEER 1975-1998

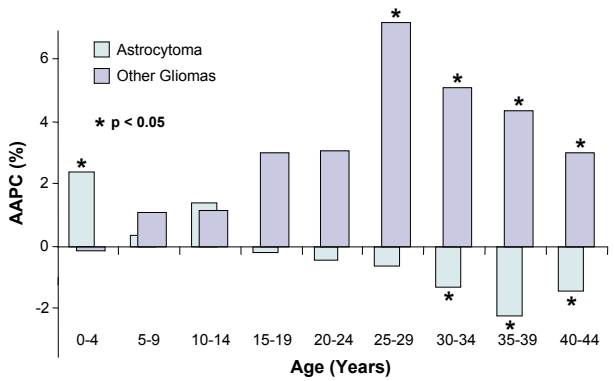

Figure 6.10: Average Annual Percent Change (AAPC) in Incidence for III(b) Astrocytoma and III(d) Other Gliomas, 1975-1998

tumors. The overall pattern of the increase in incidence indicates that most of the increase occurred in the youngest patients (Figure 6.8).

Delineation of incidence by tumor histology revealed a statistically significant increased incidence of astrocytoma and PNET in children 0 to 14 years of age (Figure 6.9). Adolescents and young adults demonstrated a statistically significant increased incidence of "other gliomas" (Figure 6.9). When the AAPC is examined according to five-year age groups and tumor type (Figure 6.10), a significant increase in incidence of "other gliomas" was demonstrated in individuals 25 to 44 years of age (Figure 6.10), and a significant decrease in incidence rate of astrocytoma was observed in individuals 30 to 44 years of age. The change in incidence of "other gliomas" over time in individuals 15 to 29 years of age as compared to those younger and older is displayed in Figure 6.11.

The increased annual incidence in "other gliomas" in adults 30 to 44 years of age despite no change in annual incidence of all CNS neoplasms could be due to better recognition of oligodendroglial elements in glial tumors. This improved recognition could shift the diagnosis from the "astrocytoma" category to the "other glioma" category, resulting in no net change in overall malignant CNS tumors, but explain the significant decrease in annual incidence of astrocytomas in adults aged 30 to 44 years. An explanation for the increased annual incidence of "other gliomas" in 15- to 29-year-olds is less apparent.

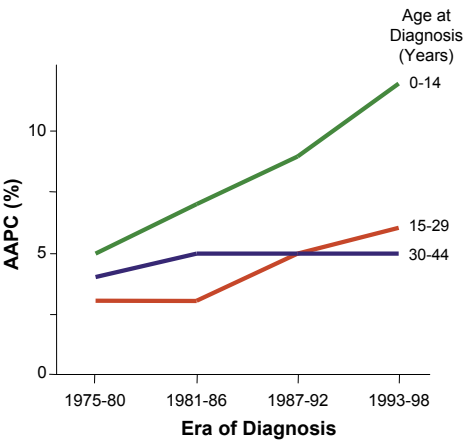

Figure 6.11: Average Annual Percent Change (AAPC) in Incidence for III(d) Other Gliomas by Era, SEER 1975-1998

The trend in incidence of "other gliomas" should be closely observed to determine if the annual incidence is truly increasing or if it is related to the use of improved technology for the diagnosis and classification of glial tumors.

OUTCOME

Mortality

Age- and Gender-Specific Mortality

The death rate for malignant CNS neoplasms was fairly stable for individuals younger than 30 years of age, ranging from 7 to 12 per year per million. The lowest rate was seen in individuals 15 to 24 years of age (Figure 6.12) and is in accordance with the incidence pattern (Figure 6.4). Two discrepancies between the incidence and mortality patterns are apparent: 1) after 25 years of age, the rise in mortality from CNS tumors (Figure 6.12) is out of proportion to the relative higher incidence (Figure 6.4), and 2) the death rate was lower than expected for the incidence in children younger than 5 years of age (Figure 6.12 versus Figure 6.4). These differences imply that survival from CNS tumors is worse for individuals older than 25 years but more favorable for children younger than 5 years of age. Survival data, presented below, confirm the former but do not substantiate the latter.

More males died of CNS tumors than females, regardless of age (Figure 6.12). This appears to reflect the increased incidence in males, which also occurs in all age groups (Figure 6.4).

To adjust for the age-dependent pattern in incidence, Figure 6.13 demonstrates the ratio of the death rate to incidence of CNS tumors by age and gender. The ratio is approximately 0.3 for individuals 15 to 29 years of age, but then steadily increases after 30 years of age to a ratio of 0.6 at 40 to 44 years of age. Thus, individuals older than 25 years are more likely to die due to their CNS tumor when compared to those younger than 25 years of age. This is particularly apparent in males but also in females over 30 years of age (Figure 6.13).

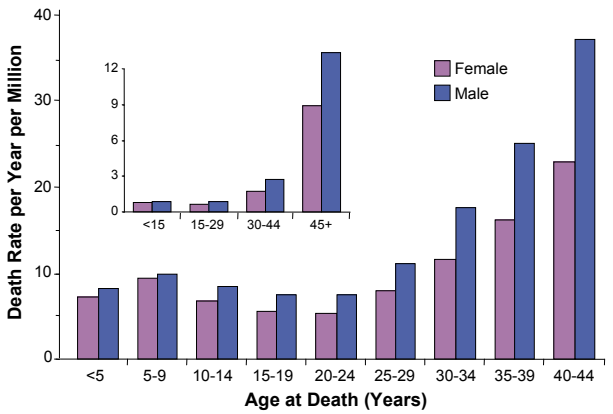

Figure 6.12: National Mortality for CNS Tumors by Gender, 1975-1999

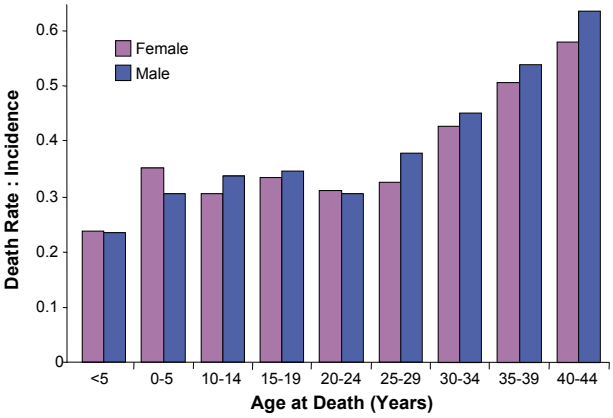

Figure 6.13: Ratio of National Mortality to SEER Incidence for CNS Tumors by Gender, 1975-1999

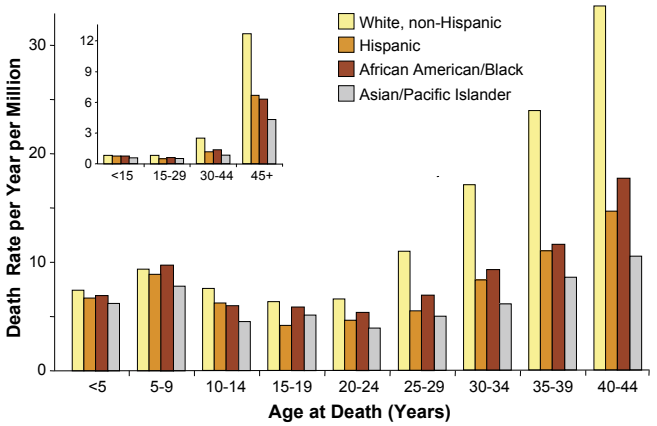

Figure 6.14: National Mortality for CNS Tumors by Race/Ethnicity, 1990-1999

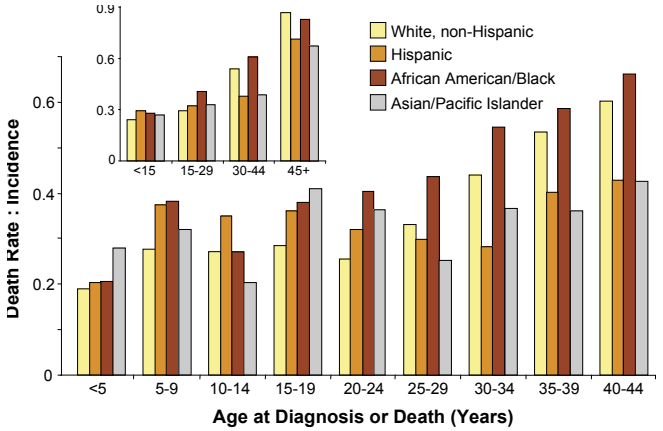

Figure 6.15: Ratio of National Mortality to SEER Incidence for CNS Tumors, 1990-1999

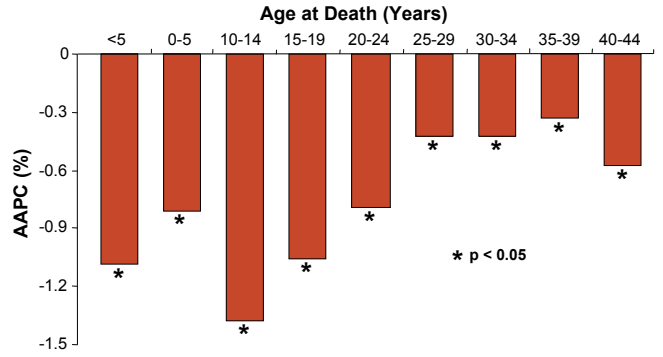

Figure 6.16: Average Annual Percent Change (AAPC) in National Mortality for CNS Tumors, 1975-1999

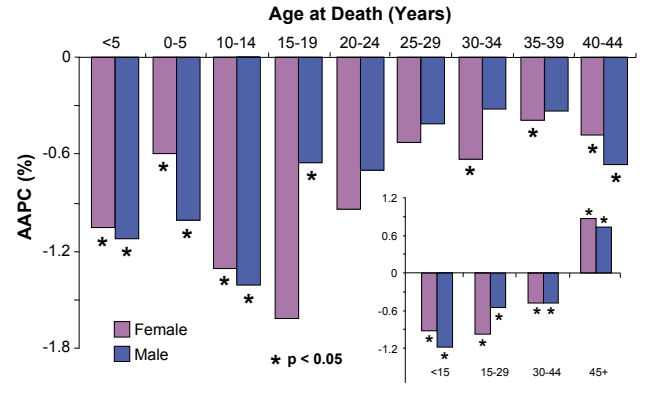

Figure 6.17: Average Annual Percent Change (AAPC) in National Mortality for CNS Tumors by Gender, 1975-1999

Racial/Ethnic Differences in Mortality

Figure 6.14 presents mortality data for CNS tumors according to race/ethnicity and age at death. The death rate was fairly similar across all racial/ethnic groups for 0- to 29-year-olds, but increased for those older than 30 years. The ratio of mortality to incidence by race/ethnicity was slightly higher for 15- to 29-year-olds than for 0- to 14-year-olds, but lower than in those over 30 years of age (Figure 6.15). AfricanAmericans/blacks had the highest ratio of mortality to incidence in the 15- to 29-year-old group compared to the other reported racial/ethnic groups, a pattern that continued through age 44. With advancing age, the ratio of mortality to incidence steadily increased, particularly in white non-Hispanic and African American/black individuals. These data suggest that older individuals, especially white non-Hispanics and African Americans/blacks, are more likely to die of their CNS tumor than younger patients or older Hispanic or Asian/Pacific Islander individuals.

Trends in Mortality

A minimal improvement in mortality was observed over the period 1975 to 1999. Figure 6.16 displays a small but significant decrease in the death rate for all age groups, with the greatest improvement seen in individuals younger than 24 years of age. The improvement in mortality was greater in females than males in the adolescent and young adult age group, particularly for 15- to 19-year-olds (Figure 6.17).

Survival

Survival after the diagnosis of a CNS neoplasm has improved, due in part to advances in diagnostic techniques and histologic classification of tumors, improvement in neurosurgical and radiation oncology techniques, and the utilization of new single and combination chemotherapeutic agents. Unfortunately, improvement in survival and durable remissions has been slower in CNS neoplasms compared to other cancers, especially leukemias and lymphomas. Long-term survivors of CNS tumors often suffer significant long-term sequelae such as hormonal deficiencies, intellectual decline and physical handicaps. These late effects compromise quality of life.

Survival data were collected between 1975 and 1998 and classified by the ICCC, thus allowing analysis across broad

histological subtypes. Racial/ethnic data were analyzed from 1990 to 1999. The 15-year survival progressively declined with advancing age at diagnosis for those older than 20 years of age (Figure 6.18). The 15-year survival for patients younger than 20 years of age exceeded 50%, but was approximately 20% for those 40 years of age and older.

For 15- to 29-year-olds, the 5-year survival rates were not significantly different among the four different racial/ethnic groups, and ranged from 64-72% (Figure 6.19).

Trends in Survival

A slow but steady improvement has been observed in 5- and 10-year survival rates (Figures 6.20 and 6.21). Individuals 15 to 29 years of age diagnosed with a CNS tumor in the period 1993 to 1997 had a 5-year survival rate near 70% and a 10-year survival rate of 55%. Although the 5-year survival rate was nearly identical to the rate for those younger than 15 years of age, the 10-year survival rate declined compared to younger patients. When observing the AAPC in survival for all CNS tumors, 15- to 34-year-olds had less improvement in survival compared to older and younger patients (excluding infants) (Figure 6.22). This observation reinforces the need to target this age group for clinical trials. Males older than 20 years of age had an improved AAPC in survival when compared to females (Figure 6.23).

Survival - Astrocytoma

Individuals diagnosed with astrocytoma between 15 and 19 years of age had 20-year survival rates in excess of 65% (Figure 6.24). However, there was a dramatic difference in survival for those diagnosed between 20 to 24 years (40%) and those diagnosed between 25 to 29 years of age (24%). "Astrocytomas," according to the SEER classification, include both low-grade and high-grade astrocytomas. Children and adolescents are more likely to have low-grade astrocytomas—accounting for the better survival rates— whereas adults are more likely to have high-grade astrocytomas or low-grade astrocytomas that undergo malignant transformation over time. During the period 1975 to 1998, there was a steady improvement in 5-year survival rates for "astrocytoma" (Figures 6.25 and 6.26). Improvement in survival rates was seen for all age groups except 20- to 24-year-olds. The improvement in survival was greatest for older individuals (Figure 6.26),

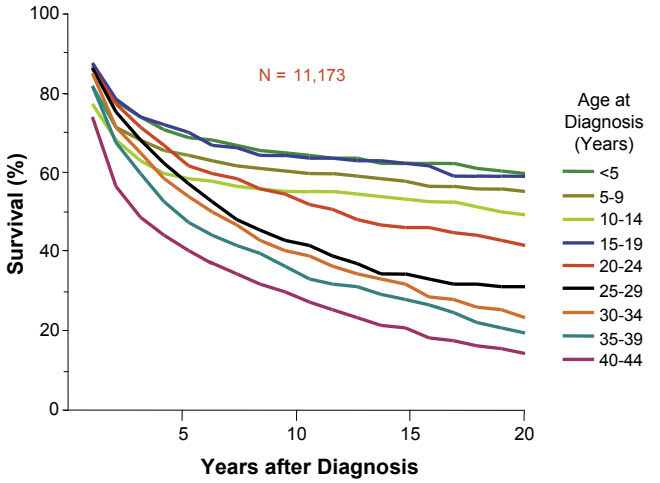

Figure **6.18:** Survival Rates for All CNS Tumors by Age, SEER 1975-1998

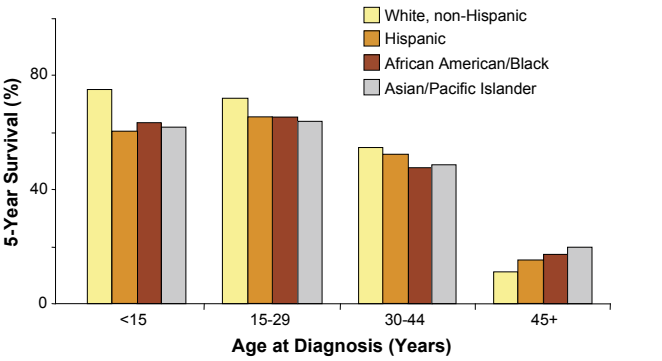

Figure 6.19: 5-Year Survival Rate for CNS Tumors by Race/Ethnicity, SEER 1991-1998

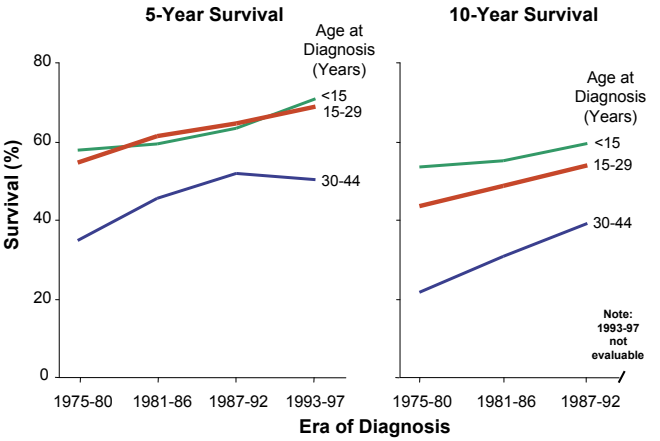

Figure 6.20: Survival Rate versus Era of Diagnosis for All CNS Tumors

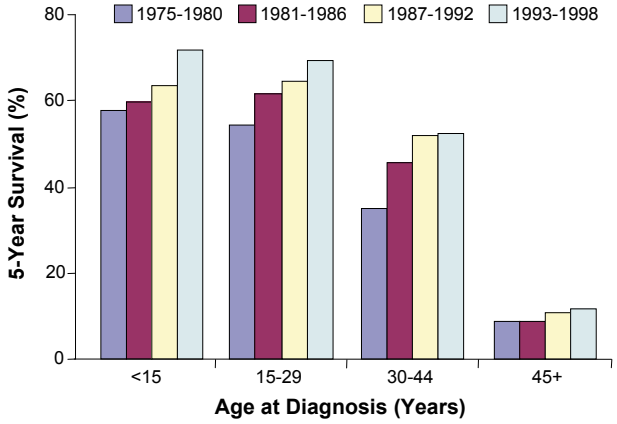

Figure 6.21: 5-Year Survival Rate for All CNS Tumors by Age and Era, SEER 1975-1998

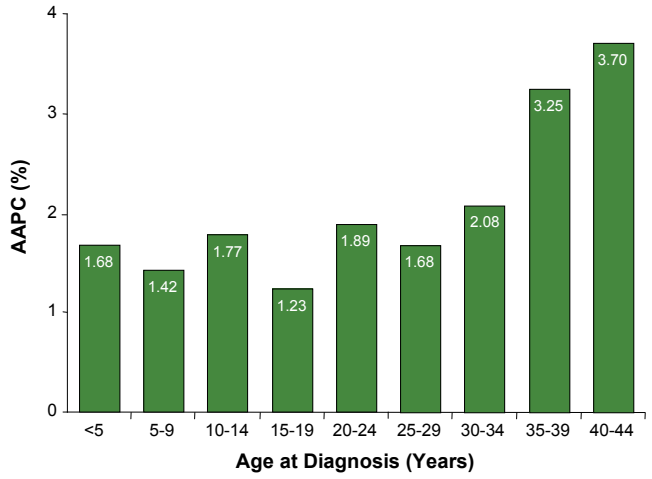

Figure 6.22: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for All CNS Tumors, SEER 1975-1998

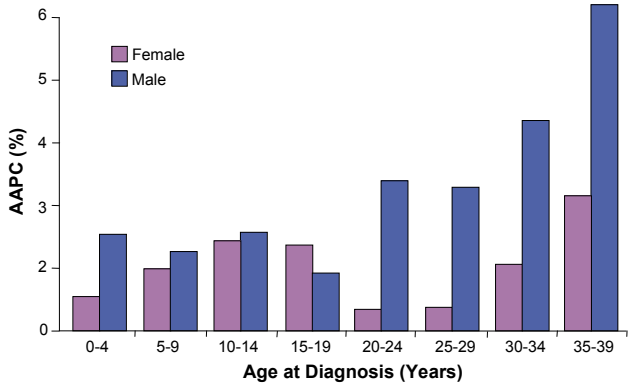

Figure 6.23: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for All CNS Tumors by Gender, SEER 1975-1998

suggesting that true progress is due to advances in the treatment of high-grade astrocytomas. This improvement may be due to the recent addition of temozolomide to the treatment regimen for adults with high-grade astrocytoma. It is unclear why 20- to 24-year-olds had a decline in 5-year survival rates over time.

Survival – Other Gliomas

"Other gliomas" are defined as malignant glioma-not otherwise specified (NOS), mixed glioma, oligodendroglioma-NOS, anaplastic oligodendroglioma, oligodendroblastoma, and other uncommon gliomas, as listed in Table 6.2. As seen in Figure 6.27, 15- to 29-year-olds had the highest survival rates when compared to other age groups, with a 20-year survival rate near 50%. The survival curves for individuals with "other gliomas" have not yet demonstrated a plateau. The continuous decline in all the curves suggests that a "cure level" has not been achieved for any of the age groups. Improvement in survival for "other gliomas" between 1975 and 1998 has occurred in all age groups, although little progress has been made since 1992 (Figure 6.28). Survival improvement was most apparent in the 20- to 24-year age group (Figure 6.29). The improvement in survival over time correlates somewhat but not completely with the first reports—in the late 1980s—of the unique sensitivity of anaplastic oligodendrogliomas to chemotherapy.

Survival - PNET

Five-year survival rates for PNET are displayed in Figure 6.30. Individuals 15 to 29 years of age had superior

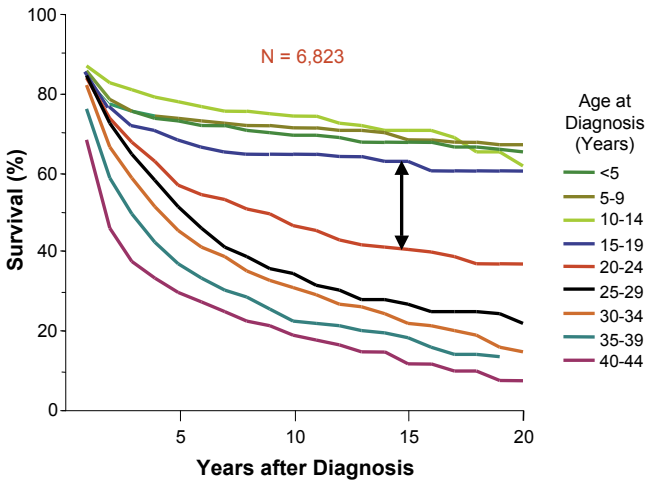

Figure 6.24: Survival Rates for Astrocytoma by Age, SEER 1975-1998

survival rates compared to those 30 to 44 years of age, with a 20-year survival rate of 40-45% compared to that of 25% for older age groups (Figure 6.31). Despite these encouraging results for adolescents and young adults diagnosed with a PNET, no improvement has been seen in this age group since the 1980s. In contrast, a slow, steady rate of improvement in survival has been observed in children (Figure 6.30), most likely due to the use of chemotherapy.

Survival - Ependymoma

Survival at 20 years for 15- to 29-year-olds with ependymoma was 65% (Figure 6.32). Individuals 15 to 44 years of age had the best chance of survival when compared to younger or older patients. The worst survival rates occurred among those younger than 15 years of age. Five-year survival rates for those younger than 1, 1 to 4, 5 to 9 and 10 to 14 years of age were 25%, 46%, 71% and 76%, respectively.[2] Thus, patients with ependymoma diagnosed between ages 5 and 44 years had a survival rate near 70%. The poorer survival in children younger than 5 years of age is likely related to factors such as the frequent posterior fossa tumor location in this age group, which makes total surgical resection more difficult, and the concern regarding administration of adequate doses of radiation therapy to this young age group. It is unclear why individuals diagnosed with ependymoma when older than 44 years of age have such poor survival rates. Although the survival is poorest for the age groups younger than 15 years and older than 44 years, both of these groups have made the greatest improvement in survival over time

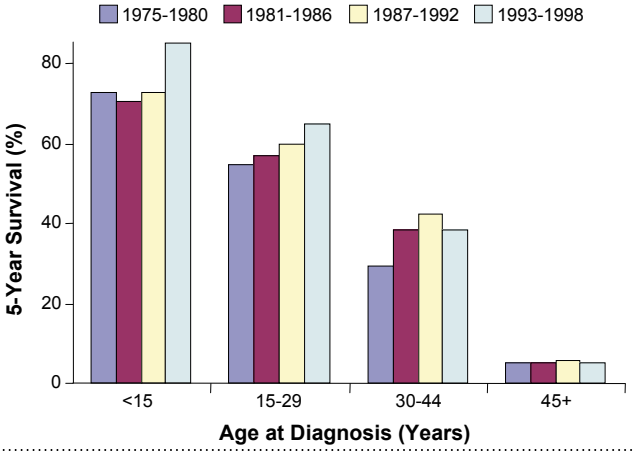

Figure 6.25: 5-Year Survival Rate for III(b) Astrocytomas by Age and Era, SEER

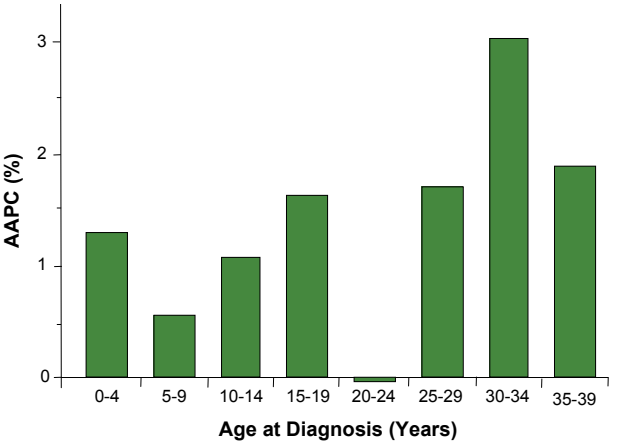

Figure 6.26: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Astrocytomas, SEER 1984-1998

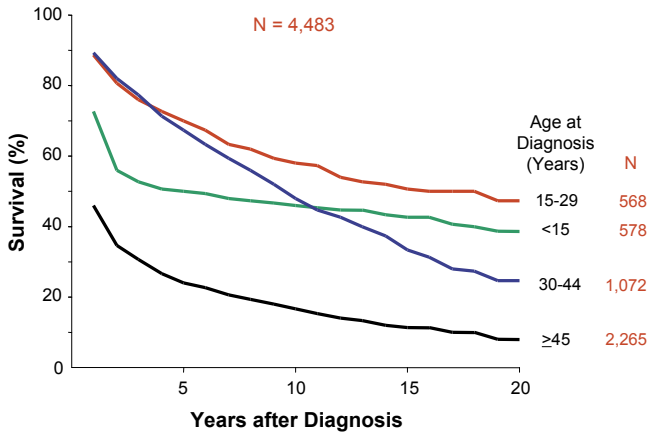

Figure 6.27: Survival Rates for Other Gliomas by Age, SEER 1975-1998

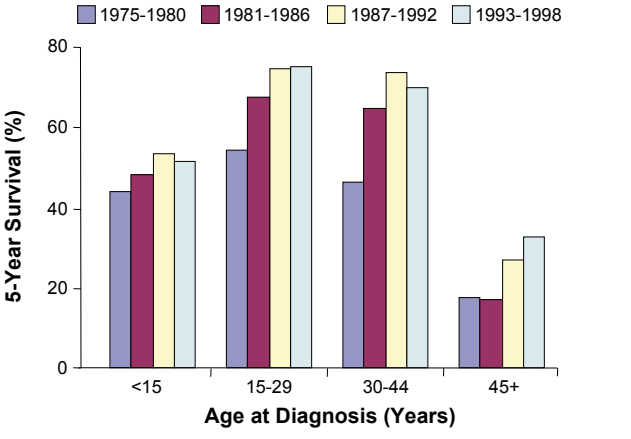

Figure 6.28: 5-Year Survival Rate for III(d) Other Gliomas by Age and Era, SEER 1975-1998

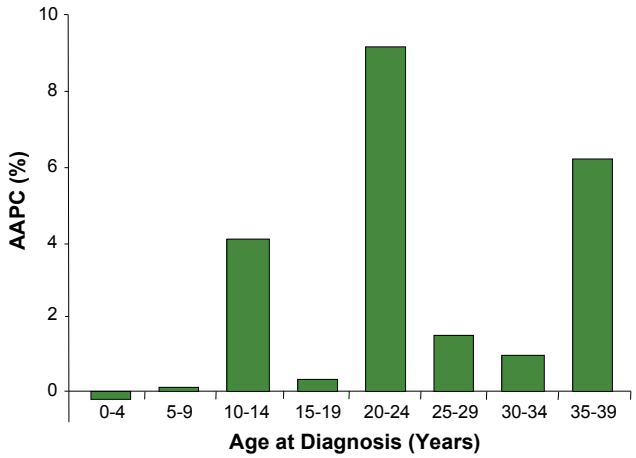

Figure 6.29: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Other Gliomas, SEER 1984-1998

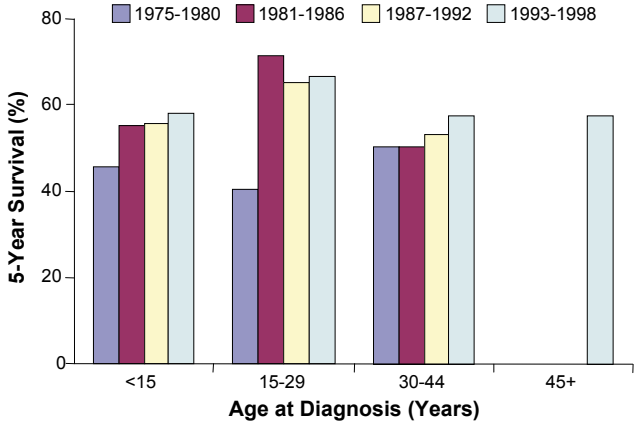

Figure 6.30: 5-Year Survival Rate for III(c) PNET by Age and Era, SEER 1975-1998

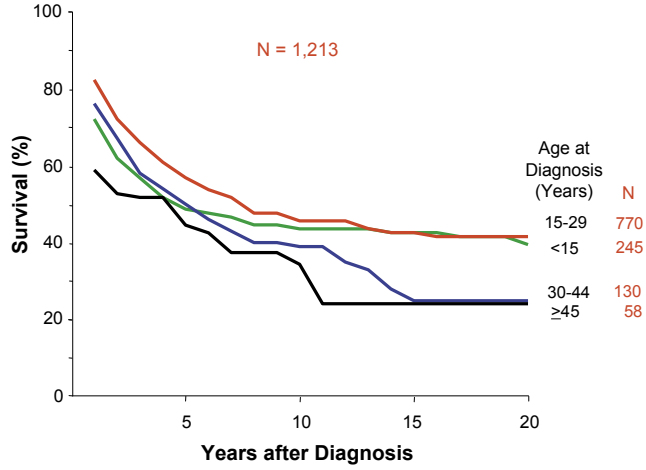

Figure 6.31: Survival Rates for PNET by Age, SEER 1975-1998

(Figures 6.33 and 6.34). Adolescents and young adults 15 to 34 years of age had the poorest improvement in survival over the time period 1984 to 1998, again indicating the need for clinical trials targeted towards this age group.

RISK FACTORS

The only known risk factors for the development of brain tumors at any age are the inheritance of several rare syndromes and previous exposure of the brain to ionizing radiation.[3] However, these factors contribute to a minority of adolescent and young adult CNS neoplasms. Despite many institutional and national cooperative group epidemiological studies, no specific risk factor or set of risk factors has been elucidated in the majority of CNS tumors.

Several inherited syndromes are associated with CNS tumors. Table 6.3 summarizes these syndromes, the related CNS tumors, and the chromosome and gene locations. Each of these syndromes has an inherited mutation in a tumor suppressor gene resulting in an increased incidence of specific types of brain tumors. Although these inherited conditions are rare and account for less than 5 percent of brain tumors, they provide translational tools to investigate the role of specific tumor suppressor genes in the genesis of different types of brain tumors.

The only environmental factor known to cause brain tumors is ionizing radiation. Therefore, individuals of any age who receive radiation therapy to the brain

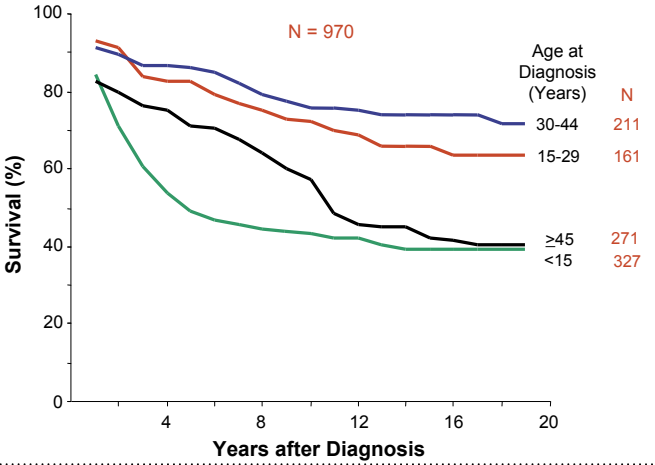

Figure 6.32: Survival Rates for Ependymoma by Age, SEER 1975-1998

for treatment of leukemia, brain tumors or other solid tumors of the head are at an increased risk for secondary CNS neoplasms. The most common secondary CNS neoplasms are gliomas and meningiomas.

The identification of risk factors for the development of brain tumors in adolescents and young adults is confounded by the fact that brain tumors are composed of multiple histologies. Each histological subtype likely has a different mechanism of tumorigenesis and therefore different risk factors. It is difficult to accrue sufficient numbers of patients to test hypotheses about specific histological subtypes of brain tumors. Very few epidemiological studies have been undertaken, and virtually none have incorporated molecular techniques for defining tumor types. Based on current knowledge, there are no immediate preventive measures for the development of adolescent and young adult CNS tumors. Future epidemiological studies may shed more light on the causes of these often debilitating and fatal neoplasms.

SUMMARY

Cancer of the CNS accounted for 6% of all neoplasms in adolescents and young adults 15 to 29 years of age, and was the 7th leading cause of cancer in this age group. The U.S. overall annual incidence of CNS tumors in this age group (approximately 22.6 per million)

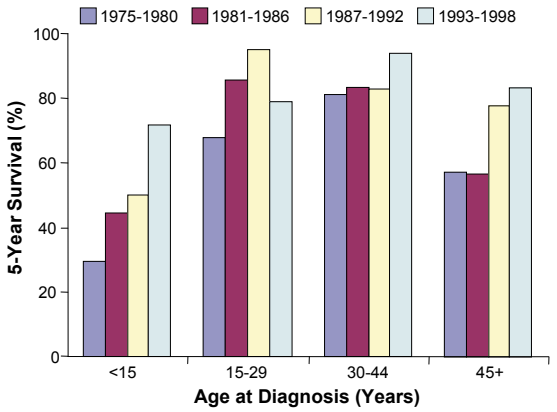

Figure 6.33: 5-Year Survival Rate for III(a) Ependymoma by Age and Era, SEER 1975-1998

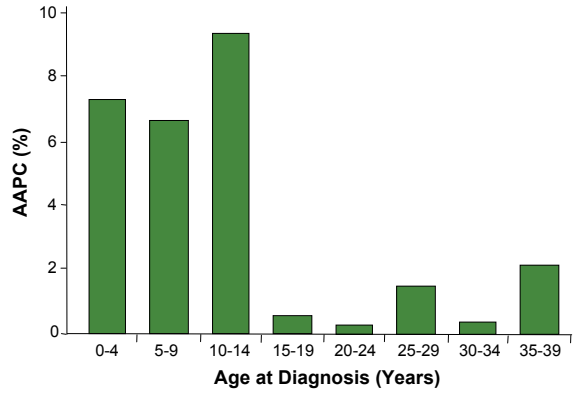

Figure 6.34: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Ependymoma, SEER 1984-1998

Table 6.3: *Inherited Syndromes Associated with CNS Tumors*[3]

SYNDROME	CNS TUMOR	CHROMOSOME LOCATION
Neurofibromatosis Type I	Glioma, Meningioma	17q12-22
Neurofibromatosis Type II	Acoustic neuroma, Schwannoma, Ependymoma, Glioma, Meningioma	22q12
Tuberous Sclerosis Type I and Type II	Subependymal Giant Cell Astrocytoma, Ependymoma, Glioma, Hamaratoma	9q32-34 (Type I) 16p13.3(Type II)
Von Hippel-Lindau syndrome	Cerebellar hemangioblastoma, Glioma	3p25-26
Li-Fraumeni Syndrome	Glioma, Medulloblastoma	17p13 (p53 mutation)
Nevoid Basal Cell Carcinoma syndrome (Gorlin's syndrome)	Medulloblastoma	1q22
Turcot's Syndrome	Medulloblastoma, Glioma	5q21-22
Hereditary Atypical Teratoid/Rhabdoid tumors	Atypical Teratoid/Rhabdoid tumors	22q11.2(INI-1 gene)
Hereditary Retinoblastoma	Pineoblastoma	13q14
Multiple Endocrine Neoplasia I (MEN-I)	Pituitary Adenomas, Ependymoma	11q13

was lower than that of any other age group. Approximately 1,500 individuals between 15 and 29 years of age were diagnosed in the year 2000 with a CNS neoplasm. Males (pediatric through adult ages) had a higher incidence of CNS tumors; the male:female incidence ratio for CNS tumors in the adolescent and young adult age group averaged 1.32. White non-Hispanics had a slightly increased incidence of CNS tumors in this age group compared to African American/black, Hispanic, and Asian/Pacific Islander groups. The distribution of specific types of brain tumors in individuals 15 to 29 years of age differed from that of children younger than 15 years of age and from adults older than 29 years of age. The incidence of astrocytomas increased, while incidence of PNETs and ependymomas decreased with advancing age. Adolescents and young adults, as well as adults up to age 44 years, had an increased annual incidence of "other gliomas". The etiology of this trend may be related to better technology in diagnosing and classifying glial tumors.

National mortality for individuals 15 to 29 years of age showed little variation across racial/ethnic groups and was similar to that of children 0 to 14 years of age. Mortality rose with increasing age. In the 15- to 29-year age group, mortality was higher for males than females and was higher for white non-Hispanic individuals compared to individuals of other races/ethnicities. Mortality improved over the years for all groups younger than 45 years.

Survival of patients with CNS tumors progressively declined as a function of age at diagnosis in individuals over 20 years of age. The overall 10-year survival for all CNS tumors in the adolescent and young adult age group paralleled the survival curves for astrocytoma. The 10-year survival rate for 15- to 29-year-olds with "other gliomas" was 50%, 70% for PNETs, and 65% for ependymomas. The 5- and 10-year survival curves for all CNS tumors have improved with time in the 15- to 29-year age group, but none of the individual age groups or major types of tumors have reached a plateau. This suggests that a "cure level" has not been achieved for most of the CNS neoplasms. Adolescents and young adults 15 to 34 years of age had the poorest improvement in survival over the time period 1984 to 1998, suggesting that this age group should be targeted for clinical trials.

Unfortunately, the causes of CNS neoplasms remain unknown. The only two definitive risk factors for CNS tumors are rare inherited conditions and previous exposure of the brain to ionizing radiation.

Acknowledgments:

Drs. Peter Burger and Bernd Scheithauer kindly reviewed the data regarding incidence and trends in incidence for the different histological subtypes and helped speculate about reasons for these trends.

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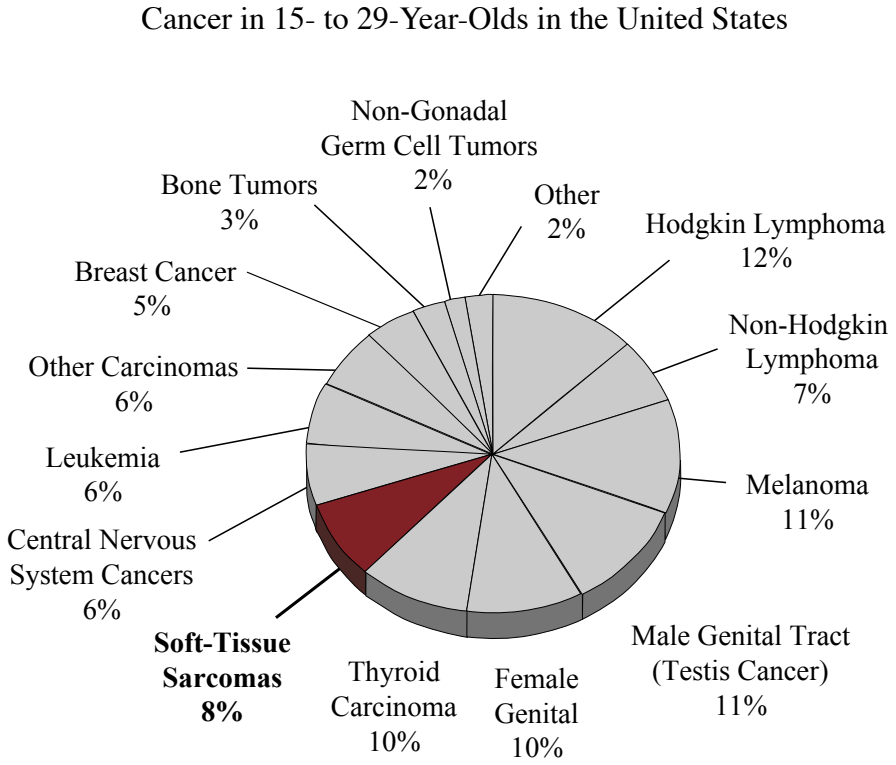
Chapter 7

Soft Tissue Sarcomas



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HIGHLIGHTS

Incidence

- Soft tissue sarcomas may occur at any age, but predominate in young adulthood. Over the period 1975 to 1999, the incidence of non-Kaposi soft tissue sarcoma increased exponentially in those older than 15 years of age.
- In the year 2000, approximately 1,700 Americans 15 to 29 years of age developed a non-Kaposi soft tissue sarcoma.
- In the 15- to 29-year age group there were far more histologic types of soft tissue sarcoma than in younger patients, with fibrosarcomas and related fibromatous entities constituting the largest histologic group.
- African Americans/blacks between the ages of 5 and 45 had a higher incidence of both non-Kaposi and Kaposi soft tissue sarcomas than any other racial/ethnic group.
- An epidemic of Kaposi sarcoma occurred in young adult males during the 1980s and early to mid-1990s as a result of the human immunodefciency virus (HIV) and the associated acquired immunodeficiency disorder syndrome (AIDS).
- At its peak incidence during the late 1980s and early 1990s, Kaposi sarcoma accounted for more cases of sarcoma in young adult males than any other type of sarcoma. Since 2000, Kaposi sarcoma has accounted for about 5% and < 0.5% of the soft tissue sarcomas in 15- to 29-year-old males and females, respectively.

Mortality & Survival

- In nearly all age categories, mortality for males with soft tissue sarcomas was higher than for females, with the exception of those in the 10- to 14-year age group, for whom survival was equal for both genders.
- Among those diagnosed during the past quarter century, 15- to 29-year-olds with non-Kaposi soft tissue sarcomas had the second highest survival rate, following that of those in the 30- to 44-year age bracket.
- Among those with rhabdomyosarcoma and embryonal sarcoma, 15- to 29-year-olds had both a lower survival rate and a less favorable survival improvement trend than children with these types of sarcoma.
- Racial/ethnic minority patients in the 15- to 29-year age group did not have, in general, an inferior outcome in survival for either non-Kaposi soft tissue sarcomas or Kaposi sarcoma; Asians/Pacific Islanders with Kaposi sarcoma who were diagnosed between 15 and 30 years of age were an exception.
- Kaposi sarcoma had the most dramatic increase in survival improvement among the major groups of soft tissue sarcomas, albeit it was still lower than for most types of soft tissue sarcomas.
- Those diagnosed with Kaposi sarcoma before age 30 had the worst survival and the least improvement in survival of all age groups.

Risk Factors

- Genetic disorders associated with an increased risk of soft tissue sarcomas are Li-Fraumeni Syndrome (LFS), von Recklinghausen's disease, and Beckwith-Wiedeman Syndrome (BWS).
- Environmental factors associated with an increased risk of rhabdomyosarcoma in children include fetal exposure to marijuana and cocaine use by the mother and/or father; it is unknown if this applies to those who develop rhabdomyosarcoma as adolescents and young adults.
- Survivors of soft tissue sarcomas, especially those who received multi-modal therapy, have a significantly increased risk for the development of second malignant neoplasms.

INTRODUCTION

Soft tissue sarcomas generally arise from malignant transformation of a mesenchymal cell of origin, which normally would mature into skeletal muscle, smooth muscle, fibrous tissue, adipose tissue, or cartilage. Current therapeutic options in the U.S. are based on

pathologic classification and other clinical and biologic characteristics, including chromosomal abnormalities.[1] This chapter will review SEER data for soft tissue sarcomas collectively as well as by specific pathologic type, by race/ethnicity, and by incidence, mortality, and survival from 1975 to 1999. Because the epidemic of Kaposi sarcoma in the U.S. occurred during the era that is the focus of this monograph, and predominantly affected young adult males, special sections on Kaposi sarcoma are presented in this chapter.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

Soft tissue sarcomas in the International Classification of Childhood Cancer (ICCC) is Category IX. Subcategory IX(a) is rhabdomyosarcoma and embryonal sarcoma, IX(b) is fibrosarcoma, neurofibrosarcoma, and fibromatous neoplasms, IX(c) is Kaposi sarcoma, IX(d) is all other specified soft tissue sarcomas, and IX(e) is other and unspecified soft tissue sarcomas.

The *Rhabdomyosarcoma and Embryonal* sarcoma category IX(a) is composed of ICD-O-2 categories 8900-8920 (various forms of rhabdomyosarcoma) and 8991 (embryonal sarcoma). Also included but not shown in ICCC is rhabdomyosarcoma with ganglionic differentiation (ICD-O-3 8921).

The *Fibrosarcoma, Neurofibroma, and Fibromatous Neoplasm* category IX(b) is comprised of fibrosarcoma (8810), malignant fibrous histocytoma (8830), fibromyxoma and fibromyxosarcoma (8811), fascial fibrosarcoma (8813), malignant solitary fibrous tumor (8815), infantile fibrosarcoma (8814), dermatofibrosarcoma (8832), pigmented dermatofibrosarcoma protuberans (8833), and malignant peripheral nerve sheath tumors (9540-9561). The *Kaposi Sarcoma* category IX(c) is a single category in the ICD-O-2: 9140.

The *Other Specified Sarcoma* category IX(d) is constituted by a variety of neoplasms: extraosseous Ewing sarcoma (category 9260); peripheral neuroectodermal tumor (9364); synovial-like neoplasms (e.g. synovial sarcoma) (9040-9044); giant cell tumor of soft parts (9251); alveolar soft-part sarcoma (9581); malignant rhabdoid sarcoma (8963); myoepithelioma (8982); mesenchymoma (8990); blood vessel neoplasms (e.g. hemangioendotheloiomas, hemangiopericytoma) (9120-9134, 9150-9161); lymphatic-like neoplasms (e.g. lymphangiosarcoma) (9170); non-osseous myxoid chondrosarcoma (9231); non-osseous mesenchymal chondrosarcoma (9240), myxomatous, myomatous and lipomatous neoplasms (8840-8896), myxosarcoma (8840), various liposarcomas (8850-8881), and various leiomyosarcomas and myosarcomas (8890-8896). Also included but not shown in ICCC are specific histologies from ICD-O-3: undifferentiated sarcoma (8805) and desmoplastic small round cell tumor (8806). Because the gastrointestinal stromal tumors are considered benignor of borderline malignancy, they are not included in the analysis.

The *Unspecified Sarcoma* category IX(d) is constituted by soft tissue sarcoma NOS , spindle cell sarcoma (8801), non-osseous giant cell sarcoma (8802), small cell sarcoma (8803), and epithelioid sarcoma (8804). The female genital tract sarcomas (e.g. uterine leiomyosarcomas) are included in the *Unspecified Sarcoma* category of ICCC. Stromal sarcoma NOS (8930, and in ICD-O-3: 8930, 8935) is included in ICCC XII(a)

As explained in the Methods chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

In attempting to apply the ICCC and SEER site recode to soft tissue sarcoma in 15- to 29-year-olds, it is apparent that the SEER site recode does not break down any of the specific sarcomas and the ICCC only uses sarcoma subgroups which would be seen among young children. Specific sarcomas which would be rare or non-existent among young children, such as leiomyosarcoma of the female genital tract, may be important for the 15- to 29-year-olds but are not shown separately in ICCC. A soft tissue sarcoma classification specific to this age group is needed.

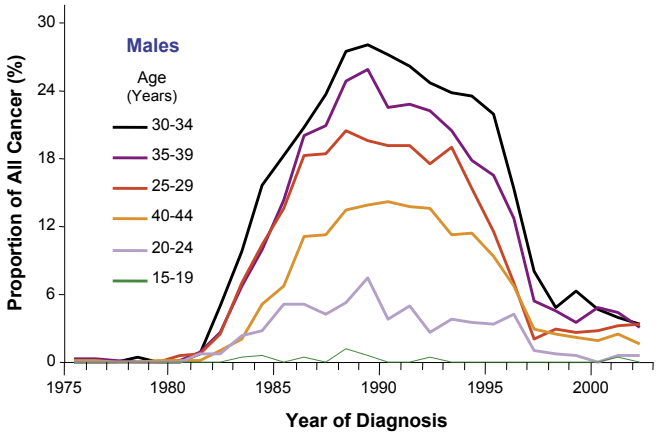

Figure 7.1: Proportion of All Invasive Cancer that was Kaposi Sarcoma, by Age, **Males**, SEER 1975-2002

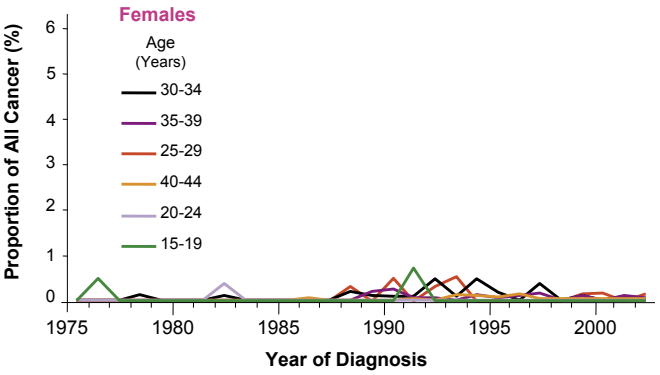

Figure 7.2: Proportion of All Invasive Cancer that was Kaposi Sarcoma, by Age, **Females**, SEER 1975-2002

INCIDENCE OF KAPOSI SARCOMA

In the U.S, the human immunodeficiency virus (HIV) epidemic of the 1980s led to an epidemic of AIDS-related Kaposi sarcoma in young adults males that peaked during 1986 to 1995 and subsided by the end of the 1990s (Figures 7.1 and 7.2).[2-4] In certain parts of the U.S, the increased incidence of Kaposi sarcoma in the early 1980s heralded the epidemic of HIV.[5] The age group most affected was 20- to 49-year-olds, with a peak in 30- to 34-year-olds, but cases in 15- to 19-year-olds were also reported. A few other cancers also increased during this interval, especially non-Hodgkin lymphoma (cf. *Introduction and Lymphoma* chapters), but no other cancer had as great an impact on the overall incidence of cancer in young adults.

The percent of all invasive cancers that was Kaposi sarcoma was as high as one in every four cancers in males who were 35 to 39 years of age (Figure 7.1). In 15- to 29-year-old males, the proportion peaked at 12%, and among 25- to 29-year-olds it peaked at 18%. Hence, Kaposi sarcoma had a profound effect on the incidence of cancer in young adult males up to end of the 1990s. This chapter therefore reviews soft tissue sarcomas during the era 1975 to 2000 era with and without Kaposi sarcoma.

INCIDENCE

Age-specific incidence

The incidence of both Kaposi sarcoma and the non-Kaposi soft tissue sarcomas were highly age-dependent.

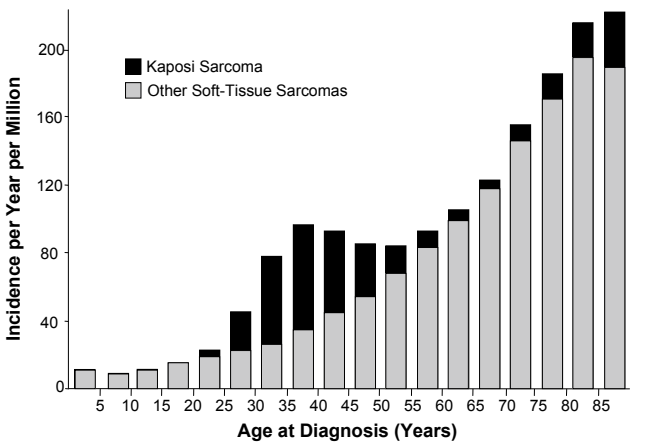

Figure 7.3: Incidence of All Soft Tissue Sarcomas, SEER 1975-2000

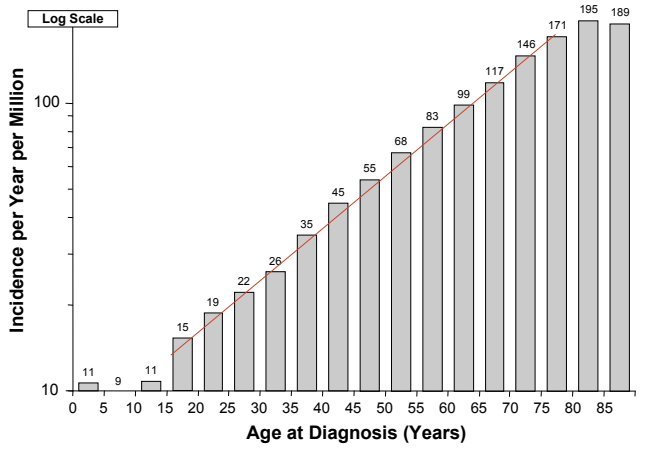

Figure 7.4: Incidence of Non-Kaposi Soft Tissue Sarcomas, SEER 1975-2000

Table 7.1: *Incidence of Soft Tissue Sarcomas in Persons Younger than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
ALL SOFT TISSUE SARCOMAS EXCLUDING KAPOSI						
Average incidence per million, 1975-2000, SEER	8.4	6.4	6.4	9.3	14.4	38.5
Average annual % change in incidence, 1975-2000, SEER	-0.4%	-0.5%	1.4%	-0.8%	2.4%	12.9%
Estimated incidence per million, year 2000, U.S.	8.2	6.2	7.3	8.2	17.9	62.3
Estimated number of persons diagnosed, year 2000, U.S.	156	127	150	165	339	1,207
FIROSARCOMA, NEUROFIBROSARCOMA, OTHER FIBROMATOSIS MALIGANCIES*						
Average incidence per million, 1975-2000, SEER	1.9	1.4	3.4	5.5	8.6	11.3
Average annual % change in incidence, 1975-2000, SEER	5.8%	9.1%	0.1%	-1.6%	0.5%	1.3%
Estimated incidence per million, year 2000 , U.S.	2.2	1.3	3.4	4.1	9.2	12.8
Estimated number of persons diagnosed, year 2000, U.S.	42	27	70	83	174	248
RHABDOMYOSARCOMA**						
Average incidence per million, 1975-2000, SEER	6.5	4.9	3.0	3.5	1.6	0.8
Average annual % change in incidence, 1975-2000, SEER	1.1%	-0.3%	3.6%	0.9%	-2.8%	^
Estimated incidence per million, year 2000, U.S.	7.3	4.7	3.8	3.9	0.5	^
Estimated number of persons diagnosed, year 2000, U.S.	140	96	78	79	10	^
KAPOSI SARCOMA***						
Average incidence per million, 1975-2000, SEER	0	0	0	0.2	4.0	25.2
Estimated incidence per million, year 2000, U.S.	0	0	0	0.1	0.9	7.5
Estimated number of persons diagnosed, year 2000, U.S.	0	0	0	^	17	145

***ICCC IX(b) **ICCC IX(a) ***ICCC IX(d) ^Too few for reliable estimate**

Whereas Kaposi sarcoma had a peak incidence in young adults during the era 1975 to 2000, the other soft tissue sarcomas did not (Figure 7.3). Between peaks in early childhood and in elderly persons, the incidence of non-Kaposi soft tissue sarcomas increased exponentially from 15 to 75 years of age (Figure 7.4).

From 1975 through 1999, the incidence of soft tissue sarcomas—excluding Kaposi sarcoma—dramatically increased among 15- to 29-year-olds as a function of age, from 9.3 per year per million among 15- to 19-year-olds to 38.5 per year per million 25- to 29-year-olds (Figure 7.5). The age-dependent incidence continued to increase until a peak among 35- to 39-year-olds and then declined among older persons (Figure 7.3). More than 40% of the non-Kaposi soft tissue sarcoma cases occurred in 25- to 29-year-olds.

During the period 1975 to 1999, non-Kaposi soft tissue sarcomas comprised approximately 4-7% of all invasive cancer in the 15- to 29-year age group (Figure 7.5 inset). Excluding Kaposi sarcoma, soft tissue sarcomas peaked as a proportion of all cancer between 25 and 35 years of age, with a maximum of 9% occurring in 30- to 34-year-olds (Figure 7.5).

By the year 2000, when the Kaposi sarcoma epidemic had all but subsided (Figure 7.1), the total number of soft tissue sarcomas diagnosed in the U.S. in 15- to 29-year-olds was approximately 1,875, based on incidence trends over the prior 25 years and on age- and year-specific population (Table 7.1). About 1,700 15- to 29-year-olds were diagnosed in the year 2000 with non-Kaposi soft tissue sarcoma and 160 persons in the age group had Kaposi sarcoma. Approximately 165 of these cases were observed in 15- to 19-year olds, 360 in 20- to 24-year olds, and 1,350 in the 25- to 29-year age group (Table 7.1). The ICCC group of fibrosarcomas and related fibromatous entities constituted the largest histologic group of sarcomas

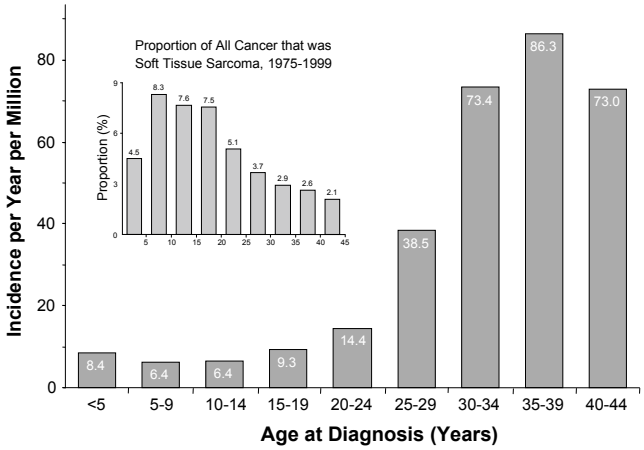

Figure 7.5: Incidence of Soft Tissue Sarcomas excluding Kaposi Sarcoma, SEER 1975-1999

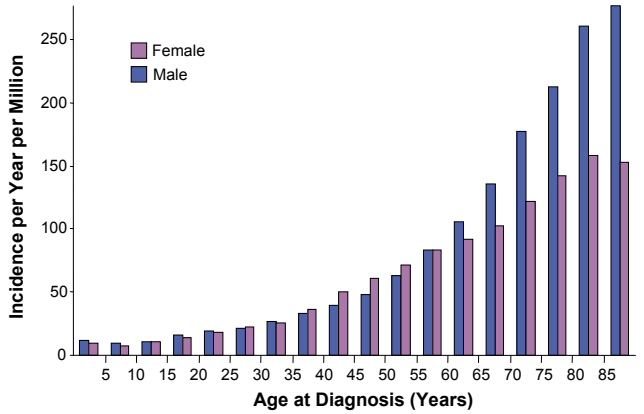

Figure 7.6: Incidence of Non-Kaposi Soft Tissue Sarcomas by Gender, SEER 1975-2000

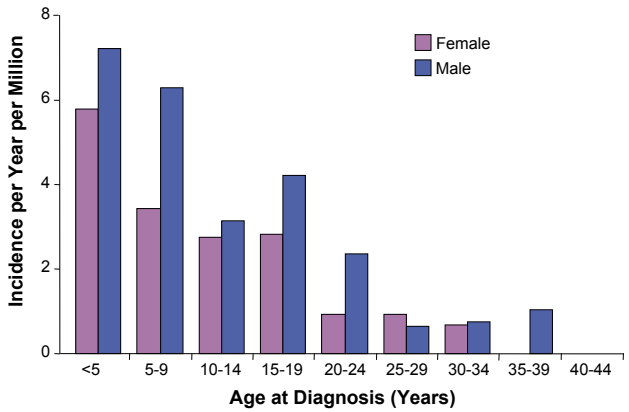

Figure 7.7: Incidence of Rhabdomyosarcoma by Gender, SEER 1975-1999

among 15- to 29-year-olds, accounting for 30% of non-Kaposi soft tissue sarcomas in the year 2000 (Table 7.1).

Histology-specific incidence

One contrast between sarcomas in the 15- to 29-year age group in comparison to those that occurred before age 15 was the much larger variety of histologic types. From 1992 to 2002, during which the Kaposi sarcoma epidemic subsided, there were a dozen histologic types accounting for 1% to 15% of the soft tissue sarcomas (Table 7.2). Rhabdomyosarcoma and other embryonal sarcomas, derived from mesenchymal cells of striated muscle origin,[6] predominated in those younger than age 15. Many connective tissues cells of non-muscle-origin contributed to the sarcomas that arose in 15- to 29-year-olds, including those of fibrous, neuroectodermal, vascular, adiopose, cartilage and synovial origin.

Gender-specific incidence

Except during middle age (35 to 55 years), males had a higher incidence of non-Kaposi soft tissue sarcoma (Figure 7.6). The male predominance was small among children, adolescents and young adults, but much greater, nearly two-fold, among older adults. Although uterine leiomyosarcomas and other genital tract sarcomas were included among the female sarcomas, they accounted for few of the sarcomas that occurred between 15 and 30 years of age.

In almost all age categories, males had a higher incidence of rhabdomyosarcoma when gender-specific incidence

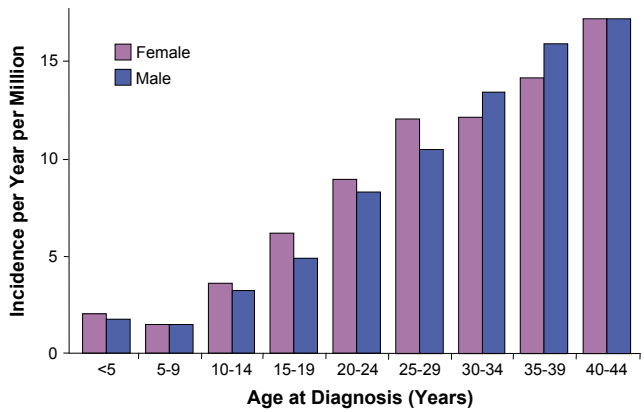

Figure 7.8: Incidence of Fibrosarcoma, Neurofibrosarcoma, and Other Fibromatous Neoplasms by Gender, SEER 1975-1999

patterns were calculated. Only in the 25- to 29-year age group was incidence in females greater than that in males (Figure 7.7). The pattern of higher incidence rates for males did not, however, persist for fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms (Figure 7.8).

In 15- to 29-year-olds, the majority of soft tissue sarcomas occurred in the trunk, head/neck and extremities (Figure 7.9). The order of frequency by anatomic location was trunk, leg, head, neck and arm/shoulder. The anatomic distribution was remarkably similar in males and females, even when uterine and other female genital tract sarcomas were included.

Racial/Ethnic Differences in Incidence

African Americans/blacks from age 10 to 45 had a higher incidence of non-Kaposi soft tissue sarcomas than any other racial/ethnic group (Figure 7.10). [They also had a higher incidence of Kaposi sarcoma]. Non-Hispanic whites, Hispanics, Asians/Pacific Islanders and American Indians/Alaska Natives generally followed in incidence. American Indians/Alaska Natives 20 years of age and older had one-half the incidence, on average, of African Americans/blacks.

Histology-Specific Incidence by Race/Ethnicity

African Americans/blacks had the highest incidence of rhabdomyosarcoma and embryonal sarcomas in the 15- to 29-year age group and Asians/Pacific Islanders had the

Table 7.2: *Soft Tissue Sarcomas by Histologic Type in 15- to 29-Year-Olds, 1992-2002*

HISTOLOGIC TYPE	% OF TOTAL
Kaposi Sarcoma	35.3%
Dermatofibrosarcoma, including protuberans	14.9%
Leiomyosarcoma, Fibrosarcoma	6.3%
Rhabdomyosarcoma	6.5%
Synovial Cell Sarcoma	6.0%
Ewing Sarcoma / PNET	4.8%
Malignant Fibrous Histiocytoma	4.3%
Liposarcoma	4.3%
Malignant Peripheral Nerve Sheath Tumor	3.8%
Angiomatous / Vascular Sarcomas	2.3%
Spindle Cell Sarcoma	1.5%
Epithelioid Sarcoma	1.4%
Alveolar Soft Part Sarcoma	1.2%
Clear Cell Sarcoma	1.0%
Small Cell Sarcoma	0.6%
Chondrosarcoma (Soft Tissue)	0.5%
Giant Cell Sarcoma	0.4%
Desmoplastic Small Round Cell Tumor	0.4%
Miscellaneous	4.5%
Total Number	**2812**

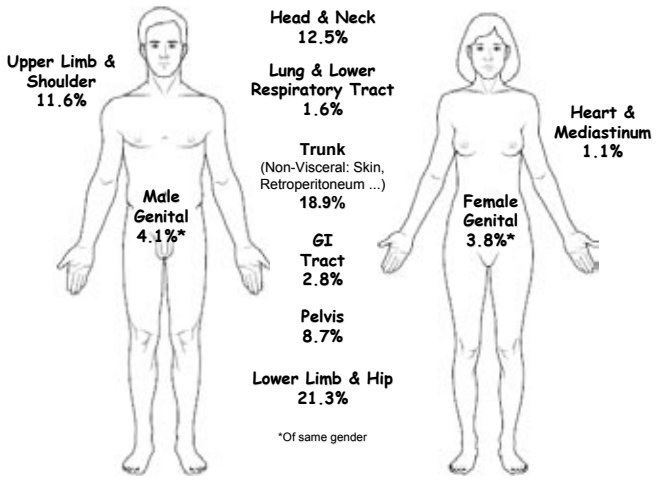

Figure 7.9: Percentage of Soft Tissue Sarcomas by Location for Age 15 to 29, SEER 1992-2002. Drawings by Medscape

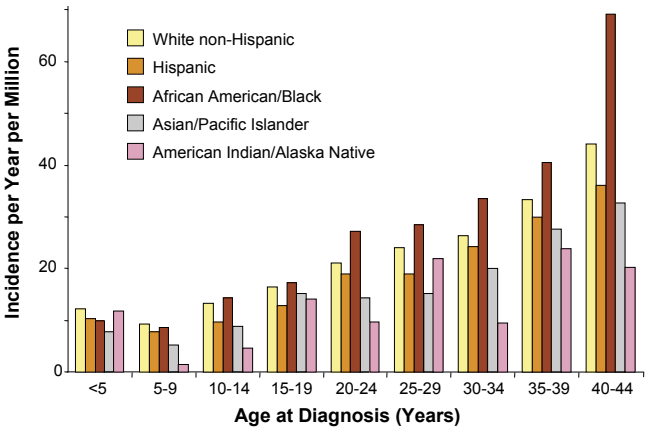

Figure 7.10: Incidence of Non-Kaposi Soft Tissue Sarcomas by Race/Ethnicity, SEER 1992-2002

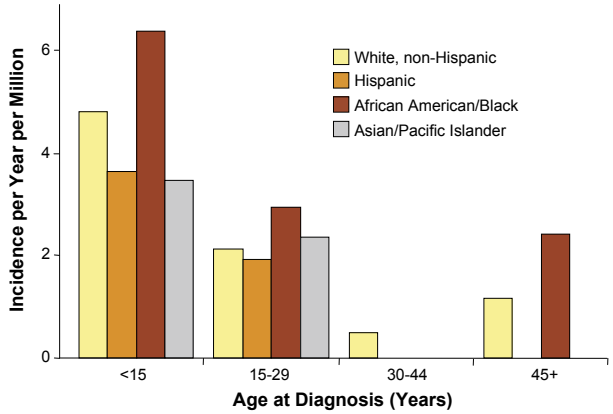

Figure 7.11: Incidence of Rhabdomyosarcoma and Embryonal Sarcoma by Race/Ethnicity, SEER 1990-1999

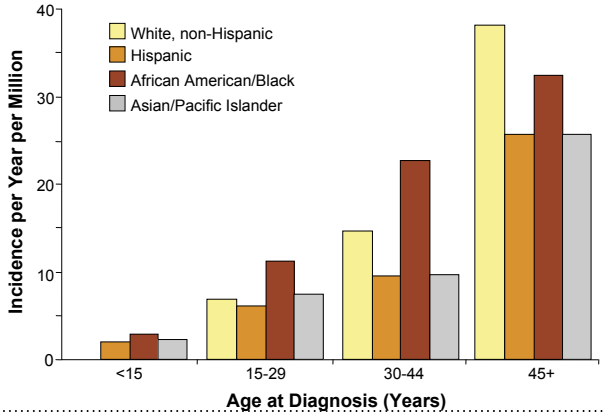

Figure 7.12: Incidence of Fibrosarcoma, Neurofibrosarcoma, and Other Fibromatous Neoplasms by Race/Ethnicity, SEER 1990-1999

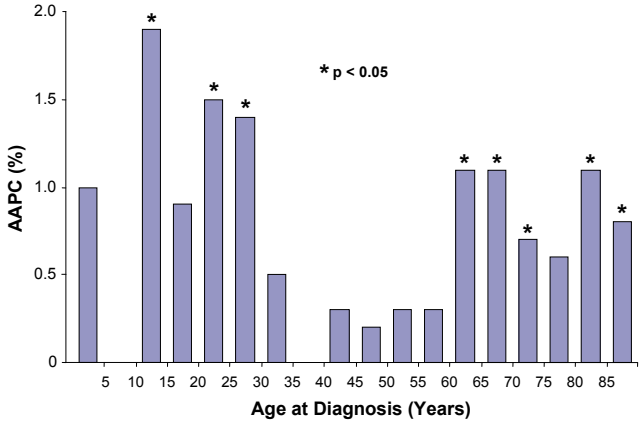

Figure 7.13: Average Annual Percent Change (AAPC) in Incidence of Non-Kaposi Soft Tissue Sarcoma, SEER 1975-2000

second highest incidence (Figure 7.10). White non-Hispanics and Hispanics had a similar incidence. Incidence of rhabdomyosarcoma and embryonal sarcoma was quite low in those 30 to 44 years of age; white non-Hispanics were the only group with enough cases to analyze (Figure 7.11). Interestingly, once over the age of 45, white non-Hispanics and African Americans had an incidence similar to, although lower than, these same groups at 15 to 29 years of age.

Variations in incidence when stratified by race/ethnicity in the adult population have also been reported. An analysis of SEER data from 1973 to 1998 for *primary upper-extremity* soft tissue sarcomas found that whites had a higher incidence when compared to African Americans/blacks.[7] A retrospective cohort analysis of children treated on the Intergroup Rhabdomyosarcoma Study Group protocols between 1984 and 1997 revealed that patients from ethnic minority groups presented with larger, more invasive tumors with positive lymph nodes.[8]

For fibrosarcoma, neurofibrosarcoma, and other fibromatous neoplasms, the incidence patterns by race/ethnicity were similar to those observed in aggregate for all soft tissue sarcomas. Specifically, African Americans/blacks had the highest incidence of those younger than 45 years of age. White non-Hispanics had the second highest incidence in this age range, but the highest incidence in persons over 45 years of age (Figure 7.12).

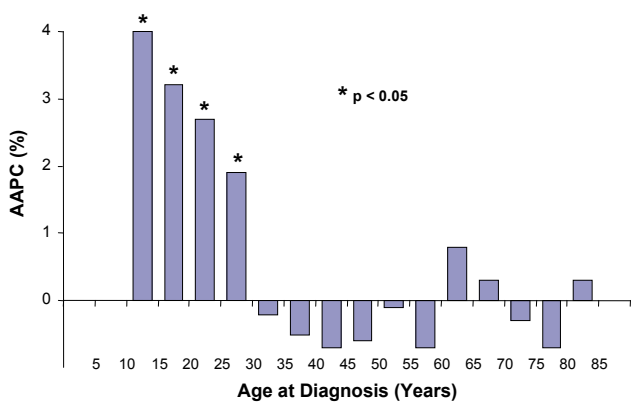

Figure 7.14: Average Annual Percent Change (AAPC) in Incidence of Other Specified Soft Tissue Sarcoma, ICCC IX(d), SEER 1975-2000

Trends in Incidence

From 1975 to 2000, non-Kaposi soft tissue sarcoma increased at a statistically significant rate in 10- to 29-year-olds and in persons over 60 (Figure 7.13). The increase was primarily due to sarcomas in the *Other Specified soft tissue sarcoma* ICCC group IX(d) (Figure 7.14) that includes extra-osseous Ewing sarcoma, peripheral neuroectodermal tumor, and synovial-cell sarcoma.

The increase in non-Kaposi soft tissue sarcomas was apparent in both males and females, but was greater in females and greater in the 15- to 29-year age group than in any other (Figure 7.15; left panel). The *Other Specified soft tissue sarcoma* group was the main contributor to both the male and female increases, and again was greater in 15- to 29-year-olds for both genders than in any other age group (Figure 7.15; right panel).

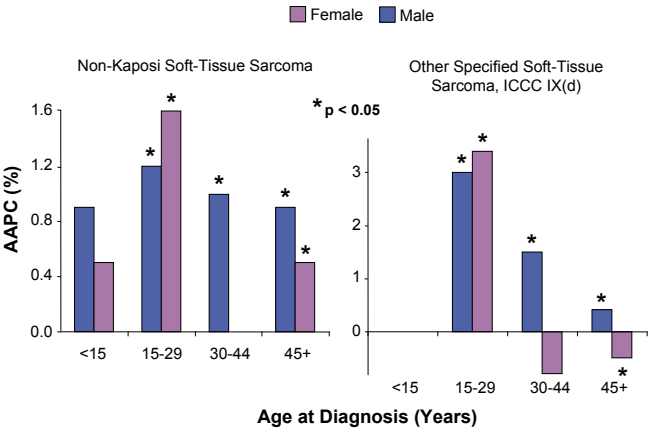

Figure 7.15: Average Annual Percent Change (AAPC) in Incidence by Gender, SEER 1975- 2000

OUTCOME

Mortality

Note: Kaposi sarcoma was not separated from the other soft tissue sarcomas for mortality assessment and trends since this information was generally not available from death certificates until 1999. Even after 1999, deaths were not assigned to Kaposi Sarcoma but to AIDS *and* Kaposi Sarcoma.

Age-and Gender-Specific Mortality

National mortality for all soft tissue sarcomas from 1975 to 1999 showed a steady increase with age, from less than 2 deaths per million for both males and females younger than five years of age to a peak of 9 deaths per million for males 40 to 44 years of age. In most age categories—except the 10- to 14-year age group—mortality for males was greater than for females (Figure 7.16).

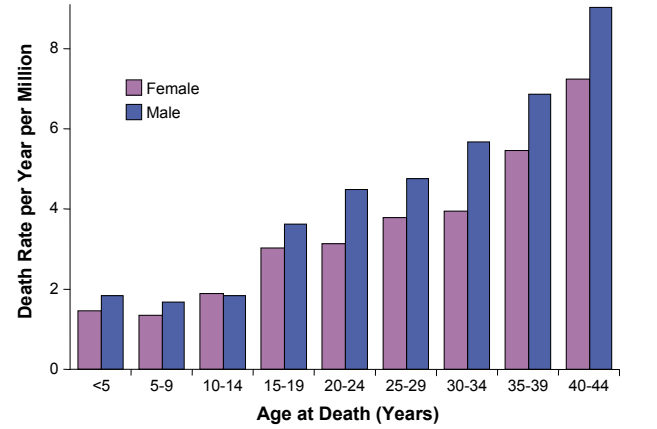

Figure 7.16: National Mortality for All Soft Tissue Sarcomas by Gender, U.S.,1975-1999

Racial/Ethnic Differences in Mortality

When mortality data were analyzed according to race/ethnicity, African Americans/blacks had the highest number of deaths per year per million in all age categories (Figures 7.17 and 7.18). The highest annual death rate was observed in the 40- to 44-year age group, at 13 deaths per million for African Americans/blacks, followed by 8 deaths per million for white non-Hispanics, 7

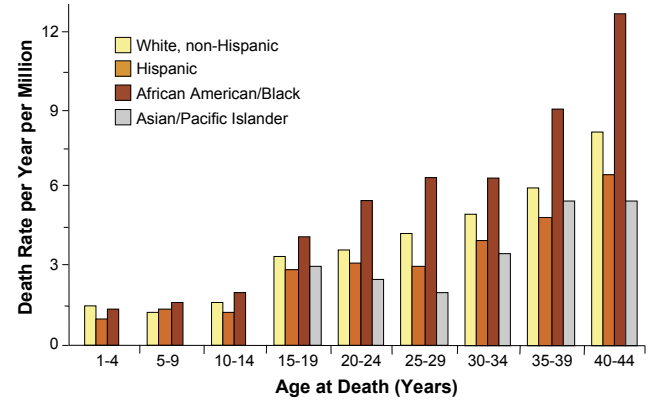

Figure 7.17: National Mortality for All Soft Tissue Sarcomas by Race/Ethnicity, 1990-2000

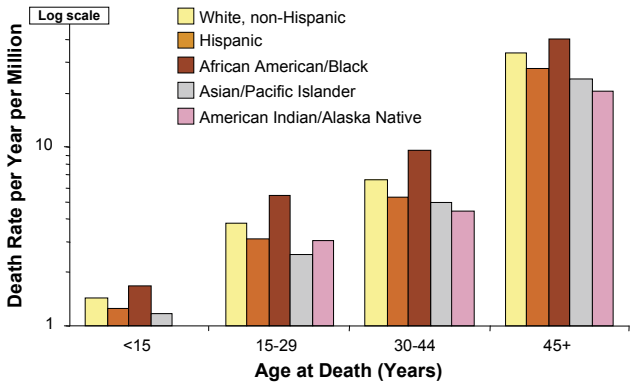

Figure 7.18: National Mortality for All Soft Tissue Sarcomas by Race/Ethnicity, U.S., 1990-2000

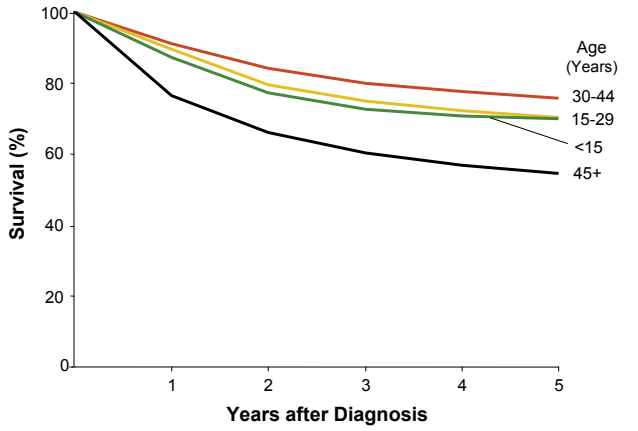

Figure 7.19: Relative Survival Rate for Non-Kaposi Soft Tissue Sarcoma by Age, SEER 1975-2000

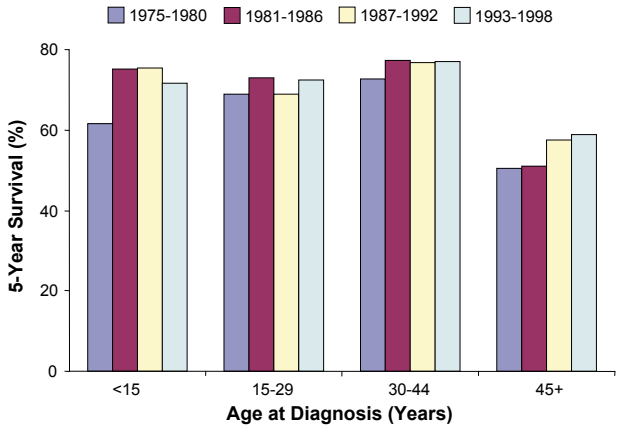

Figure 7.20: 5-Year Survival Rate for Non-Kaposi Soft Tissue Sarcomas by Era, SEER

deaths per million for Hispanics, and 6 deaths per million for Asians/Pacific Islanders (Figure 7.18).

Survival

Life table analysis disclosed that between 1975 and 2000, children, adolescents and young adults with non-Kaposi soft tissue sarcomas had a better than 75% relative survival (Figure 7.19). Those 30 to 44 years of age had the best outcome—approximately 80% at 5 years—and those in the 15- to 29-year age group had the next best outcome. Even in children, age has been reported to be an independent prognostic factor for treatment failure: children with rhabdomyosarcoma who are younger than one year of age or older than ten years have a poor outcome.[8]

Little-to-no progress was made during the past quarter century in prolonging the survival of patients with non-Kaposi soft tissue sarcomas in the 15- to 29-year age groups (Figure 7.20). Younger and older patients have had lives prolonged, particularly those over 45 years of age.

It has been shown that patients with unresectable tumors and/or metastatic disease have a very poor long-term prognosis, and recent studies have shown that certain genetic markers can affect prognosis.[9] However, cytogenetics of the various soft tissue sarcomas and staging of the individuals represented in the adolescent and young adult cohort are not known.

When survival rates for rhabdomyosarcoma and embryonal sarcoma were analyzed by treatment eras, only those younger than 15 years of age showed an improvement in survival over time. The 5-year survival rates for adolescents and young adults were low—approximately 40%—throughout all treatment eras. Survival rates for those in the 30- to 44-year age group decreased from approximately 42% in the early treatment eras to under 20% in the most recent treatment era, and as discussed above, were primarily due to the HIV epidemic and the associated occurrence of Kaposi sarcoma. The survival rates remained constant, although low at approximately 30%, for those 45 years and older (Figure 7.21).

Five-year survival rates for fibrosarcomas, neurofibrosarcomas and other fibromatous neoplasms were nearly 90% for all age groups from 15 to 44 years. The survival rate

for the 45 and older age group was not quite as high but reached a maximum of approximately 75% in the most recent treatment era (Figure 7.22).

When evaluating the average annual percent change in 5-year survival for all soft tissue sarcomas over the period 1975 to 1997, a decrease in survival is noted in all age groups between 15 and 44 years. These findings have also been observed in a recent study that reported the lowest survival improvement in those between the ages of 15 and 45 years, with the exception of Kaposi sarcoma.[10] Furthermore, the study found that age-dependent survival improvement and clinical-trial accrual patterns were directly correlated ($p < 0.005$). This suggests that the lack of survival improvement in persons between the ages of 15 and 44 years in the U.S. with non-Kaposi sarcomas may have been a result of limited participation in clinical trials (Figure 7.23).[10]

Survival by Race/Ethnicity

Small variations in 5-year survival rates for all soft tissue sarcomas were noted among the different racial/ethnic groups (Figure 7.24). For adolescents and young adults, Hispanics and white non-Hispanics demonstrated the highest survival rates, at approximately 80%, followed closely by African Americans/blacks and Asians/Pacific Islanders, with survival rates of approximately 75%. For adults in the 30- to 44-year age group, survival was almost 90% for white non-Hispanics, 85% for Hispanics and African Americans/blacks and 77% for Asians/

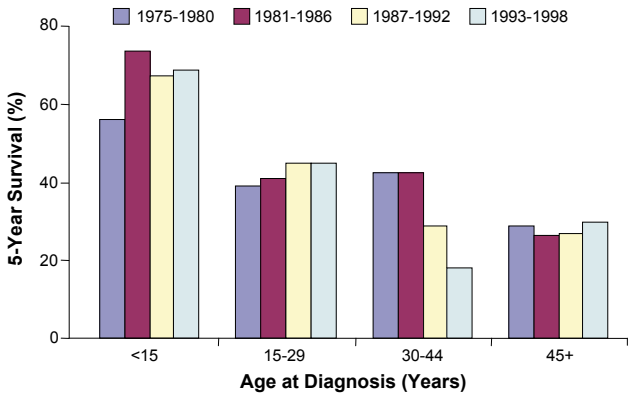

Figure 7.21: 5-Year Survival Rate for Rhabdomyosarcoma and Embryonal Sarcoma, ICCC IX(a), by Era, SEER

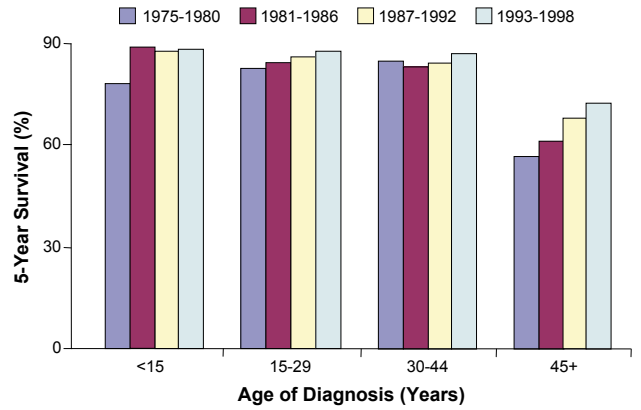

Figure 7.22: 5-Year Survival Rate for Fibrosarcoma, Neurofibrosarcoma and Other Fibromatous Neoplasms, ICCC IX(b), by Era, SEER

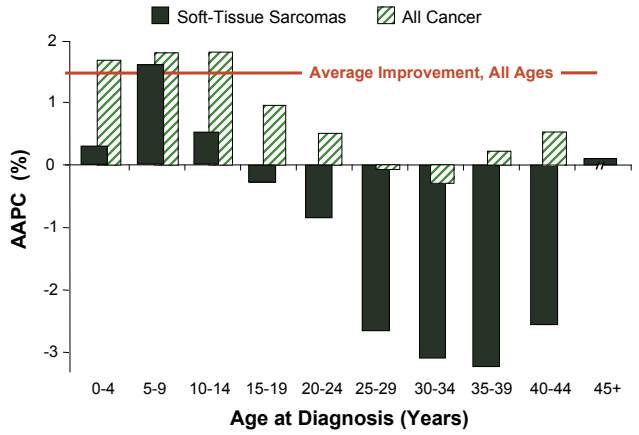

Figure 7.23: Average Annual Percent Change (AAPC) in 5-Year Survival, 1975-1997

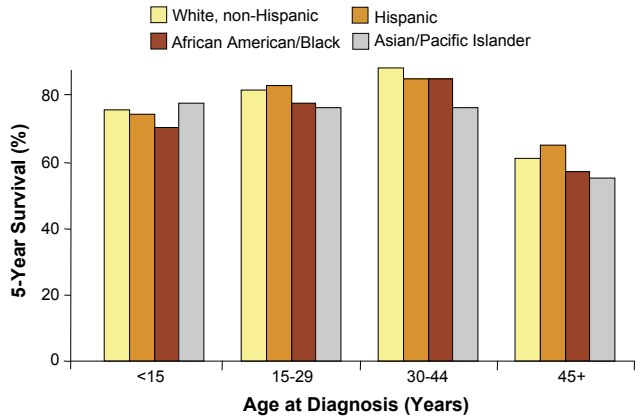

Figure 7.24: 5-Year Survival Rate for All Soft Tissue Sarcomas by Race/Ethnicity, SEER 1990-1999

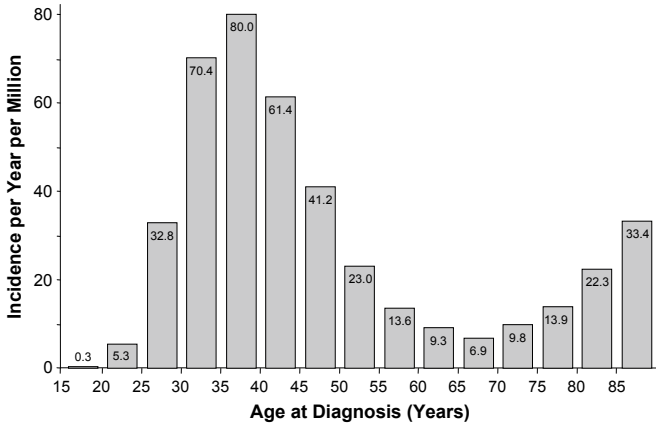

Figure 7.25: Incidence of Kaposi Sarcoma, SEER 1983-2002

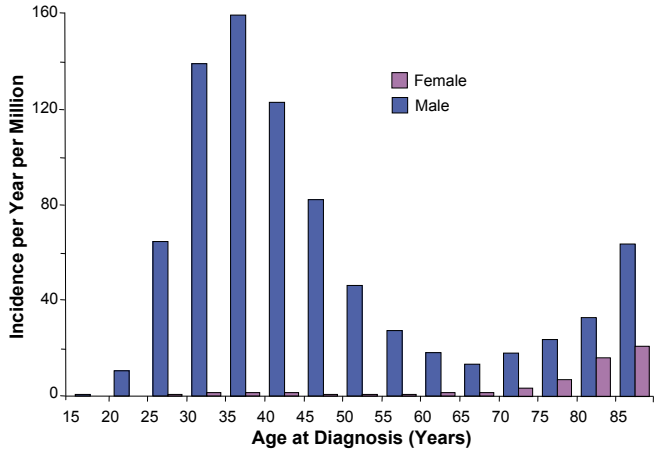

Figure 7.26: Incidence of Kaposi Sarcoma by Gender, SEER 1983-2002

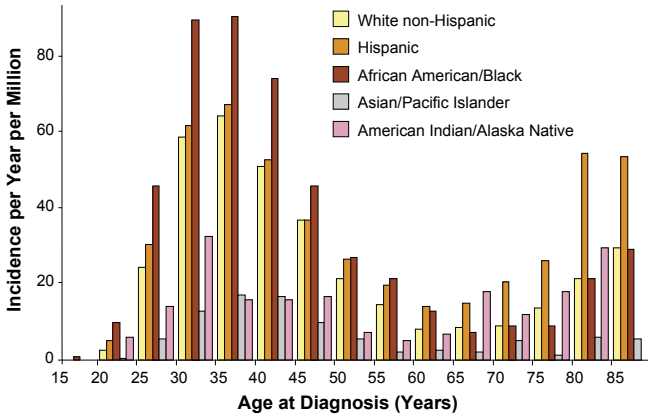

Figure 7.27: Incidence of Kaposi Sarcoma by Age and Race/Ethnicity, SEER 1992-2002

Pacific Islanders. The lowest survival rates occurred for those over 45 years of age, and were between 58% and 62% for all groups.

KAPOSI SARCOMA

Incidence

As mentioned at the beginning of this chapter, the dramatic increase and decline of Kaposi sarcoma among young males during the 1980s and 1990s (Figure 7.1) requires that this disease be considered separately when describing the history of sarcoma epidemiology during the past quarter century. There was a bimodal distribution of incidence as a function of age, with the young adult peak occurring between 35 and 40 years of age and a peak occurring in the elderly after 85 years of age (Figure 7.25). The youngest age group with a measurable rate was 15 to 19 years. Nearly all cases in young adults have occurred in males; females, however, had an increasing incidence after age 60 and approached one-third to one-half the male incidence after age 80 (Figure 7.26).

During the latter half of the Kaposi epidemic, when race and ethnicity were ascertained by the U.S. Census Bureau, African Amercans/blacks had the highest incidence of Kaposi sarcoma in all ages up to 60 years (Figure 7.27). In elderly persons, Hispanics had the highest incidence, approximately twice that of other races/ethnicities. In young adults, non-Hispanic whites and Hispanics had similar rates of Kaposi sarcoma. The lowest rates occurred in Asians/Pacific Islanders, and American Indians/Alaska Natives had intermediate rates.

Survival

Historically, 15- to 29-year-olds with Kaposi sarcoma had the same poor survival—15% at 5 years—as those 30 to 44 years of age, and both of these age groups had a distinctly worse outcome than those 45 years of age and older (Figure 7.28). Historically, the two races with the highest incidence of Kaposi sarcoma in 15- to 29-year-olds—African Americans/blacks and whites—had nearly identical survival rates (Figure 7.29). Both races experienced a doubling in 5-year survival rates, albeit the 1-year survival rate among African Amercans/blacks lagged behind that of whites (Figure 7.28).

The 5-year survival among young adults with Kaposi sarcoma declined before it improved, however, with the 1987 to 1992 era having the worst outcome in all age groups (Figure 7.30). This decline across all age groups is unexplained. It is unlikely to have been due to the HIV epidemic, since HIV-related Kaposi sarcoma occurred during the prior era—1981 to 1986—and because persons older than those who developed AIDS (the 45+ year age group), were similarly affected (Figure 7.30). Since then, however, remarkable progress has been made in prolonging survival. The age group with the least improvement in the 5-year survival rate was the 15- to 29-year-old group (Figure 7.30); those in the 20- to 24-year age group had a deterioration in survival from the survival rate of the early 1980s (Figure 7.31).

Among 15- to 29-year-olds, Asians/Pacific Islanders had the worst survival during the most recent era, 1992 to 1999. Their 5-year rate was 6% compared to 16-23% for the other racial/ethnic groups (Figure 7.32). Hispanic patients had the best survival among 30- to 44-year-olds, and non-Hispanic whites and African Americans/blacks had the best outcome of those 45 years of age and older.

RISK FACTORS

There are reports in the pediatric literature documenting that certain syndromes with known chromosomal abnormalities place children at risk for the development of soft tissue sarcomas. It should also be noted, however, that the majority of cases of soft tissue sarcomas occur sporadically, with no identifiable risk factor. Three genetic disorders associated with an increased incidence of soft tissue sarcomas are Li-Fraumeni Syndrome (LFS), von Recklinghausen's disease, and Beckwith-Wiedeman Syndrome (BWS). LFS has been associated with soft tissue sarcomas in children and the early onset of breast cancer in adult family members. This heterogeneous familial cancer syndrome is most notably associated with germline mutations in the p53 tumor suppressor gene, but other genetic abnormalities have also been noted.[11] There is an increased incidence of soft tissue sarcomas in patients with von Recklinghausen's disease, which is associated with abnormalities at the 17q11.2 locus.[12,13] Rhabdomyosarcoma has also been reported to have a higher incidence in children with Beckwith-Wiedeman

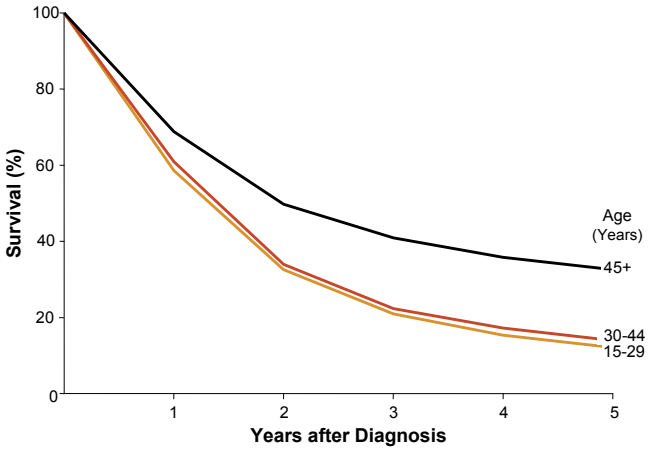

Figure 7.28: Relative Survival Rate for Kaposi Sarcoma by Age, SEER 1975-2000

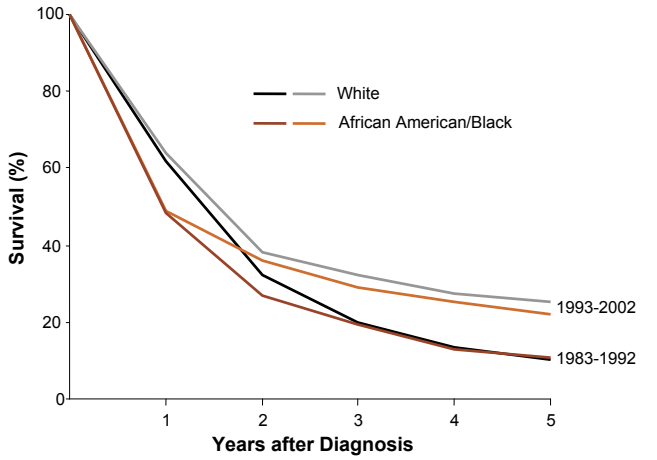

Figure 7.29: Relative Survival Rate for Kaposi Sarcoma by Era and Race, Age 15-29 at Diagnosis, SEERSEER 1981-1999

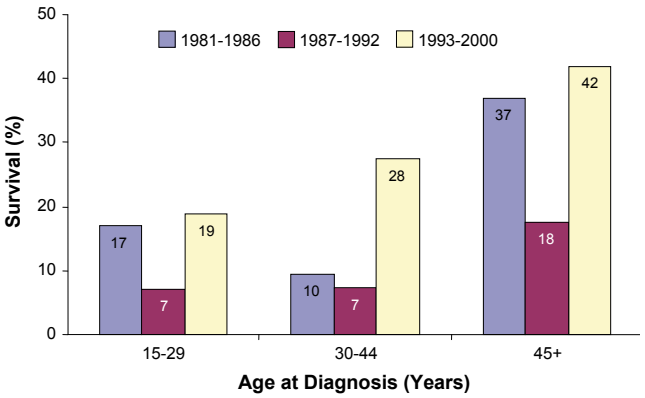

Figure 7.30: 5-Year Relative Survival Rate for Kaposi Sarcoma by Age and Era, SEER 1981-1999

Syndrome (BWS), a fetal overgrowth syndrome. BWS is associated with abnormalities on 11p15.[14]

Environmental factors that have been associated with an increased risk of rhabdomyosarcoma in children include fetal exposure to marijuana and cocaine use by the mother and/or father.[15] Whether or not this applies to adolescents and young adults with rhabdomyosarcoma is not known. It is also important to recognize that for *survivors* of childhood soft tissue sarcomas, there is a significantly increased risk for the development of second malignant neoplasms for all histologic types; this appears to be greatest among patients who received combination multi-modal therapy including ionizing radiation and chemotherapy,[16] and with combination chemotherapy.

SUMMARY

From 1975 through 1999, approximately 15 cases per year per million of soft tissue sarcomas (including Kaposi sarcoma) were diagnosed in 15- to 19-year-olds, approximately 25 cases per year per million were diagnosed in 20- to 24-year-olds, and nearly 50 cases per year per million were diagnosed in 25- to 29-year-olds. Soft tissue sarcoma incidence reached its peak in 35- to 39-year-olds, at 125 per year per million. There were different incidence patterns for the various histological subtypes for the older and younger age groups represented in this sample. One such difference included a higher incidence—up to 7 per year per million cases of rhabdomyosarcoma and other embryonal sarcomas—for those younger than 20 years of age, but a lower incidence—approximately one per year per million—for those older than 20 years. At its peak incidence, during the late 1980s and early 1990s, Kaposi sarcoma accounted for more cases of sarcoma in young adult males than any other type of sarcoma. Since 2000, Kaposi sarcoma accounted for about 5% and < 0.5% of the soft tissue sarcomas in 15- to 29-year-old males and females, respectively.

Differences in gender-specific incidence rates for soft tissue sarcomas were also observed. In those 20 years of age and older, male incidence was much higher than that of females. Incidence variations were also observed among the different racial/ethnic groups. For almost all age categories, African Americans/blacks had the highest incidence overall for soft tissue sarcomas. Fortunately, racial/ethic minority patients in the 15- to 29-year age group have not had, in general, an inferior outcome in survival, as has been similarly observed for children with the most common sarcoma in their age group.[17] This equity is true for both Kaposi sarcoma, with the notable exception of Asian/Pacific Islander patients, and non-Kaposi soft tissue sarcomas.

Among Americans diagnosed with non-Kaposi soft tissue sarcoma during the past quarter century, 15- to 29-year-olds had the second highest survival rate, following that of those in the 30- to 44-year age bracket. Among those with rhabdomyosarcoma and embryonal sarcoma, however, 15- to 29-year-olds had both a lower survival rate and a less favorable survival improvement trend than children with these types of sarcomas. With the possible exception of Asians with Kaposi sarcoma, racial/ethnic minority patients in the 15- to 29-year age group have not

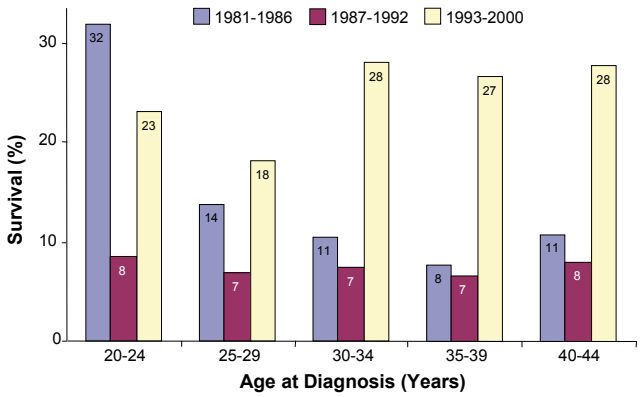

Figure 7.31: 5-Year Relative Survival Rate for Kaposi Sarcoma by Age and Era SEER 1981-1999

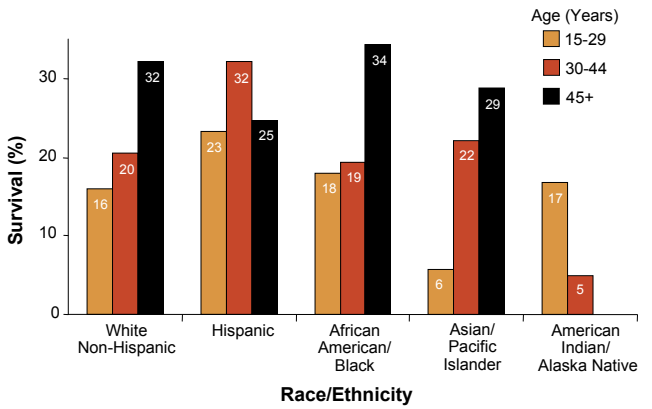

Figure 7.32: 5-Year Relative Survival Rate for Kaposi Sarcoma by Race/Ethnicity and Age, SEER 1992-1999

had an inferior outcome in survival of either non-Kaposi soft tissue sarcoma or Kaposi sarcoma.

Kaposi sarcoma had the most dramatic increase in survival improvement among the major groups of soft tissue sarcomas, albeit it was still lower than most types of soft tissue sarcomas. Those diagnosed with Kaposi sarcoma before age 30 had the worst survival and the least improvement in survival of all age groups.

The relative lack of progress in prolonging the lives of young adults with sarcomas has been correlated with the degree to which the disease has been studied in the age group (clinical trials, number of patients entered, etc.).[10] It is important to continue careful surveillance of soft tissue sarcoma survivors, considering their elevated risk for second malignant neoplasms, particularly if exposed to multi-modal treatment regimens.

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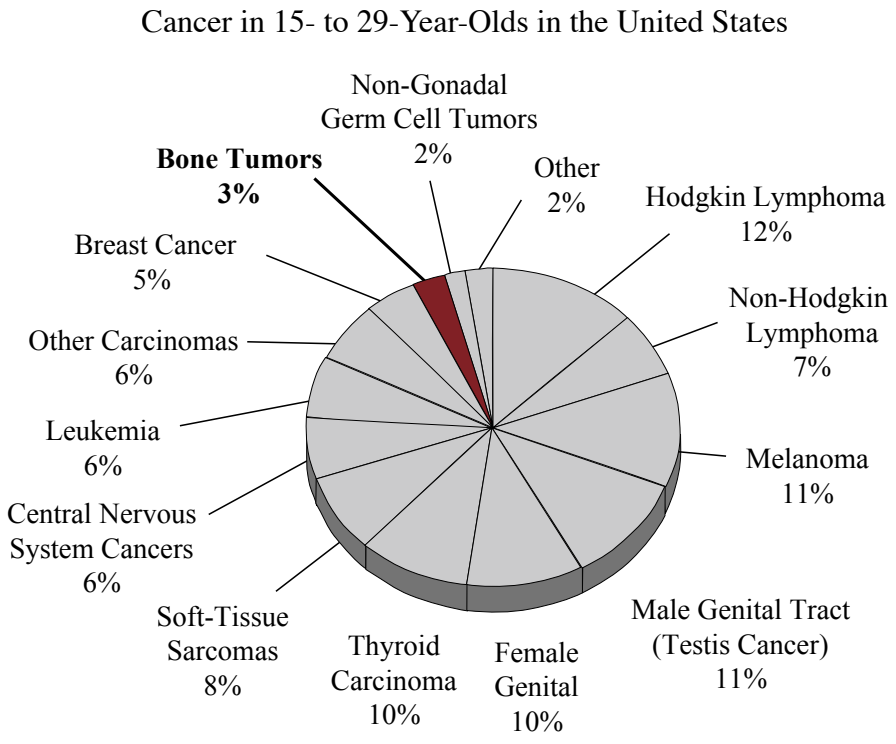
Chapter 8

Malignant Bone Tumors



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HIGHLIGHTS

Incidence

- Primary neoplasms of the bone are uncommon in adolescents and young adults and accounted for 3% of all neoplasms in this age group. Osteosarcoma was the most frequent malignant bone tumor (approximately 47% of all bone neoplasms among 15- to 29-year-olds) followed by Ewing sarcoma/peripheral primitive neuroectodermal tumor (pPNET *of bone*) (27%) and chondrosarcoma (15%).
- In 15- to 29-year-olds, as in children and young adolescents, most osteosarcomas occurred in the metaphyses of long bones and particularly the distal femur, proximal humerus and proximal tibia. In Ewing sarcoma and chondrosarcoma, however, the central axis was the most frequent site of disease; these diseases had a remarkably similar anatomical distribution.
- The average annual incidence of bone cancer peaked at 15 per million in those 15 to 19 years of age, and fell to 6 per million by 25 to 29 years of age.
- Bone cancer in males occurred at a rate almost double that of females in the 15- to 19-year age group—approximately 200 per year. There were approximately 100 patients a year diagnosed with Ewing sarcoma/pPNET from 15 to 19 years of age, two-thirds of whom were males. Osteosarcomas occurred at an earlier age in females than in males.
- The incidence of osteosarcoma in males was higher than in females for all ages except those younger than 9 years. Ewing sarcoma/pPNET was also more common in males, with a lower predominance than osteosarcoma.
- Between 1975 and 1999, the incidence of osteosarcoma increased at an average of 1.4% per year ($p < 0.05$) in the 15- to 29-year age group. In contrast, the incidence of Ewing sarcoma remained stable during the past quarter century.
- Ewing sarcoma/pPNET occurred predominantly in white non-Hispanics and Hispanics, with a lower incidence in Asians/Pacific Islanders. Over the age of 30, Ewing sarcoma/pPNET occurred almost exclusively in white non-Hispanics. Osseous Ewing sarcoma rarely occurred in the African American/black population.

Mortality & Survival

- Mortality for bone tumors in adolescents and young adults was higher in males than females over the adolescent and young adult age range and much higher than expected in 20- to 24-year-olds, even taking into consideration the higher incidence in males than females.
- The U.S. bone cancer mortality was highest for males and females 15 to 19 years of age.
- The survival rate for all bone sarcomas was similar across age groups, with an overall modest improvement in survival from 1975 to 1980 and from 1993 to 1998.
- In the U.S., the 5-year survival rates for osteosarcoma and Ewing sarcoma were comparable among 15- to 29-year-olds, about 60% for the most recent era. Survival rates for chondrosarcoma exceeded 90% in the most recent era.
- Patients with osteosarcoma between the ages of 30 and 44 years had a slightly better outcome than patients aged 15 to 29 years, the reasons for which are unclear. Patients with osteosarcoma who were older than 45 years of age had a poorer outcome than all other age groups.
- Patients with Ewing sarcoma, regardless of age, showed an overall improvement in survival from 1975 to 1998.

Risk Factors

- Known risk factors for osteosarcoma are ionizing radiation, alkylating agents, Paget disease, hereditary retinoblastoma, Rothmund –Thomson syndrome, Werner syndrome, Bloom syndrome and the Li-Fraumeni familial cancer syndrome.
- Ionizing radiation has been implicated as a causative factor in approximately 3% of osteosarcomas.
- Aside from the difference in incidence by race/ethnicity (whites have a much higher incidence than African Americans/blacks), there are no known risk factors for Ewing sarcoma/pPNET.
- For chondrosarcoma, Marfucci's syndrome, Ollier's disease, multiple osteochondromatosis and hereditary multiple exostoses are the few known risk factors.

INTRODUCTION

Malignant bone cancers are sarcomas of bone, cartilage and associated tissues such as endothelial and neuroectodermal cells that participate in bone formation and maintenance. The Ewing family of tumors is particularly fascinating since the cell of origin remains uncertain and both soft-tissue and osseous forms are known to exist. Although they are among the relatively infrequent cancers in individuals 15 to 29 years of age, they have special significance in this age group. In these older adolescents and young adults, two tumors alone—osteosarcoma and Ewing sarcoma—account for three-fourths of all bone cancer. And if the next most common bone cancer in this age group—chondrosarcoma—is included, the three account for more than 90% of all bone cancer diagnosed. The older adolescent and young adult years are those during which the incidence of Ewing sarcoma declines dramatically and that of chondrosarcoma increases, such that by age 25 to 30 these two types of bone cancer are approximately equal in incidence. The treatment of bone cancer is highly challenging to the young adult or adolescent patient, since amputation and extensive surgical procedures such as limb salvage and hemipelvectomies are often necessary.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), malignant bone tumors are described in category VIII. There are 5 subdivisions in VIII: *osteosarcoma* (VIII(a)), *chondrosarcoma* (VIII(b)), *Ewing sarcoma* (VIII(c)), *other specified malignant bone tumors* (VIII(e)), and *unspecified malignant bone tumors*. The emphasis in this chapter is on subgroups (a), (b), and (c).

Osteosarcomas derive from primitive bone-forming mesenchymal stem cells and most often occur in the metaphyseal portions of long bones,[1,2] especially during the first decades of life. *Osteosarcoma*, the most common bone cancer in adults, is category VIII(a) in the ICCC based on ICD-O codes 9180-9200 at any site in the body. This includes osteosarcoma [NOS (9180), chondroblastic (9181), fibroblastic (9182), telangiectatic (9183), in Paget disease (9184), small cell (9185), juxtacortical (9190)] and osteoblastoma (9200). New histologies that also fall into VIII(a) from ICD-O-3 are: central osteosarcoma (9186), intraosseous well differentiated osteosarcoma (9187), periosteal osteosarcoma (9193), high grade surface osteosarcoma (9194), and intracortical osteosarcoma (9195).

Chrondrosarcoma, the second most common of the bone malignancies in older adults,[3] is category VIII(b) in the ICCC. The equivalent ICD-O categories are chondrosarcoma [NOS (9220), juxtacortical (9221)] and malignant chondroblastoma (9230) for all sites in the body, and myxoid chondrosarcoma (9231) and mesenchymal chondrosarcoma (9240) for bones, joints and articular cartilage of limbs. New histologies that also fall into VIII(b) from ICD-O-3 are clear cell chondrosarcoma (9242) and dedifferentiated chondrosarcoma (9243).

The *Ewing Sarcoma Family of Tumors* includes Ewing, atypical Ewing, and peripheral primitive neuroectodermal tumor (pPNET) of bone. These tumors are believed to be of neural crest origin and to also occur in soft tissue sites. The latter occurrences are not included in this chapter (cf. Soft Tissue Sarcomas), albeit they may occur at virtually any site in the body. As osseous tumors, Ewing sarcoma occurs at approximately equal incidence in the extremities and central axis.[4] Ewing sarcoma is category VIII(c) in the ICCC: 9260 (classic Ewing tumor of bone), 9364 (peripheral neuroectodermal tumor), 9363 (malignant melanotic neuroectodermal tumor), and the SEER modification adds 9473 (primitive neuroectodermal tumor (PNET) of bone and joints.

Other Specified Malignant Bone Tumors are category VIII(d) in the ICCC and ICD-O categories 8812 (periosteal fibrosarcoma), 9250 (malignant giant cell tumor of bone), 9261 (adamantinoma of long bones), 9270-9330 (malignant odontogenic tumors), and 9370 (chordoma, NOS). Malignant tenosynovial giant cell tumor (ICD-O-3 9252) is included with fibrous histiocytoma (8830) in ICCC IX(b). Unspecified Malignant Bone Tumors are category VIII(e) in the ICCC, which includes histologies commonly indicative of soft tissue sarcoma that have arisen in bone (8800-8804) and unspecified malignant tumors (8000-8004).

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age

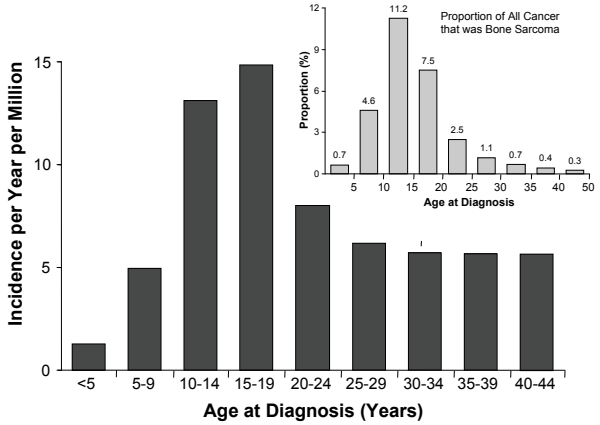

Figure 8.1: Incidence of All Bone Sarcomas, SEER 1975-1999

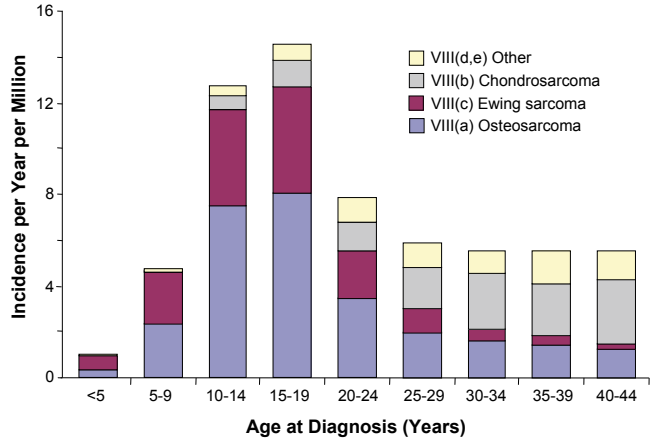

Figure 8.2: Incidence of Bone Sarcomas by Type, SEER 1975-2000

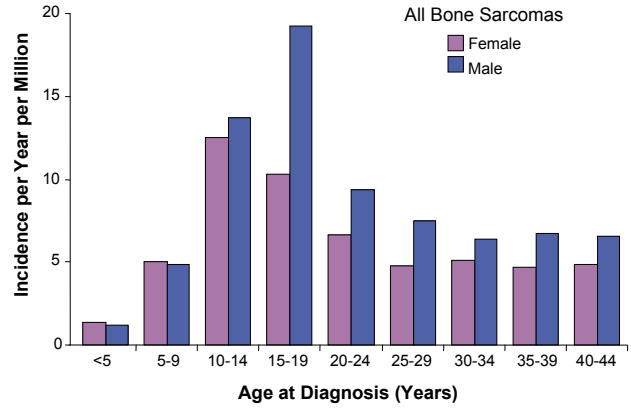

Figure 8.3: Incidence of All Bone Sarcomas by Gender, SEER 1975-1999

groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

INCIDENCE

As estimated from SEER data and the U.S. 2000 census, the average incidence of bone cancer in adolescents and young adults 15 to 29 years of age was 9.8 per year per million persons. The histology-specific rates were 4.6 per million for osteosarcoma, 2.6 per million for Ewing sarcoma and 1.5 per million for chondrosarcoma.

Bone tumors are classified as osteosarcoma, Ewing sarcoma, chondrosarcoma, "other specified malignant bone tumor" and "unspecified malignant bone tumor."[1] The three most common bone cancers in 15- to 29-year-olds are osteosarcoma, Ewing sarcoma, and chondrosarcoma, which account for 48%, 27% and 15% of bone cancers in the age group, respectively. From the trends in incidence for the 25-year period from 1975 to 2000, an estimated 325, 163 and 109 15- to 29-year-olds were diagnosed in the U.S. with osteosarcoma, Ewing sarcoma, and chondrosarcoma, respectively (Table 8.1).

Age-Specific Incidence

Bone cancer represented only 3% of all malignancies in the 15- to 29-year age group. It accounted for 7.5% of all cancers in those 15 to 19 years, 2.5% for those 20 to 24 years, and 1.1% for 25- to 29-year olds (Figure 8.1; inset). The incidence of bone cancer peaked at 15 per year per million for those 15 to 19 years of age, and then fell to 8 per year per million for 20- to 24-year-olds and 6 per year per million for those 25 to 29 years of age (Figure 8.1). Figure 8.2 displays specific rates for specific histologic subtypes according to the different age groups.

Gender-Specific Incidence

The incidence of malignant bone tumors was higher in males than in females in the adolescent and young adult population (Figure 8.3); both osteosarcoma and Ewing sarcoma had a higher incidence in males (Figures 8.4 and 8.5). The remaining types of malignant bone tumors, in aggregate, also demonstrated a male predominance (Figure 8.6).

Racial/Ethnic Differences in Incidence

Figure 8.7 depicts the comparable incidence of bone cancer among various racial/ethnic groups over the past decade. The overall incidence for white non-Hispanics in the 15- to 29-year age group was slightly higher, 11.3 per year per million, in comparison to incidence for other races/ethnicities—8.1, 10.2, and 9.1 per year per million for African Americans/blacks, Hispanics, and Asians/Pacific Islanders, respectively (Figure 8.7). However, this was not true across histological subtypes. For osteosarcoma, Hispanics had the highest incidence in those 15 to 29 years of age (Figure 8.8). For Ewing sarcoma, racial variation was dramatic. There was no discernable incidence of Ewing sarcoma in African Americans/blacks and Asians/Pacific Islanders over 15 years of age. For those over 30 years of age, this disease occurred nearly exclusively in the white non-Hispanic population (Figure 8.9). An absence of Ewing sarcoma has also been observed in several African countries.[5] The underlying biological mechanism behind these observations is yet to be elucidated (see *Risk Factors* section).

Trends in Incidence

The incidence of osteosarcoma, Ewing sarcoma and all bone cancers, according to 5-year periods between 1975 and 1995, is shown in Table 8.2.

Figure 8.10 (left panel) shows an increase in the incidence of malignant bone tumors of 0.92% per year ($p < 0.05$) during the period 1975 to 1999 in the adolescent and young adult population as compared to children < 15 years of age. This increase was due to more male patients being diagnosed, the reasons for which are unclear. Histology-specific incidence by single year of diagnosis for 1975 to

Table 8.1: *Incidence of Malignant Bone Tumors in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
ALL MALIGNANT BONE TUMORS						
Average incidence per million, 1975-2000, SEER	1.3	5.0	13.1	14.8	8.0	6.2
Average annual % change in incidence, 1975-2000, SEER	^	1.4%	0.9%	1.0%	1.0%	2.2%
Estimated incidence per million, year 2000, U.S.	^	5.7	14.5	16.5	9.0	7.5
Estimated number of persons diagnosed, year 2000, U.S.	^	118	298	333	170	146
OSTEOSARCOMA						
Average incidence per million, 1975-2000, SEER	0.4	2.4	7.6	8.2	3.5	2.1
Average annual % change in incidence, 1975-2000, SEER	^	1.0%	1.8%	1.1%	1.5%	4.8%
Estimated incidence per million, year 2000, U.S.	^	10.8	9.0	9.4	4.2	2.8
Estimated number of persons diagnosed, year 2000, U.S.	^	65	184	190	80	55
EWING SARCOMA						
Average incidence per million, 1975-2000, SEER	0.6	2.3	4.3	4.6	2.1	1.9
Estimated incidence per million, year 2000, U.S.	^	2.0	4.1	5.1	2.1	1.1
Estimated number of persons diagnosed, year 2000, U.S.	^	41	85	103	39	21
CHONDROSARCOMA						
Average incidence per million, 1975-2000, SEER	^	0.1	0.6	1.2	1.3	1.9
Average annual % change in incidence, 1975-2000, SEER	^	3.3%	2.8%	-20.5%	4.9%	3.3%
Estimated incidence per million, year 2000, U.S.	^	0.2	0.7	1.3	1.7	2.5
Estimated number of persons diagnosed, year 2000, U.S.	^	3	15	27	33	49

^Too few for a reliable estimate

Table 8.2: *Average Age-Adjusted Incidence per Year per Million for All Malignant Bone Tumors, All Races/Ethnicities, Both Genders, Age 15 to 29 Years, SEER 1975-1995*

	1975-80	1981-86	1987-92	1993-99
OSTEOSARCOMA	4.1	4.6	5.1	5.2
EWING SARCOMA	2.4	3.1	2.7	2.8
CHONDROSARCOMA	1.4	1.2	1.5	1.6
ALL BONE CANCER	8.7	9.9	10.2	10.7

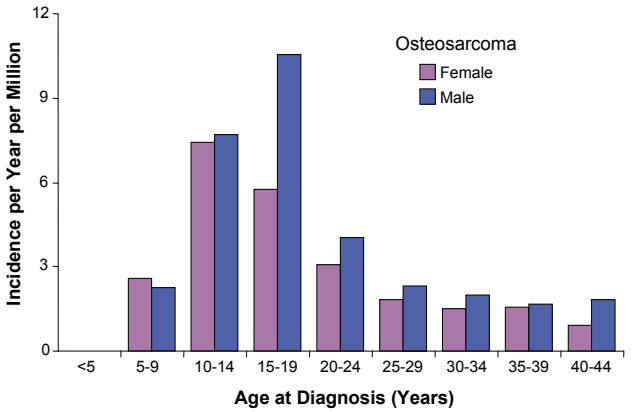

Figure 8.4: Incidence of Osteosarcoma by Gender, SEER 1975-1999

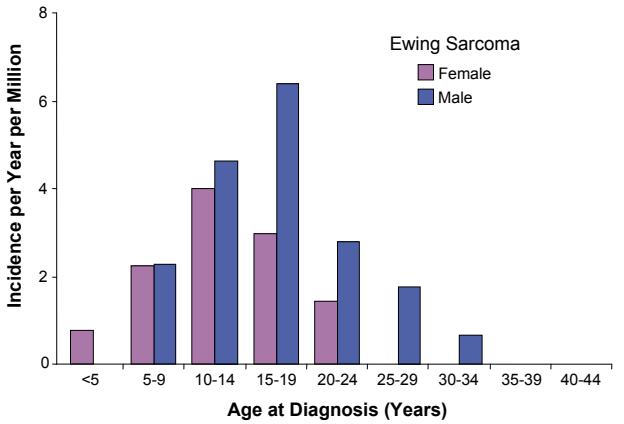

Figure 8.5: Incidence of Ewing Sarcoma by Gender, SEER 1975-1999

1999 revealed that this increase was predominantly due to an increase in the rate of osteosarcomas in 15- to 29-year-olds, an increase averaging 1.4% per year ($p < 0.05$) (Figure 8.11, right panel). The increase in osteosarcoma incidence was inversely proportional to age in those 15 to 29 years of age, with an average percent increase of 2.3%, 2.2%, and 0.7% per year from 1975 to 1999 for 15- to 19-year-olds, 20- to 24-year-olds, and 25- to 29-year-olds, respectively (Table 8.1). There was no discernable change in the osseous Ewing sarcoma incidence during the same interval, despite the development of the concept of a Ewing family of tumors, including PNET of soft tissue.

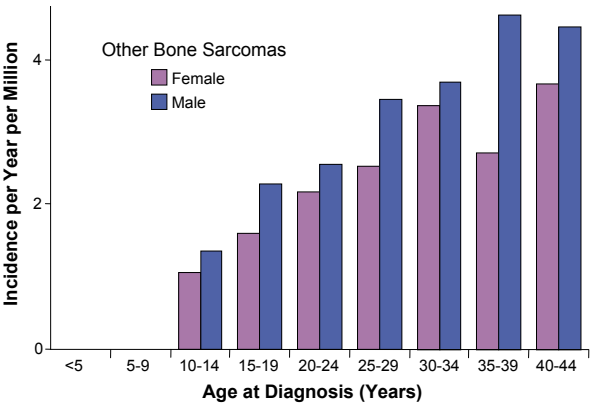

Figure 8.6: Incidence of Other Bone Sarcomas by Gender, SEER 1975-1999

Bone Cancer Location

The most frequent site of bone cancer development was the long bone of the lower limb. The site distribution of Ewing sarcomas, however, differed substantially from that of osteosarcomas and chondrosarcoma (Figure 8.11). In 15- to 29-year-olds, as in children and young adolescents, most osteosarcomas occurred in the metaphyses of long bones and particularly the distal femur, proximal humerus and proximal tibia. In Ewing sarcoma and chondrosarcoma, however, the central axis (vertebral column, ribs, sternum, clavicle, pelvis, sacrum and coccyx) was the most frequent site. Ewing sarcoma and chondrosarcoma had a remarkably similar anatomical distribution, with the only major difference being that chondrosarcoma had an increased occurrence in the calvarium and decreased incidence in the spine (Figure 8.11).

OUTCOME

Mortality

Mortality for all bone tumors was highest—approximately 8 deaths per million—for patients 15 to 24 years of age, especially for males, and lowest—less than 1 death per million—for patients younger than 9 years of age (Figure 8.12). In all age categories over 15 years, mortality for males was greater than that for females. In general, these differences reflect incidence patterns. They are, however, out of proportion to the trends in incidence; the mortality rate is higher than expected among 15- to 29-year-olds. This is indicated by the ratio of mortality rate to incidence as a function of age (Figure 8.13). The excess mortality rate was particularly apparent in males who were 20 to 24 years of age. This is borne out by the average rate of reduction in mortality, which was less significant for patients 15 to 44 years of age than in younger or older persons (Figure 8.14).

When evaluated according to race/ethnicity, mortality from malignant bone tumors during the period 1990 to 2000 was not significantly different among the different racial/ethnical groups (Figure 8.15), and where comparable, was generally reflective of incidence patterns.

Survival

Long term survival varied remarkably among the three major types of bone tumors that occur in 15- to 29-year-olds (Figure 8.16). Chondrosarcoma had the best survival, exceeding 75% at 20 years. Ewing sarcoma (and other peripheral primitive neuroectodermal tumors) had the

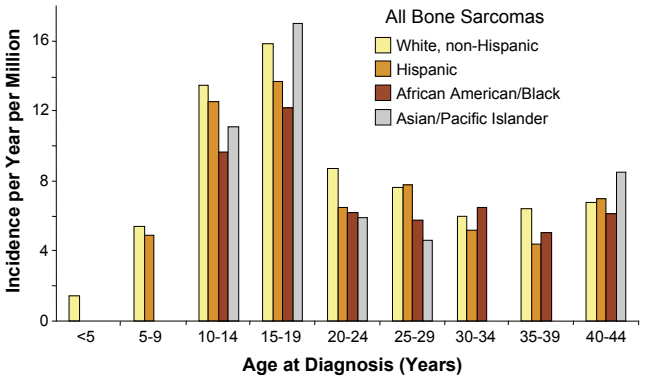

Figure 8.7: Incidence of All Bone Sarcomas by Race/Ethnicity, SEER 1990-2000

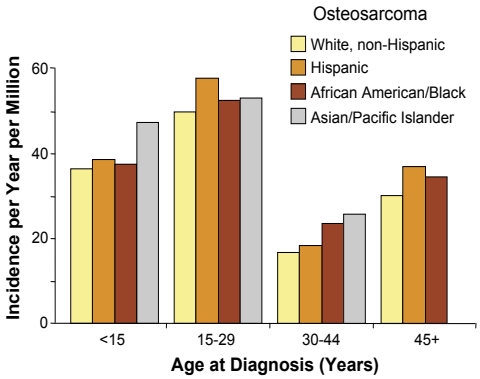

Figure 8.8: Incidence of Osteosarcoma by Race/Ethnicity, SEER 1990-1999

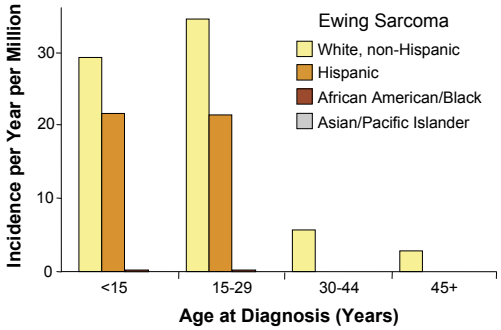

Figure 8.9: Incidence of Ewing Sarcoma by Race/Ethnicity, SEER 1990-1999

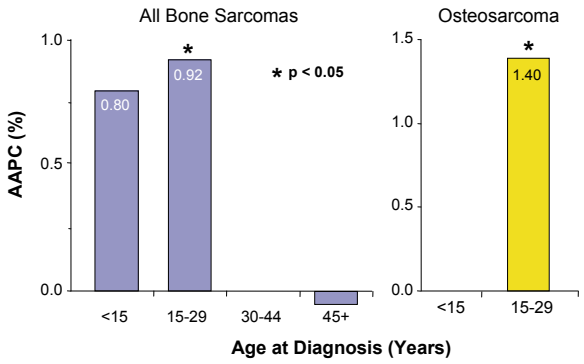

Figure 8.10: Average Annual Percent Change (AAPC) in Incidence of All Bone Sarcomas and Osteosarcoma, SEER 1975-1999

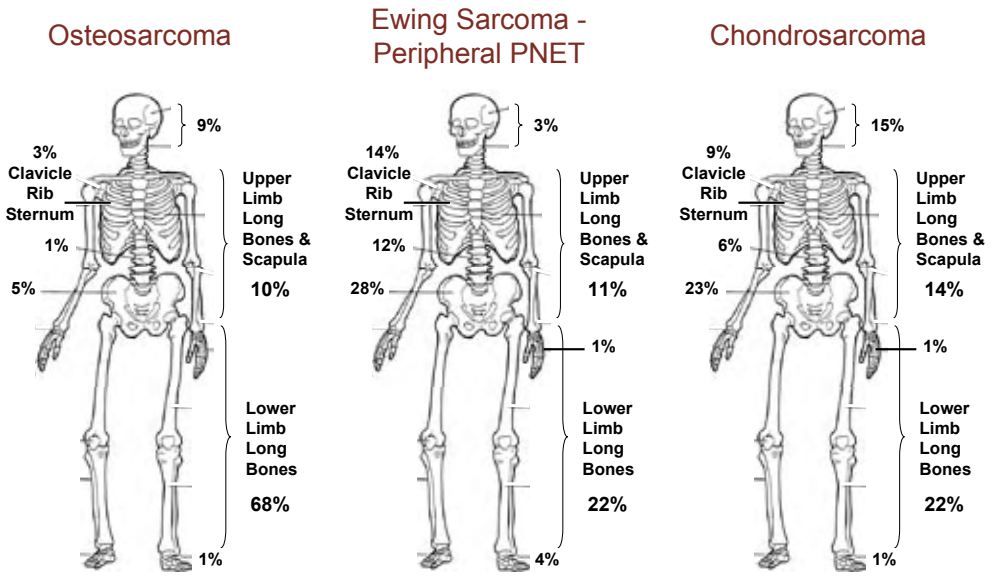

Figure 8.11: Most Frequent Sites of Bone Cancer Development in 15- to 29-Year-Olds, SEER 1992-2002. Drawings by Medscape

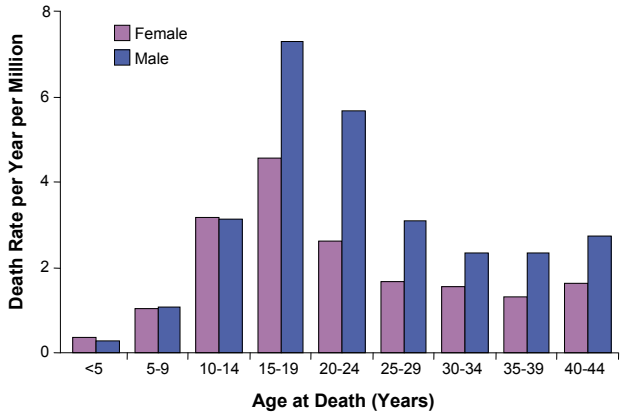

Figure 8.12: National Mortality by Gender for All Bone Sarcomas, U.S., 1975-1999

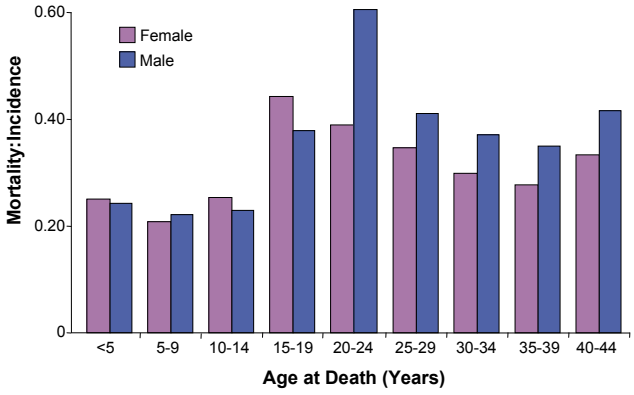

Figure 8.13: Ratio of National Mortality to SEER Incidence for All Bone Sarcomas by Gender, U.S., 1975-1999

worst survival, approximately 30% at 20 years. Osteosarcoma had a lower survival rate after 4 years of follow-up. Chondrosarcoma and osteosarcoma showed a plateau on their survival curves, suggesting that cure of the disease was achieved in nearly all patients by ten years. The Ewing sarcoma survival curve did not reveal a plateau, indicating that very late relapses of this malignancy were not uncommon.

For osteosarcoma, the survival curves for the age groups younger than 45 were nearly identical from 1975 to 2000 (Figure 8.17). In older patients, survival was considerably worse, approximately half that of patients younger than 45. For those diagnosed with Ewing sarcoma between 15 and 30 years of age, long-term survival was about half that of children and young adolescents diagnosed during the same era, and not unlike long-term survival for older patients (Figure 8.18). Patients with chondrosarcoma had a better survival than those with either osteosarcoma or Ewing sarcoma, regardless of age (Figure 8.19). Survival rates for 15- to 29-year-olds with chondrosarcoma were not as high as for 30- to 44-year-olds, although at 18 years from diagnosis both survival curves converged.

Survival for patients younger than 45 years with bone tumors has seen a modest but constant improvement, from less than 60% in the 1975 to 1980 treatment era, to greater

than 70% in the 1993 to 1998 treatment era (Figure 8.20). The 30- to 44-year age group had the highest survival rate in all treatment eras, with survival reaching almost 80% since 1987. This improvement in survival over time has also been noted for patients with osteosarcoma (Figure 8.21) and Ewing sarcoma (Figure 8.22), although survival rates for 15- to 29-year-olds were lower than for younger children in the latter group. The 5-year survival rates for patients younger than 45 years of age with osteosarcoma was greater than 65%, but continued to be less than 45% for the 45 year and older age group. The 5-year survival rate for patients younger than 15 years of age with Ewing sarcoma has improved to greater than 65%. However, the 5-year survival rate remains less than 50% for those older than 15 years of age. Patients with chondrosarcoma did not show a consistent trend in survival improvement, albeit evidence for some progress is apparent in those who were over 45 years of age at diagnosis (Figure 8.23).

Small differences in 5-year survival rates for all bone tumors were noted for the different racial/ethnic groups (Figure 8.24). For those younger than 15 years of age, the highest survival rate was observed in white non-Hispanics, at almost 80%. The lowest survival rate was observed in Hispanics at approximately 60%. In the 15- to 29-year age group, no significant survival differences were seen. In the 30- to 44-year age group, the survival was almost 80% for white non-Hispanics and Asians/Pacific Islanders, and nearly 60% for African Americans/blacks. The lowest survival rates were for the 45-year and older age groups. The 5-year survival rate for white non-Hispanics was 60%, decreasing slightly for Hispanics, African Americans/blacks and Asians/Pacific Islanders.

RISK FACTORS

There are few known risk factors for bone sarcomas. Certain genetic susceptibility syndromes (hereditary retinoblastoma, Li-Fraumeni syndrome, Rothmund-Thomson syndrome, and Werner syndrome) and prior treatment for childhood cancer with radiation and/or chemotherapy have all been shown to increase the risk of osteosarcoma,[6-14] but these factors account for a small proportion of cases. The descriptive epidemiology of osteosarcoma also strongly suggests an etiology related to pubertal development and bone

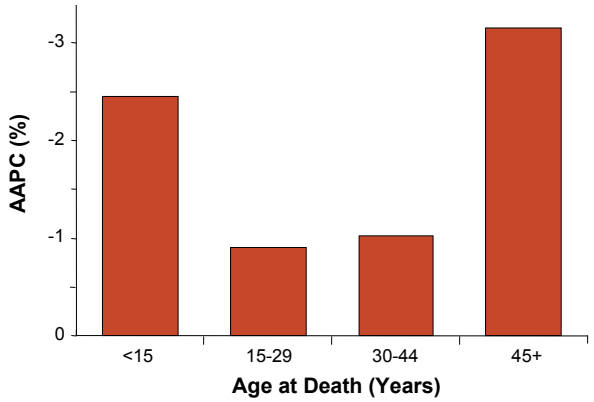

Figure 8.14: Bone Sarcomas, Average Annual Percent Change (AAPC) in National Mortality, U.S., 1975-1999

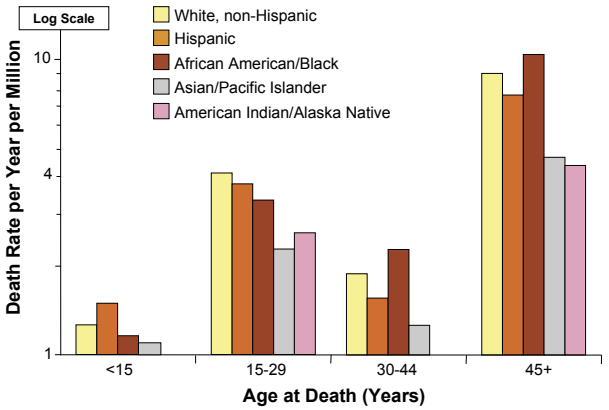

Figure 8.15: National Mortality for All Bone Sarcomas by Race/Ethnicity, U.S., 1990-2000

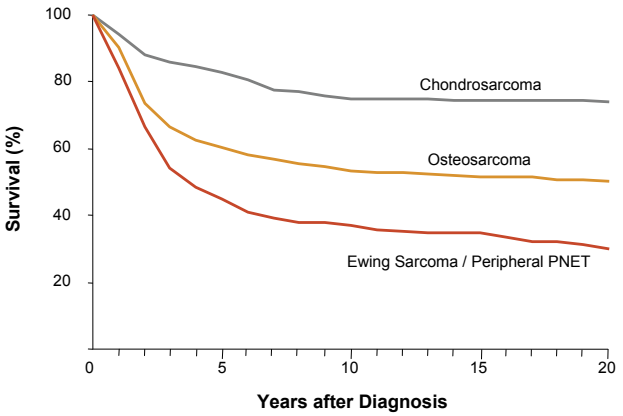

Figure 8.16: Relative Survival, Bone Sarcomas in 15- to 29-Year-Olds, SEER 1975-2000

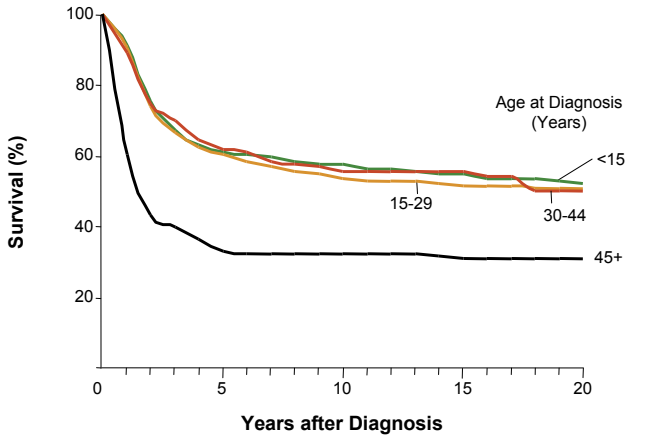

Figure 8.17: Relative Survival by Age, Osteosarcoma, SEER 1975-2000

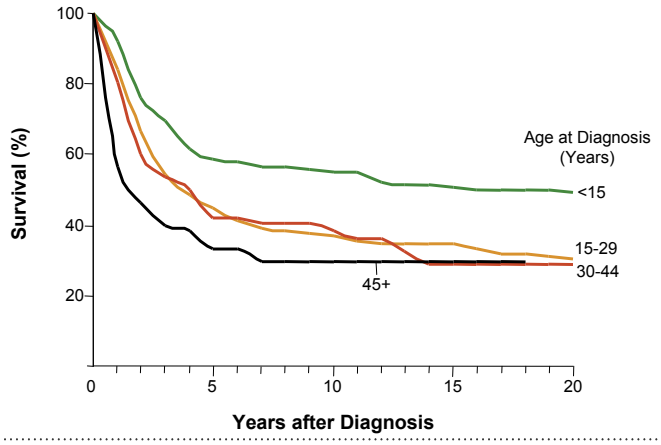

Figure 8.18: Relative Survival by Age, Ewing Sarcoma & Peripheral Primitive Neuroectodermal Tumors, SEER 1975-2000

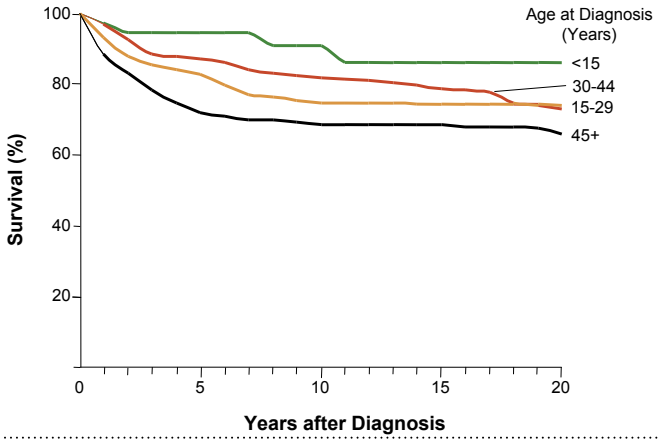

Figure 8.19: Relative Survival by Age, Chondrosarcoma, SEER 1975-2000

growth.[15] However, analytic studies of height, the rate of bone growth, and the timing of puberty have been inconsistent.[16-21] The only known risk factor for Ewing sarcoma is race/ethnicity (see Figure 8.9). The rate of Ewing sarcoma in whites is nearly nine times that of African Americans/blacks.[18,22,23] While these data are consistent with a genetic predisposition, no associations of Ewing sarcoma with congenital syndromes are apparent. Intriguingly, four studies have found an association between Ewing sarcoma and hernia,[24-27] while a fifth did not.[18] The consistency of the association, given the small size of the literature and the memorable nature of the exposure, make these findings credible. Genetic syndromes such as Marfucci's syndrome, Ollier's disease, multiple osteochondromatosis, and hereditary multiple exostoses are the few known risk factors for chondrosarcoma.[28-30]

SUMMARY

In this descriptive analysis of the population-based SEER data, bone cancer represented about 3% of malignancies in the adolescent and young adult population, with an average annual incidence of 9.8% over the time period 1975 to 1999. Incidence declined with increasing age from 15 to 44 years. Rates differed by gender in the adolescent and young adult group, with incidence in males higher than in females. Osteosarcoma and Ewing sarcoma were the most common malignancies

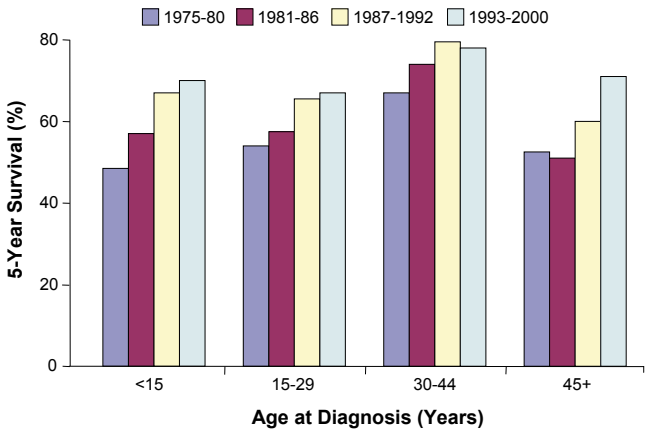

Figure 8.20: 5-Year Survival Rate for All Bone Sarcomas by Era, SEER

of bone in adolescents and young adults. There were no significant racial/ethnic differences in the incidence of osteosarcoma. However, Ewing sarcoma was dramatically higher in the white population. The most common site for the development of osteosarcoma was the long bones of the lower limbs, while Ewing sarcomas and chondrosarcomas were more common in the central axis. The incidence of bone cancer has increased minimally, mainly due to an increase in the number of male patients with osteosarcoma. The etiology of bone cancer remains uncertain and few risk factors have been identified, which explain only a very small proportion of these cancers. The 5-year relative survival for adolescents and young adults with bone cancer improved from 54% in the time period 1975 to 1980 to 67% in the period 1993 to 1998. In general the 5-year survival for osteosarcoma is slightly better than for Ewing sarcoma. Males and females appear to have equal survival for both diseases.

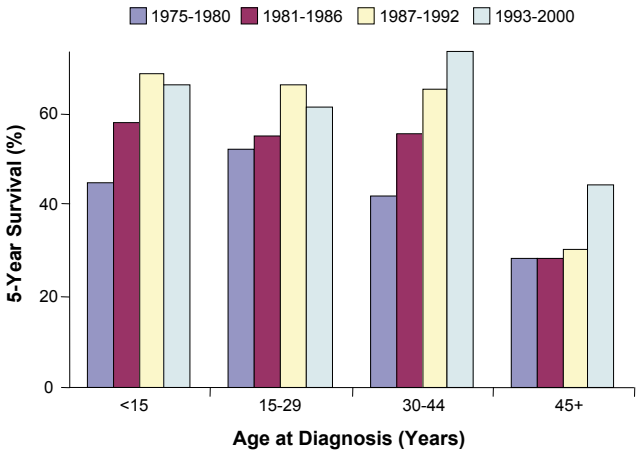

Figure 8.21: 5-Year Survival Rate for Osteosarcoma by Era, SEER

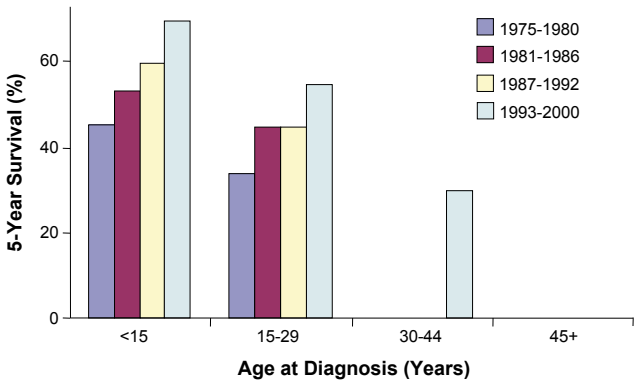

Figure 8.22: 5-Year Survival Rate for Ewing Sarcoma by Era, SEER

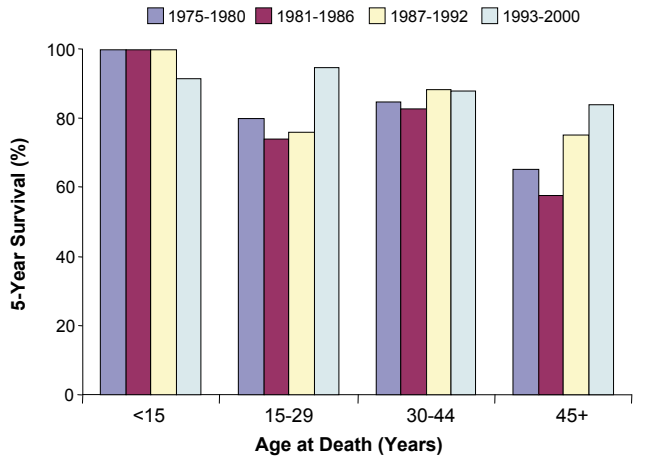

Figure 8.23: 5-Year Survival Rate for Chondrosarcoma by Era, SEER

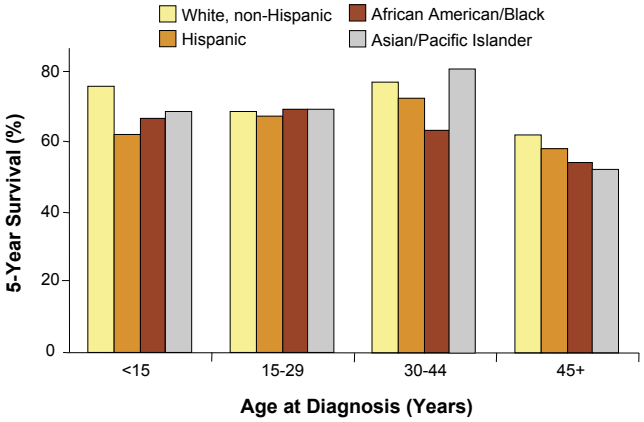

Figure 8.24: 5-Year Survival Rate for All Bone Sarcomas by Race/Ethnicity, SEER 1975-1999

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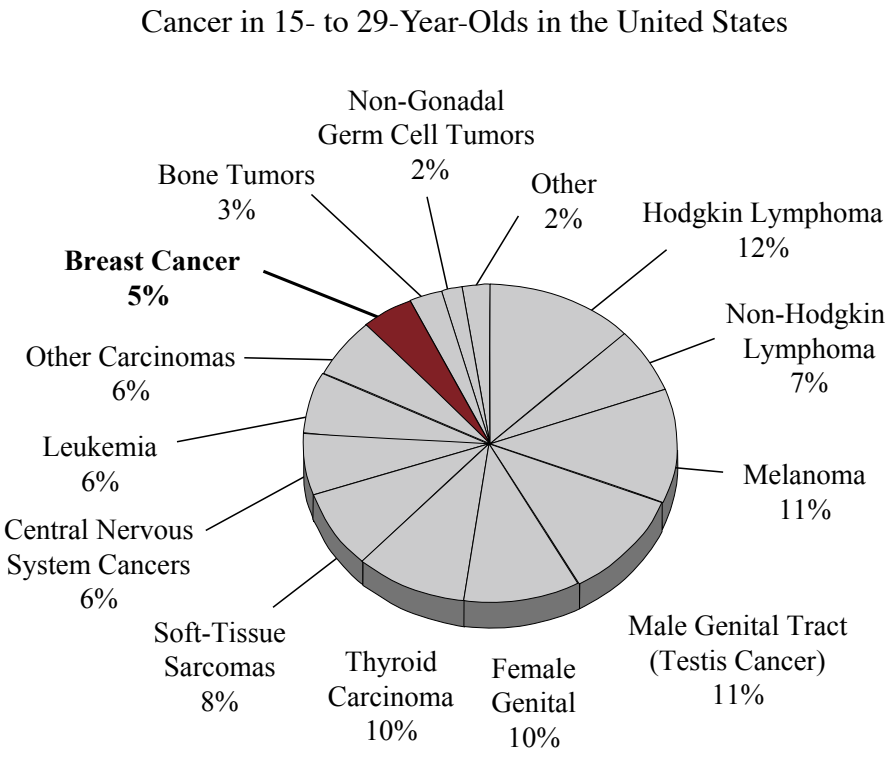
Chapter 9

Breast Cancer



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HIGHLIGHTS

Incidence

- Breast cancer in adolescents and young adults is rare. From 1975 to 2000, less than 0.1% of all breast cancer occurred in young women under 30 years of age.
- There was an increase in the average incidence of breast cancer per million females per year across the adolescent and young adult age groups during the period 1975 to 2000: incidence was 1.3 in 15- to 19-year-olds, 12.1 in 20- to 24-year-olds, rising to 81.1 in 25- to 29-year-olds.
- Breast cancer incidence for African American/black adolescents and young adults was more than twice that of white non-Hispanic women of similar age. This incidence trend reversed between the ages of 45 and 50 years; African American/black women 45 years and older had a lower incidence than white women.
- American Indian/Alsaka Native women had the lowest incidence of breast cancer, regardless of age.

Mortality & Survival

- Death rates for breast cancer rose steadily with increasing age.
- Mortality was much higher for African Americans/blacks and to a lesser extent those of Hispanic ethnicity at all ages than for white, non-Hispanic young women.
- Survival rates have improved over time. White non-Hispanic patients experienced greater improvements in survival rates than Hispanic and African American/black patients.
- Survival is lower for women 15 to 29 years of age than for older women, regardless of histologic subtype and stage.
- Socioeconomic factors, including access to care and health insurance coverage, affect mortality.

Risk Factors

- The primary risk factor for the development of breast cancer in women of all ages is a family history of breast cancer.
- Risk factors in adolescence and young adulthood include germline mutations of BRCA1, BRCA2, p53 (Li Fraumeni syndrome), Muir's Syndrome and PTEN (Cowden's syndrome).
- Prior mantle radiation for Hodgkin disease is a risk factor for the development of breast cancer in young women.
- Age younger than 35 years at diagnosis is a risk factor for the development of aggressive disease.
- African American/black race, particularly for those younger than 45 years of age, and increased parity in young African/black women are risk factors.
- Increased breast tissue density in women over the age of 35 is considered a risk factor.

INTRODUCTION

Breast cancer is rare in adolescent girls and young women, and even more rare in males of this age group. Due to lack of data about male breast cancer, this chapter will present data pertaining to female patients only. When breast cancer occurs in adolescents and young women, it tends to be more aggressive and has a worse prognosis than when it occurs in older women.[1-3] Adolescents and young women tend to have more advanced disease, in part due to the poor correlation of standard mammography findings with extent of disease.[1,4] Age is an independent prognostic factor even when size and nodal status are considered—younger aged patients have a worse prognosis.[1,2] These patients have a higher incidence of invasive ductal carcinoma with an aggressive biological behavior and are more likely to have lymphovascular invasion.[3] Young women are more likely to have tumors that are estrogen-receptor negative.[1,4,5]

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

The International Classification of Childhood Cancer (ICCC) has no specific category for breast cancer. These cancers are contained with category XI(f), *Other and Unspecified Carcinomas,* as one of the *Carcinomas and Other Epithelial Neoplasms* (category XI). Hence, the SEER site recode based on the International Classification of Diseases for Oncology (ICD-O) was used exclusively for this chapter.

For breast cancer, the ICD-O Topography codes are C50.0-C50.9 (all tissues in the breast except overlying skin) and the ICD-O categories include general carcinomas and adenocarcinomas (8010-8041, 8140, many others) and specific carcinomas of the breast. The latter are found in the ICD-O group *Ductal and Lobular Neoplasms* (8500-8543) and include intraductal, lobular, inflammatory, comedo-, intracystic, and Paget's types, and various combinations of these histologies.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

Since the ICCC was set up as a classification for childhood cancer, it does not have a separate category for breast cancer. Topography and histology from ICD-O can be used to examine differences among very young breast cancer patients compared to older patients, but it is unclear whether this is sufficient to explain all of the biologic differences, given that the younger breast cancer patients in general experience poorer survival than older breast cancer patients.

INCIDENCE

The SEER incidence data in this section were collected between 1975 and 2000. Less than 1% of all breast cancer cases occurred in women under the age of 30. Breast cancer incidence rose steadily with age, stabilized, and then dropped slightly after 80 years of age (Figures 9.1, 9.2).

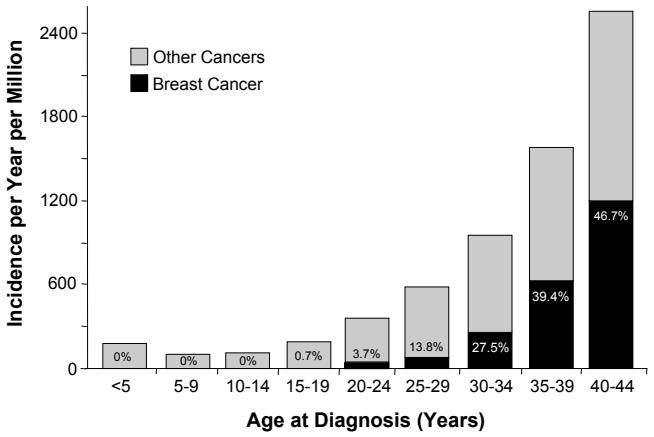

Figure 9.1: Incidence of Breast Cancer Relative to All Cancer in Females, U.S., SEER 1975-2000

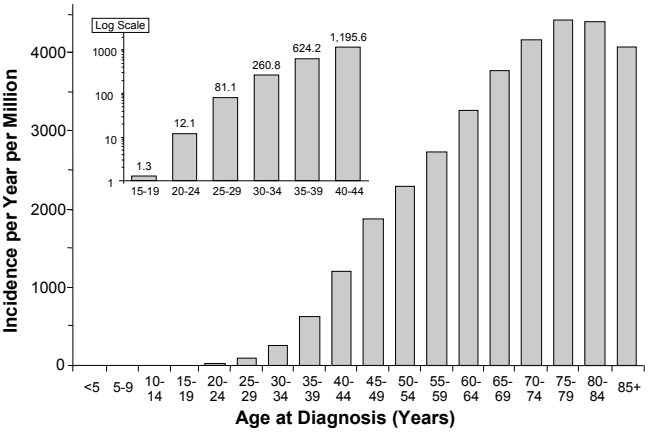

Figure 9.2: Incidence of Breast Cancer in Females, SEER 1975-2000

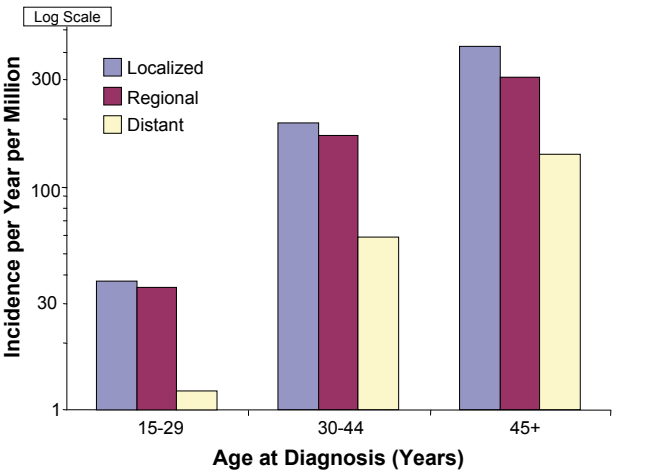

Figure 9.3: Incidence of Breast Cancer in Females by Extent of Disease at Diagnosis, SEER 1975-2000

Table 9.1: *Incidence of Breast Cancer in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions), females	9.365	10.026	10.008	9.829	9.276	9.583
Average incidence per million, 1975-2000, SEER	^	^	^	1.3	12.1	81.1
Average annual % change in incidence, 1975-2000, SEER	^	^	^	0	0	0
Estimated incidence per million, year 2000, U.S.	^	^	^	1.3	12.1	81.1
Estimated number persons diagnosed, year 2000, U.S.	^	^	^	13	112	777

^ Too few for a reliable estimate

Over the period 1975 to 2000, there was an increase in incidence of breast cancer with increasing age, from an average incidence per million of 1.3 in 15- to 19-year-olds, to 12.1 in 20- to 24-year-olds, to 81.1 in 25- to 29-year-olds (Table 9.1). However, there was no annual increase within each age group apparent over the same time period.

As shown in Figure 9.3, the incidence of regional spread of disease was higher for adolescents and young adults than for women older than 30 years of age.

Racial/Ethnic Differences in Incidence

From 1992 to 2002, African American/black women from 10 to 34 years of age had a higher rate of breast cancer than any other race/ethnicity (Figure 9.4). Above age 50, however, breast cancer predominated in non-Hispanic white women (data not shown). At all ages, American Indian/Alaska Native women had the lowest incidence of breast cancer (Figure 9.4; data not shown for older females).

Trends in Incidence

The incidence of breast cancer in young women has remained relatively stable over the period 1975 to 2000 (Figures 9.5).

OUTCOME

Mortality

During the period 1975 to 2000, breast cancer mortality rose steadily with age (Figure 9.6), reflecting an increasing breast cancer incidence (Figure 9.2). The mortality:incidence ratio was lower in the 15- to 29-year age range than in the 30- to 44-year range (Figure 9.7), implying that survival was better among the younger patients. This apparent advantage for the younger age group may be due either to a higher cure rate or to a longer interval to death, such that the deaths from breast cancer among those diagnosed between 15 and 29 years of age occur primarily after age 30. Survival data shown below indicate that it was not due to a higher survival rate.

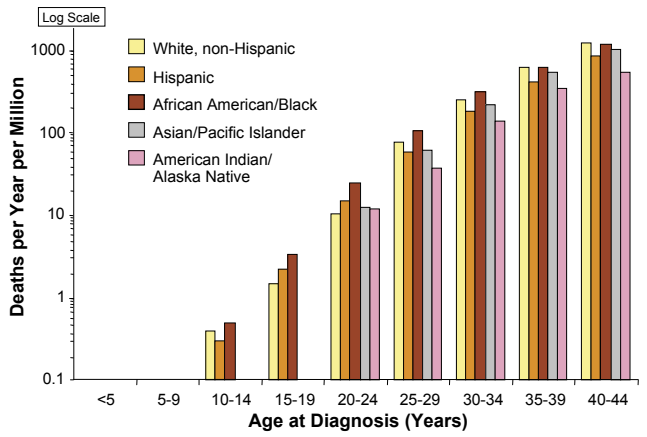

Figure 9.4: Incidence of Breast Cancer in Females by Race/Ethnicity, SEER 1992-2001

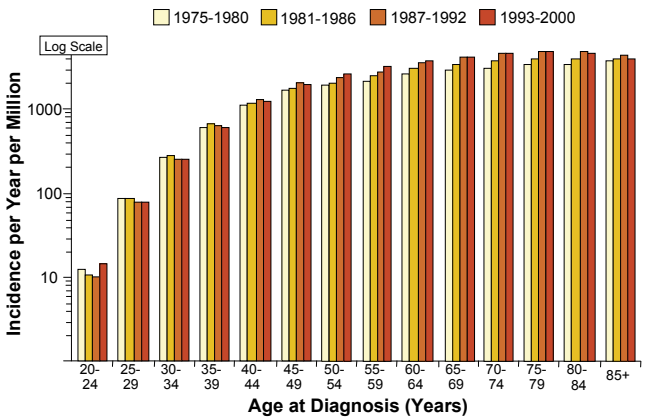

Figure 9.5: Change in Incidence of Breast Cancer in Females by Era, SEER

Mortality for all age groups remained stable or dropped since 1981. The decrease in mortality was more pronounced for those over 30 years of age, particularly in the most recent treatment era (Figure 9.8), and likely reflects the use of screening programs, improved diagnostic techniques, and adjuvant chemotherapy and radiation therapy. There was a more significant improvement in mortality over time for older age groups.

Racial/Ethnic Differences in Mortality

For women younger than 45 years of age, mortality for African Americans/blacks was nearly twice as high as for other racial/ethnic groups (Figure 9.9). Although African Americans/blacks had an increased incidence of breast cancer compared to other groups, the death rate for this group was disproportionately higher than the incidence difference (Figure 9.4). African American/black patients have been reported to present with higher stage or more advanced disease.[6,7] White non-Hispanic women were significantly more likely to be older and to have smaller tumors, have less lymph node involvement, have tumors with positive estrogen receptor and progesterone receptor status compared with Hispanic or African American/black women.[6]

An additional analysis of treatment modalities used for women under 35 years of age with invasive breast cancer revealed that African American/black women—and to some extent Hispanic females—received less aggressive initial therapy than white non-Hispanic women, despite similar prognostic variables. These analyses were multivariate and were adjusted for stage, grade, lymph node status, and treatment. Overall, 9% of the women in this study were registered on clinical trials, yet African American/black women were less likely than others to be among those registered. African American/black and Hispanic women had poorer outcomes and a higher mortality than white, non-Hispanic women.[6]

Figure 9.10 displays mortality data for white and African American/black women over the period 1975 to 2000. For white Americans there was a relatively consistent decline in the death rate across all age groups, but for African Americans/blacks, either an increase in death rate or stable death rate was observed.

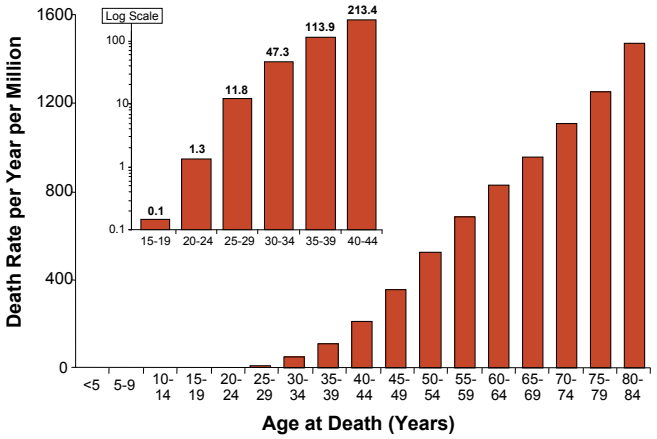

Figure 9.6: National Mortality for Breast Cancer in Females, U.S., 1975-2000

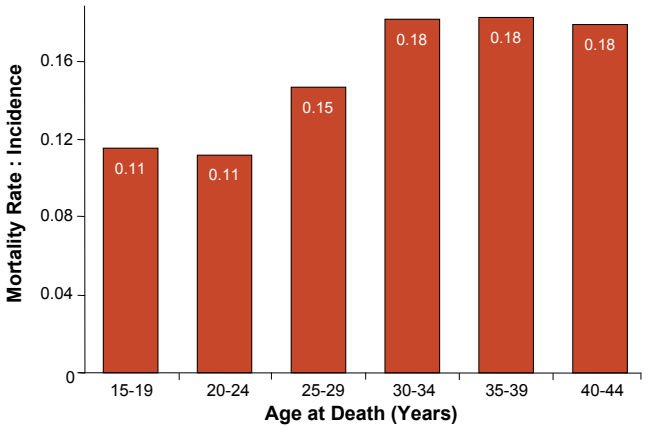

Figure 9.7: Ratio of National Mortality to SEER Incidence for Breast Cancer in Females, U.S., 1975-2000

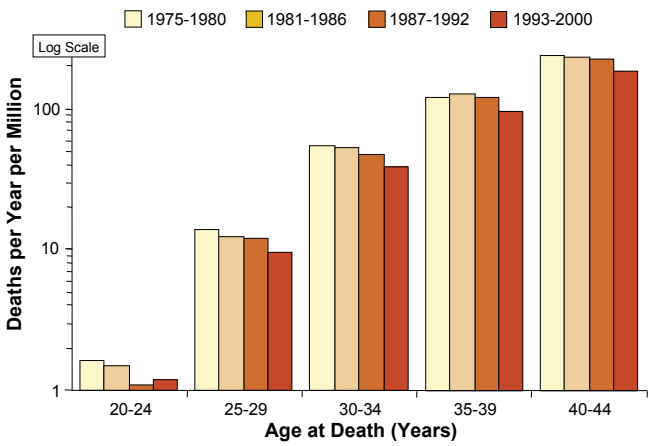

Figure 9.8: National Mortality for Breast Cancer in Females, U.S., by Era

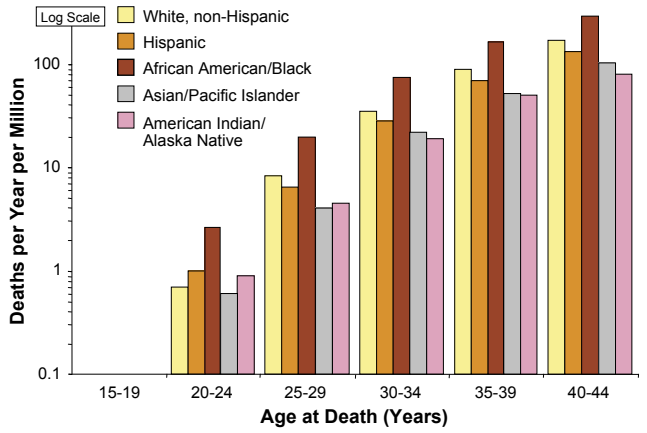

Figure 9.9: National Mortality for Breast Cancer in Females by Race/Ethnicity, 1990-2000

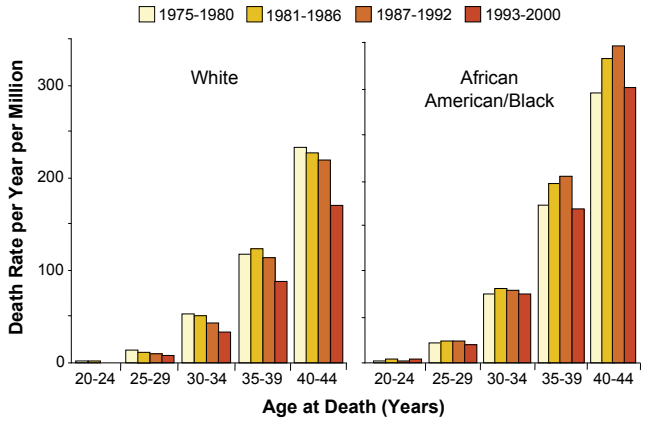

Figure 9.10: National Mortality for Breast Cancer in Females by Era, 1975-2000

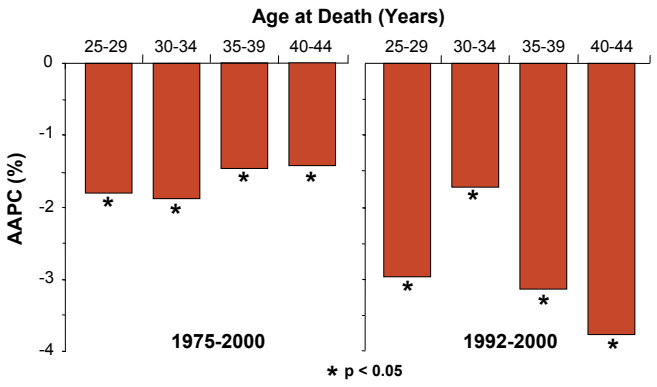

Figure 9.11: Average Annual Percent Change (AAPC) in National Mortality for Breast Cancer in Females, 1975-2000

Data analysis of death from breast cancer (1973 to 2000) and its association to age at diagnosis, stage, and ethnicity indicates that breast cancer was the cause of death more often in younger patients as compared to older patients, and was associated with advanced stage and race. African American/black women did not achieve survival rates similar to white non-Hispanic women.[8]

Trends in Mortality

A reduction in breast cancer mortality occurred over time, and was significant for each age group. This improvement has been considerable in more recent years (Figure 9.11).

The average annual percent change in mortality for whites compared to African Americans/blacks reveals a significant discrepancy between the two racial groups. Whites experienced substantial improvements in survival in all age groups in the period 1975 to 2000—improvements not observed in the African American/black population. Decreases in mortality during this period were three times greater for whites than for African Americans/blacks (Figure 9.12).

Survival

Five-year survival rates for breast cancer, by age, revealed that survival was lowest for those in the adolescent and young adult age group. Within that group, 25- to 29-year-old women had slightly lower survival rates than those younger or older (Figure 9.13). This lower survival rate for 15- to 29-year-old women may be due to several factors: breast cancer in young women is typically invasive, more aggressive and associated with a worse prognosis

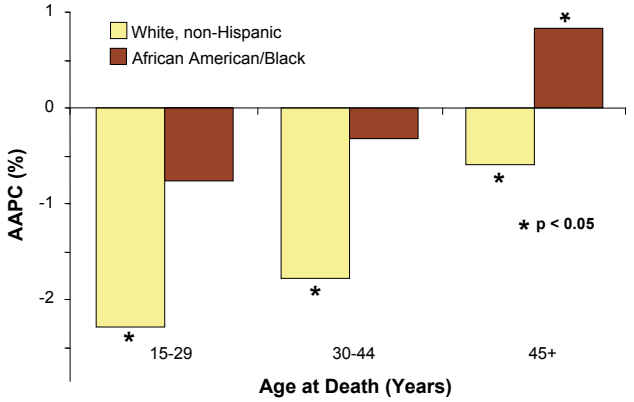

Figure 9.12: Average Annual Percent Change (AAPC) in National Mortality for Breast Cancer in Females, by Race, 1975-2000

than in older women,[1,2] detection rates are lower due to lack of suspicion in the general population and medical community, and breast tissue in younger women is commonly more dense than in older women, resulting in mammography results which may be inconclusive.

Five-year survival rates, by era, revealed that although survival rates for the adolescent and young adult population remained relatively stable over time, slight improvement was seen in the most recent era (Figure 9.14).

Breast cancer survival is consistently lower for adolescent and young adult women than for other age groups, regardless of histologic type. For all age groups, 5-year survival is limited for women with inflammatory disease (Figure 9.15). Lower survival rates reflect the aggressive biologic and pathologic characteristics of tumors specific to this age group, and the fact that routine screening for breast cancer is not the standard of care in adolescents and young adults. Although treatment modalities have improved considerably over the last 30 years, due to National Cancer Institute initiatives for the care of breast cancer patients, improvements in survival have not been observed in adolescents and young adults to the extent seen in older females.

Five-year survival rates were generally low for 20- to 24-year-old women, except for those with localized disease at diagnosis. For localized disease, women in the age groups 20 to 24 and 40 to 44 had high survival rates, although rates were relatively high for all ages (Figure 9.16). For regional and distant disease, survival rates increased with age. As expected, survival for all women was best for those with localized disease, followed by those with regional disease. Survival was poor for all women with distant disease (Figure 9.16).

The average annual percent change in 5-year survival rates from 1975 to 2000 is shown in Figure 9.17. For young women 15 to 29 years of age, decreases in 5-year survival rates were noted for localized and regional disease. Decreases were also seen for women 30 to 44 years of age with regional disease, but significantly better survival was noted for those with localized or distant disease. For those over 45 years of age, improvement—which was significant—was observed only for those with localized disease. This may indicate the benefit of awareness campaigns and breast cancer screening in the older population.

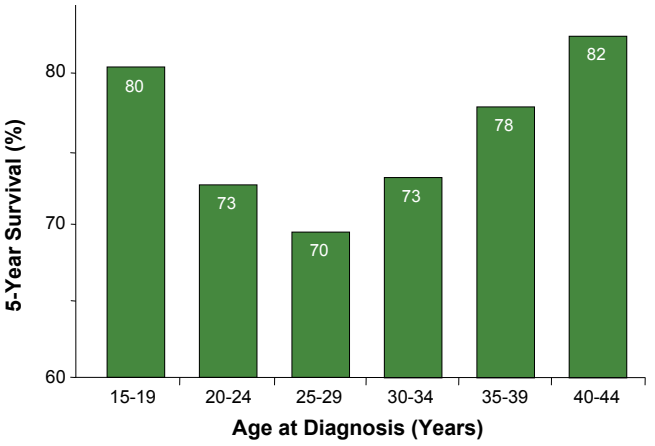

Figure 9.13: 5-Year Survival Rate for Breast Cancer in Females, SEER 1975-1999

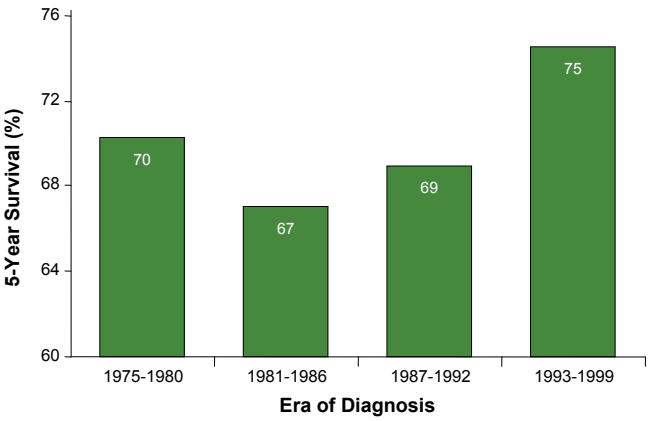

Figure 9.14: 5-Year Survival Rate for Breast Cancer in 15- to 29-Year-Old Females, by Era, SEER 1975-1999

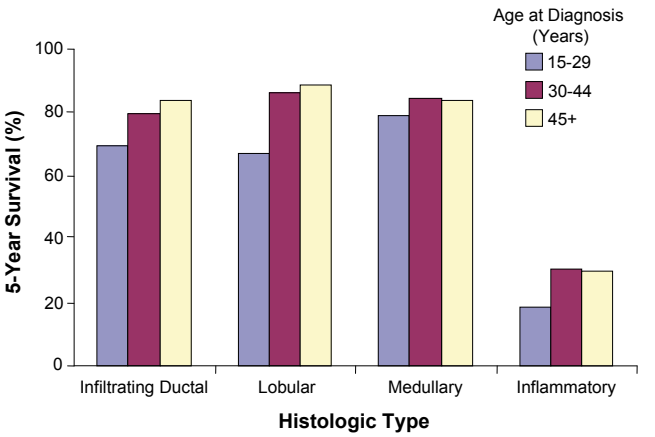

Figure 9.15: 5-Year Survival Rate for Breast Cancer in Females by Histologic Type and Age, SEER 1975-1999

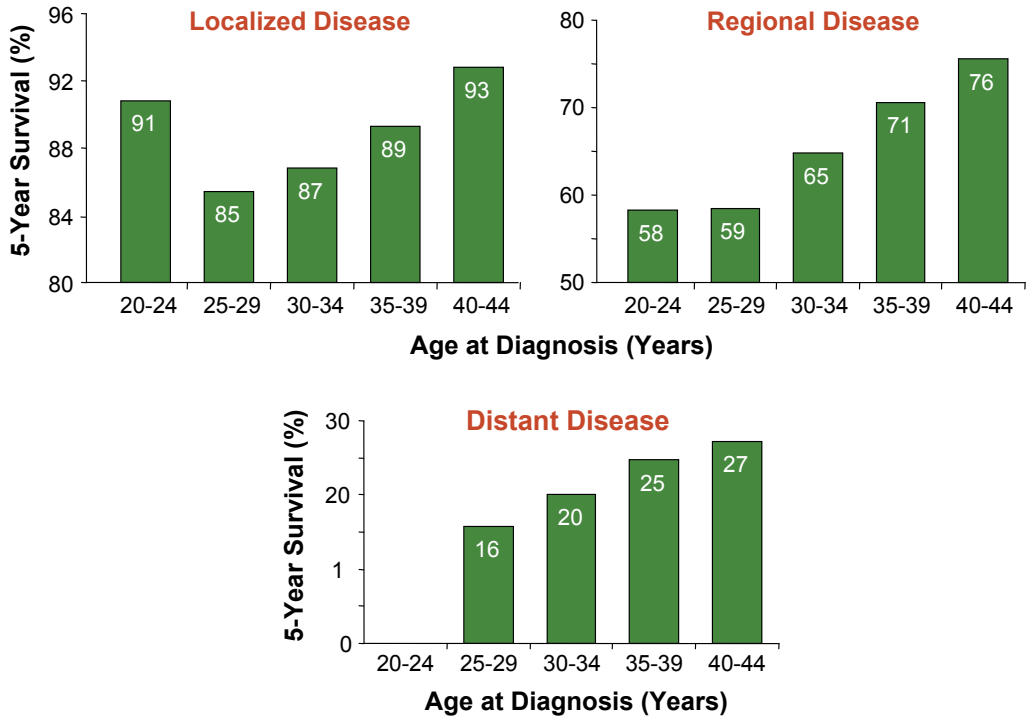

Figure 9.16: 5-Year Survival Rate for Breast Cancer in Females by Age and Extent of Disease at Diagnosis, SEER 1975-1999

RISK FACTORS

Due to the low incidence of breast cancer in adolescents and young adults, relatively few epidemiological studies have been undertaken with the focus on this age group. Much of the information listed below is based on studies of women under 35 or 40 years of age; in a few studies age was stratified at above and below 50 years.

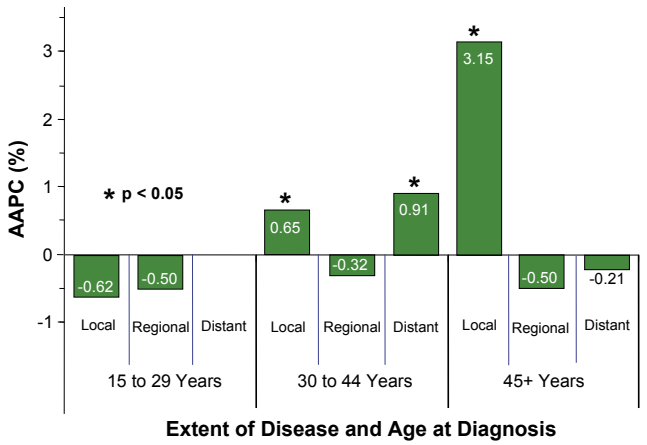

Figure 9.17: Average Annual Percent Change (AAPC) in 5-Year Survival Rates for Breast Cancer in Females by Age and Extent of Disease, SEER 1975-2000

General risk factors for the development of breast cancer include age, reproductive history, personal or family history of breast cancer, and environmental exposure to carcinogens.[9] A significant risk factor for breast cancer is family history—specifically in a first- or second-degree relative. However, even with increased risk, only 5 percent of familial breast cancers studied are consistent with hereditary breast cancer.[10-12]

Young women with germline mutations in BRCA1, BRCA2, p53 (Li Fraumeni syndrome), Muir syndrome, or PTEN (Cowden's syndrome) are at increased risk for breast cancer.[9,13] Women who carry a BRCA1 or BRCA2 mutation have a lifetime risk of breast cancer as high as 80-90%, although lower risk estimates of 37-56% have also been reported.[14]

Young female patients are more likely to carry p53 mutations, and perturbations of the p53 pathway are associated with more aggressive and therapeutically refractory tumors.[15] Li Fraumeni syndrome is a rare, dominantly inherited condition caused by a germline mutation in the Tp53 gene on chromosome 17.[16] Affected

patients have a 50% risk of developing cancer by age 35 and a 90% risk of developing cancer in their lifetime. Muir syndrome is a familial cancer family variant with basal cell carcinomas and benign and malignant colon tumors.[17] Cowden's syndrome is caused by a rare mutation in PTEN gene on chromosome 10.[18] Affected patients have an increased risk of developing breast or thyroid carcinoma at a young age and often have multiple hamartomas.

Race/ethnicity is a risk factor for the development of breast cancer. Incidence is higher in African Americans/black women younger than 50 years of age than for other racial/ethnic groups, even in the adolescent and young adult subset.[19] African American/black women more often present with distant disease than white women, and mortality in this group exceeds that of the white population. Yet for women born after 1950, mortality has decreased, and the African American/black population has experienced more benefit than the white population.[20]

Reasons for these racial/ethnic disparities include age, tumor histology, premenopausal endogenous hormones and growth factors levels, and parity. African American/black women younger than 45 years of age were more likely to develop breast cancer than those over 45, whereas white women over the age of 45 were more likely to develop breast cancer than those under 45.[7] African American/black women under the age of 50 were also noted to have more aggressive tumor histology.[19] In a population-based study of women with breast cancer, a significant difference in the expression of p53, late stage tumors, larger tumors, positive lymph nodes, and higher histologic grade was seen in African American/black women as compared to white women.[21] Racial differences in levels of endogenous hormones and growth factors indicate that African American/black women under 45 years of age are at higher risk of developing breast cancer than their white counterparts.[22] African American/black women were more likely to have had an early first birth (when younger than 20 years of age) and higher parity than white women, with a higher risk of breast cancer at younger ages.[23,24] African American/black women were more likely to have estrogen-receptor negative tumors than white women, which is a risk factor in itself.[25] In regards to treatment for breast cancer, African American/black women are more likely than white women to undergo breast-conserving surgery or have no surgery for their disease.[26] They are also less likely to receive post-operative radiation therapy than white women.[6] Treatment is affected by socioeconomic factors such as access to care, lack of health insurance, and type of health insurance coverage.[26]

Age is an independent risk factor; women under 35 years more often have a palpable mass at diagnosis, undifferentiated tumors, grade 3 tumors, negative hormone receptor status, and microscopic lymph node involvement.[1,2] An increase in the incidence of infiltrating ductal carcinoma in women younger than 39 years of age was noted in a British study, with a decrease in regional and distant disease with advancing age.[3] A French study found that women younger than 40 years of age had tumor histology associated with high nuclear grade and vascular invasion.[27]

Other risk factors include circulating enzyme and hormone levels and breast tissue density. A recent study indicated that increased cytochrome P450 1A2 function may be associated with an increased risk of developing breast cancer.[28] The risk of developing estrogen-negative breast cancer may be higher in women with particular enzyme genotypes.[29] In women over 35 years of age and particularly over age 50, increased density of breast tissue—independent of ethnicity—is a risk factor for the development of breast cancer.[30]

A unique group at risk for the development of breast cancer consists of adolescent and young adult survivors of Hodgkin lymphoma. The risk of developing breast cancer appears to be related to the quantity and location (chest/mantle) of prior radiation therapy, with or without alkylating agent-based chemotherapy; this risk increases over time.[13,31,32]

SUMMARY

Breast cancer is rare in adolescents and young women but has a worse prognosis than for older women. Young females with breast cancer are more likely to present with regional spread prior to diagnosis.[5] Adolescents and young women are not considered at risk for breast

cancer, therefore they may not seek early medical attention or concerns may be dismissed by medical practitioners. Breast cancer in this age group may also be more difficult to detect due to dense breast tissue. Nonetheless, there is evidence that breast cancer is more virulent in young females, with a worse prognosis for the same stage of disease at diagnosis. There is a higher incidence of germline mutations of BRCA1, BRCA2, Tp53, and PTEN in this age group. Survival data demonstrate striking racial differences. African Americans/blacks—and to a lesser degree Hispanics—fare poorly compared to whites. Although progress has been made, there is much to accomplish for the youngest women and women of color. Effective screening programs are needed to help identify early disease in these at-risk groups. These young women should be encouraged to participate in such programs at an early age and throughout their lives.

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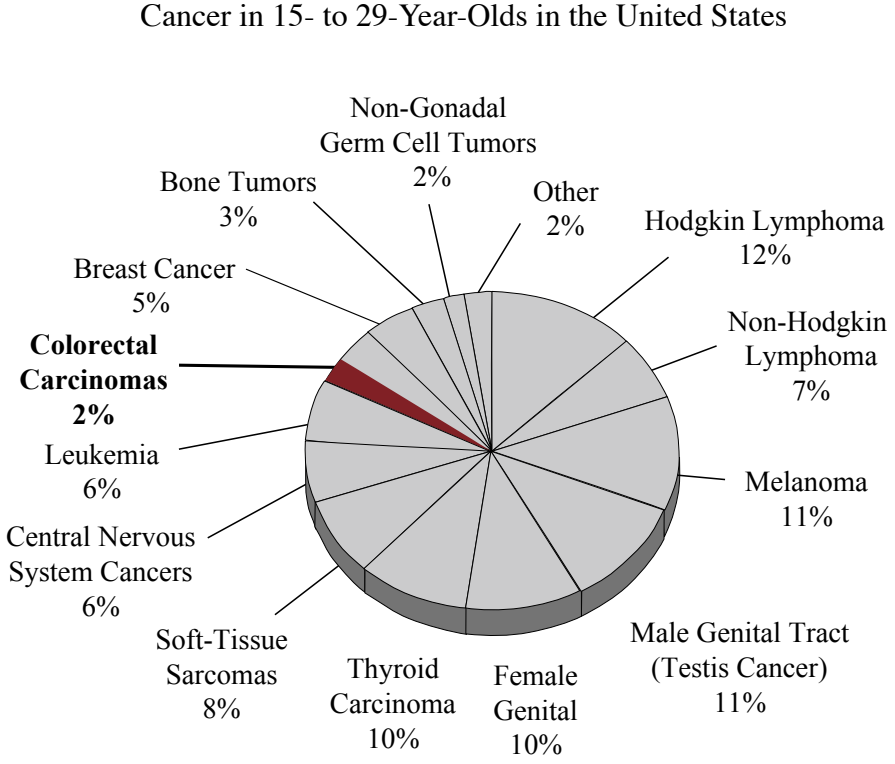
Chapter 10

Colon and Rectal Cancer



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HIGHLIGHTS

Incidence

- Colorectal carcinoma occcurs in adolescents and young adults at an incidence that increases exponentially between 10 and 35 years of age.
- During 1975 to 2000, colorectal cancer accounted for 2.1% of all neoplasms diagnosed in 15- to 29-year-olds.
- In the year 2000, an estimated 432 individuals 15 to 29 years of age were diagnosed with cancer of the colon.
- The incidence of colorectal carcinoma relative to other cancers rose from 1% in the 15- to 19-year age group, to 1.7% in the 20- to 24-year age group, to 2.7% in the 25- to 29-year age group.
- Males had a higher incidence of colorectal carcinoma than females at all ages, except in individuals 15 to 19 years of age.
- Although the incidence of colorectal carcinoma in individuals over 45 years declined during the period 1975 to 2000, the incidence in 15- to 29-year-olds increased.
- The incidence of colorectal carcinoma was approximately equal in white non-Hispanics, Hispanics, African Americans/blacks, and Asians/Pacific Islanders who were 15 to 29 years of age when diagnosed.
- American Indians/Alaska Natives between 20 and 35 years of age tended to have a lower incidence of colorectal carcinoma than other racial/ethnic groups.

Mortality & Survival

- Five-year survival for individuals 15 to 29 years of age was similar to that of older individuals.
- Colorectal carcinoma survival improved over time, although it remained relatively stable for individuals in the 15- to 29-year age group.
- A 54% 5-year survival rate for colorectal carcinoma for the age group was achieved in the era 1975 to 1980; the 5-year survival rate increased to 58% in the era 1993 to 1999.
- Females had higher 5-year survival rates than males at virtually all ages; the disparity was particularly marked in individuals 15 to 29 years of age.
- African Americans/blacks in the 15- to 29-year age group had the worst survival, approximately 20% worse than whites, non-Hispanics, and Asians/Pacific Islanders.
- Whites tended to have the best prognosis.

Risk Factors

- Predisposing factors for colorectal carcinoma in children and young adults include hereditary conditions (polyposis and non-polyposis syndromes), inflammatory bowel disease, and prior radiation exposure.
- Hamartomatous polyposis syndromes carry a lower risk of colorectal carcinoma than adenomatous polyposis syndromes.

INTRODUCTION

Although colorectal carcinoma is among the most common malignancies of adulthood, the disease is uncommon in adolescents and young adults. Between 1975 and 2000 in the U.S., colorectal carcinoma accounted for 2.1% of all neoplasms in adolescents and young adults 15 to 29 years of age. In the year 2000, 432 individuals in this age group were diagnosed with colorectal carcinoma in the U.S.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

The International Classification of Childhood Cancer (ICCC) has no specific category for colorectal cancer. These cancers are contained with category XI(f), *Other and Unspecified Carcinomas*, as one of the *Carcinomas and Other Epithelial Neoplasms* (category XI). Hence, the SEER site recode based on the International Classification of Diseases for Oncology (ICD-O) was used exclusively for this chapter.

Table 10.1: *Incidence of Colorectal Carcinoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	^	^	0.6	2.0	5.6	14.6
Average annual % change in incidence, 1975-2000, SEER	^	^	0	0	0	0
Estimated incidence per million, year 2000, U.S.	^	^	0.6	2.0	5.6	14.6
Estimated number of persons diagnosed, year 2000, U.S.	^	^	13	41	107	284

^ Too few for a reliable estimate

For colorectal cancer, the ICD-O Topographical categories are C18.0-C20.9, C26.0 (colon, rectum, and intestine NOS) and the ICD-O Morphologic categories include general carcinomas and adenocarcinomas (8010-8041, 8140, many others) and specific cancers of the colon/rectum. The latter include carcinoid tumors (8240-8245). No attempt was made to separate cancer of the colon from rectal cancer. Cancer of the anus is not included in this chapter.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

Since the ICCC was set up as a classification for childhood cancer, it does not have a separate category for colorectal cancer. Topography and histology from ICD-O can be used to examine differences among very young colorectal cancer patients compared to older patients, but it is clear that this method needs to be complemented with other biologic determinants such as microsatellite instability, which is far more common in the colorectal carcinomas that occur in adolescents and young adults, as opposed to the sequential gene mutations—including p53 mutations—that occur in older adults.

INCIDENCE

According to SEER data, colorectal carcinoma accounted for 2.1% of all malignancies diagnosed in individuals 15 to 29 years of age between 1975 and 2000, and occurred at a rate of 7.21 per million, age adjusted to the 2000 census and to 5-year age intervals. It was the 11th most common cancer in this age bracket. By using the data in *Trends in Incidence* (section below), a total of 432 new cases of colorectal cancer were estimated to have been diagnosed in the U.S. in the year 2000 (Table 10.1).

Age-Specific Incidence

The striking dependence of the incidence of colorectal carcinoma on age is shown in Figure 10.1. During 1975 to 2000, it increased exponentially between ages 10 and 35, as highlighted by the red line in the semilog plot in the inset to figure 10.1.

Figure 10.2 shows the incidence of colorectal carcinoma relative to that of all cancers in 5-year age groups from 0 to 44 years. The incidence of colorectal carcinoma relative to all cancers increased steadily with advancing age—again, even within the 15- to 29-year age group.

Gender-Specific Incidence

The incidence of colorectal carcinoma in males and females was similar before age 20, and higher in males than females older than 20 years. The predilection for male gender increases with age, such that by 50 years of age, males had a nearly 50% greater incidence (Figure 10.3).

Racial/Ethnic Differences in Incidence

The incidence of colorectal carcinoma was approximately equal in white non-Hispanics, Hispanics, African Americans/blacks, and Asians/Pacific Islanders who were 15 to 29 years of age when diagnosed (Figures 10.4 and 10.5 [the log version of 10.4]). American Indians/Alaska Natives between 20 and 35 years of age tended to have a lower incidence of colorectal carcinoma than other racial/ethnic groups. African Americans/blacks had a lower incidence from 0 to 20 years of age (Figure 10.5).

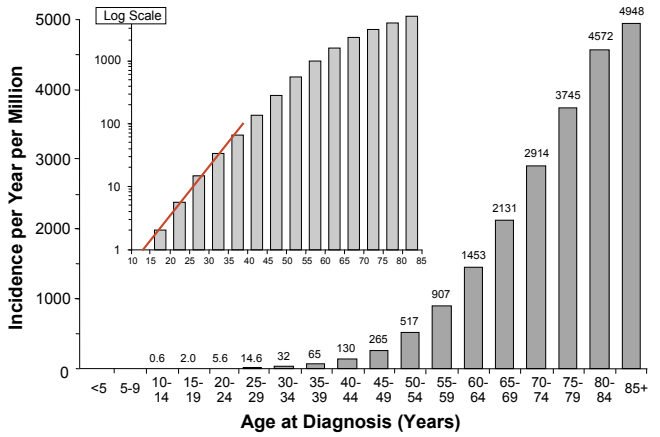

Figure 10.1: Incidence of Colorectal Carcinoma, SEER 1975-2000

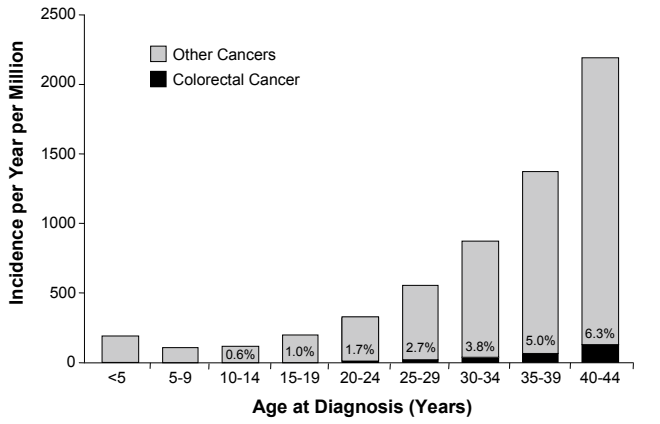

Figure 10.2: Incidence of Colorectal Cancer Relative to All Cancer, SEER, 1975-2000

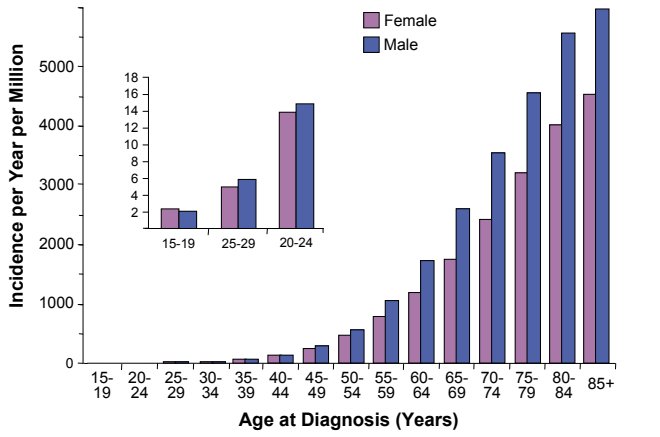

Figure 10.3: Incidence of Colorectal Carcinoma by Gender, SEER 1975-2000

Trends in Incidence

Figure 10.6 displays the incidence of colorectal carcinoma in 5-year age groups over 4 time periods: 1975 to 1980, 1981 to 1986, 1987 to 1992, and 1993 to 2000. For individuals over 45 years of age, the incidence in the most recent time period (1993 to 2000) was lower than during earlier years.

As shown in Figure 10.7, a decline in colorectal carcinoma incidence in younger individuals was not readily apparent. The rarity of colorectal carcinoma in patients under 45 years of age may explain the difficulty in identifying a trend in incidence in this age group.

Figure 10.8 displays the average annual percent change in incidence of colorectal carcinoma by age group during the years 1975 to 2000. The incidence of colorectal carcinoma in patients in the 15- to 29-year age group increased during this period, whereas the incidence in patients over 30 years of age declined.

OUTCOME

Mortality

As with incidence (Figure 10.7), mortality of colorectal cancer was directly proportional to age and was higher in males than females (Figure 10.9). In the U.S., African Americans/blacks had higher mortality from colorectal carcinoma than any other racial/ethnic group. This was true not only for older adults but also for young adults 25 years of age and older (Figure 10.10).

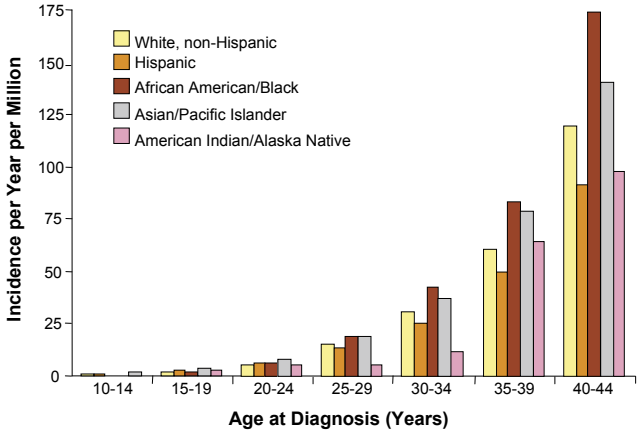

Figure 10.4: Incidence of Colorectal Carcinoma by Race/Ethnicity, SEER 1992-2000

Since 1975, colorectal carcinoma mortality has declined among 15- to 29-year-olds (Figure 10.11), despite the increased incidence in this age group (Figure 10.8). The reduction in national colorectal cancer mortality during the past quarter century averaged 1.4% per year in patients younger than age 45 ($p < 0.05$), and the decline was also statistically significant in each 5-year age group under age 45 (Figure 10.12). There is a suggestion that the trend in national colorectal cancer mortality reduction is directly proportional to age, with patients younger than 35 years of age experiencing less of a reduction in mortality than those 35 to 44 years of age (Figure 10.12).

Survival

Five-year survival of individuals with colorectal carcinoma 15 years of age and older was between 50% and 61% for all five-year age groups (Figure 10.13). Five-year survival rates improved in successive eras, though rates for individuals 15 to 29 years of age remained relatively stable (Figure 10.14).

Gender-Specific Survival

Females had a consistently higher 5-year survival rate compared to males; this was most apparent in patients younger than 40 years of age (Figures 10.15 and 10.16)

Racial/Ethnic Differences in Survival

Survival—as a function of race/ethnicity—for 15- to 29-year-olds diagnosed with colorectal cancer during the period 1992 to 1999 is shown in Figure 10.17. African Americans/blacks had the worst survival in this age group. White non-Hispanics, Hispanics, and

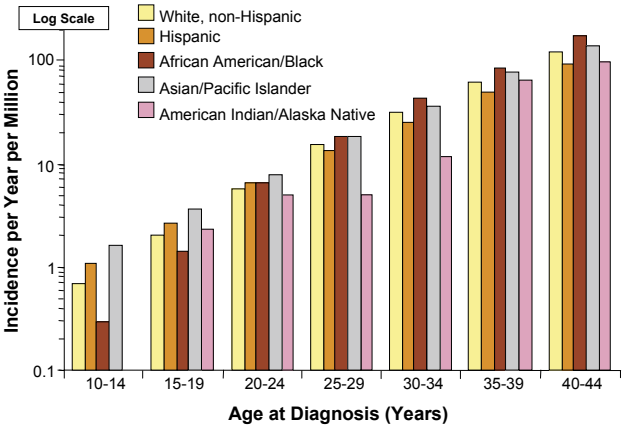

Figure 10.5: Incidence of Colorectal Carcinoma by Race/Ethnicity, SEER 1992-2000

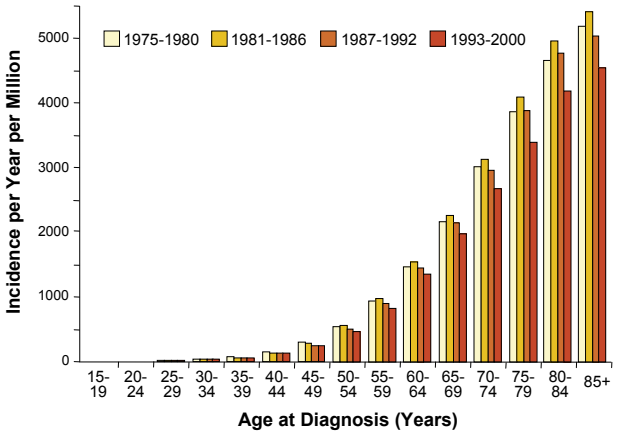

Figure 10.6: Change in Incidence of Colorectal Carcinoma by Era, SEER 1975-2000

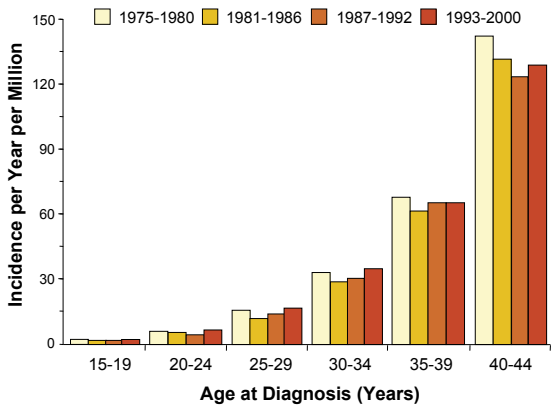

Figure 10.7: Change in Incidence of Colorectal Carcinoma by Era, SEER 1975-2000

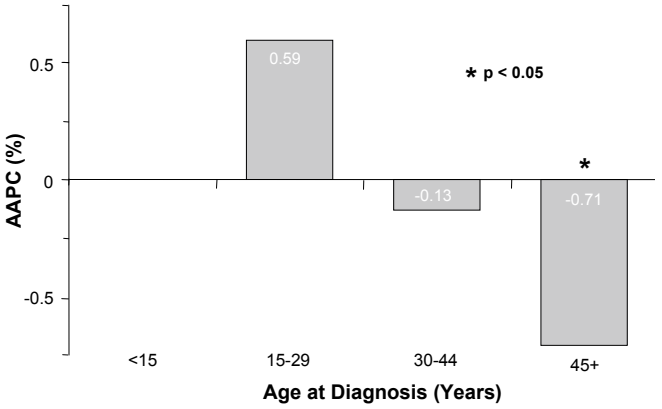

Figure 10.8: Average Annual Percent Change (AAPC) in Incidence of Colorectal Carcinoma, SEER 1975-2000

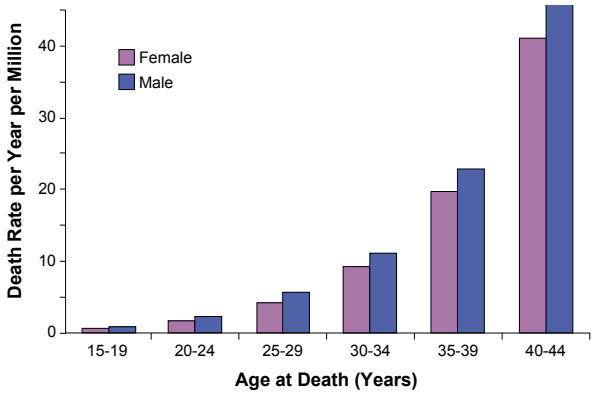

Figure 10.9: National Mortality of Colorectal Carcinoma by Gender, U.S., 1975-2000

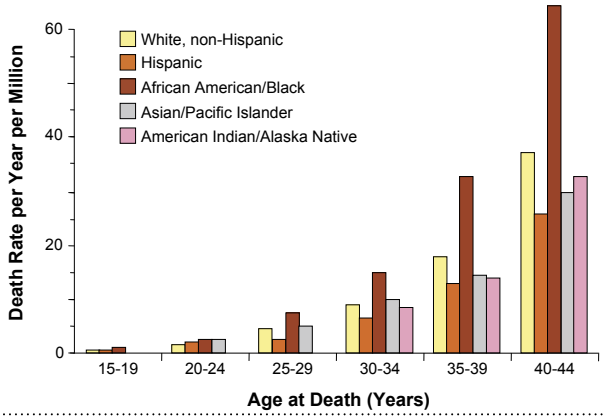

Figure 10.10: National Mortality of Colorectal Carcinoma by Race/Ethnicity, U.S., 1975-2000

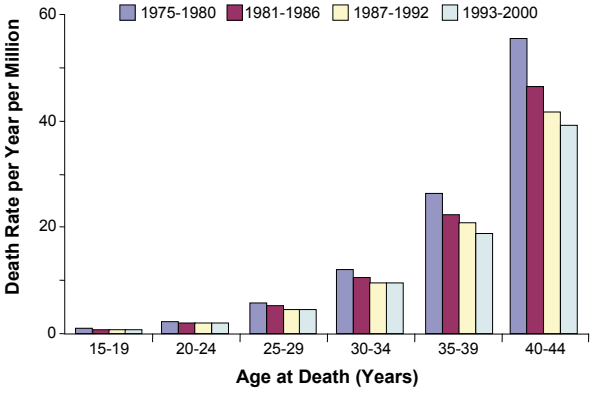

Figure 10.11: National Mortality of Colorectal Carcinoma by Era, U.S

Asians/Pacific Islanders had comparable survival, which was from 15% to 20% better than for African Americans/blacks as early as 1 year after diagnosis and persisting for at least five years. Whites (including Hispanic whites) tended to have the best prognosis.

Survival According Extent of Disease

Figure 10.18 displays 5-year survival rates for individuals with colorectal carcinoma according to disease extent. There were no apparent differences in survival in individuals 15 to 29 years of age compared to older individuals.

RISK FACTORS

Predisposing factors for colorectal carcinoma in children and young adults include hereditary conditions affecting the bowel (polyposis and nonpolyposis syndromes), inflammatory bowel disease, and radiation exposure. Approximately 15 to 20% of colorectal cancer patients have familial colon cancer without a defined genetic pattern,[1] about 5% have hereditary nonpolyposis colon cancer,[2] and 1% have hereditary polyposis syndromes.[3]

Hereditary Nonpolyposis Colon Cancer (HNPCC)

HNPCC was defined by Lynch,[4] who observed a number of families with an increased risk of colon cancer in the absence of polyposis. HNPCC accounts for approximately 5% of all colorectal cancer cases and is associated with an early age at diagnosis, proximal colonic site predominance, mucinous phenotype and multiple synchronous and metachronous tumors.[5,6] Families with HNPCC also have a higher incidence of other tumors, including stomach, small intestine, hepatobiliary system, ovary,

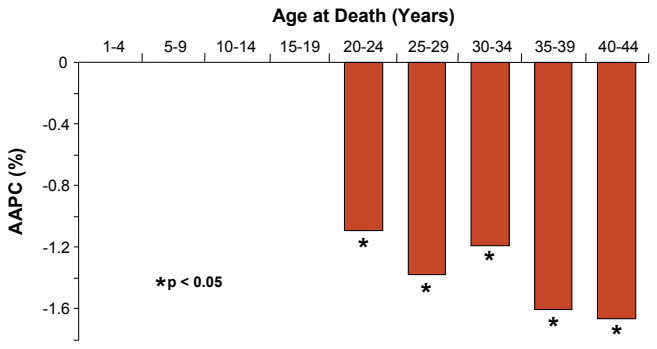

Figure 10.12: Average Annual Percent Change (AAPC) in National Mortality, Colorectal Carcinoma, 1975-2000

endometrium, and upper urinary tract cancers.[7] HNPCC is associated with a lower stage at diagnosis, a lower incidence of metastases, and a better prognosis than sporadic colorectal carcinoma.[8]

Germline mutations of DNA mismatch repair genes are responsible for the predisposition to colorectal carcinoma among patients with HNPCC. Absence of normal mismatch repair function in colonic epithelial cells leads to microsatellite instability and malignant transformation.[9] The Amsterdam criteria for defining HNPCC[10] include colorectal cancer in at least three individuals spanning two generations, at least one of whom is a first-degree relative of the other two. In a small series of colorectal cancer patients who were 21 years of age or less at diagnosis, microsatellite instability was observed in about half, though few fulfilled the diagnostic criteria for HNPCC.[11]

Polypoid Disease of the Gastrointestinal Tract

Colonic polyps can be divided by histology into adenomatous and hamartomatous categories. Adenomatous polyps represent a growth alteration in the colonic mucosa resulting in neoplastic proliferation and substantial malignant potential. Hamartomatous polyps, though less proliferative in nature, are also associated with a significant cancer risk.

Hamartomatous Polyposis Syndromes

Only two hamartomatous polyposis syndromes have been clearly associated with an increased risk of colorectal carcinoma. Juvenile polyposis, which encompasses juvenile polyposis coli and diffuse juvenile polyposis,

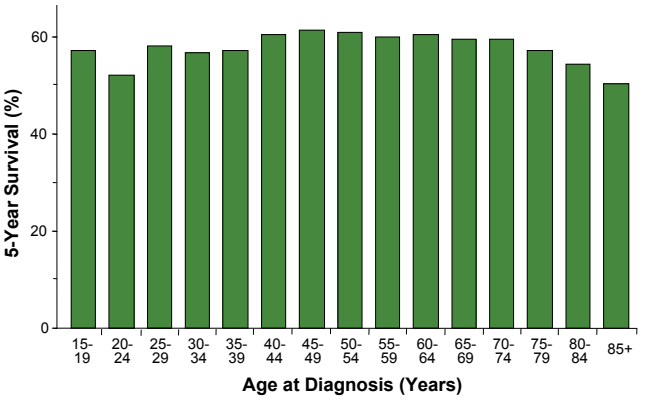

Figure 10.13: 5-Year Survival Rate for Colorectal Carcinoma, SEER 1975-1999

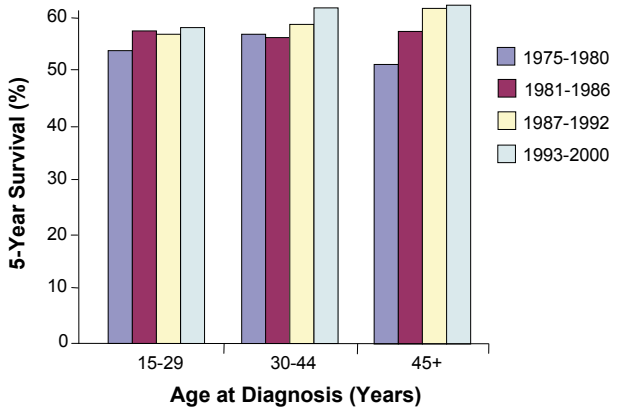

Figure 10.14: 5-Year Survival Rate for Colorectal Carcinoma by Era, SEER

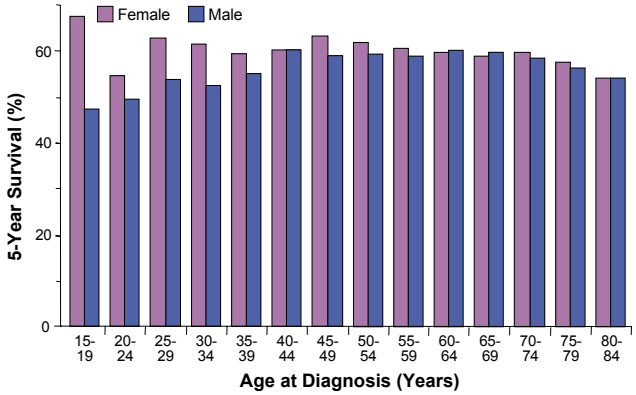

Figure 10.15: 5-Year Survival Rate for Colorectal Carcinoma by Gender, SEER 1975-1999

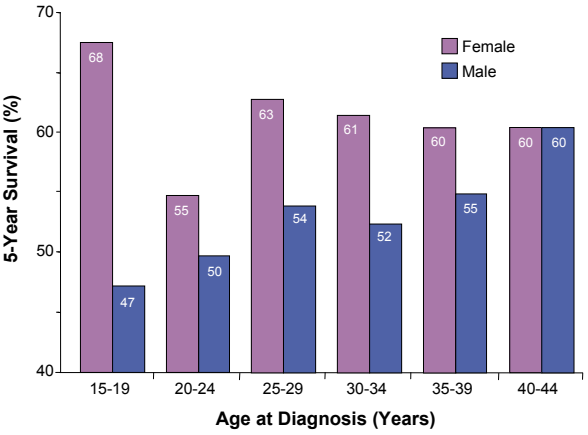

Figure 10.16: 5-Year Survival Rate for Colorectal Carcinoma by Gender, SEER 1975-1999

typically presents with rectal bleeding and anemia in patients between 4 and 30 years of age.[12,13] Other symptoms include intussusception or bowel obstruction, rectal or polyp prolapse, abdominal pain, and protein-losing enteropathy. The polyps may occur throughout the gastrointestinal tract, but most often affect the stomach, distal colon, and rectum. Juvenile polyposis is transmitted as an autosomal dominant trait; SMAD4 and BMPR1A gene mutations have been implicated in the etiology of this syndrome.[14] In a review of cases reported in the English literature, Coburn et al. found that 17% of patients developed gastrointestinal malignancies, at a mean age of 35.5 years (range, 4-60 years).[15] The cumulative risk of colorectal malignancy has been reported to be 68% by 60 years of age.[16]

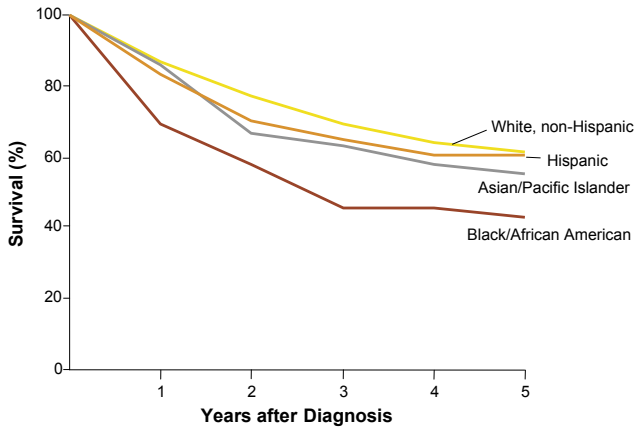

Figure 10.17: Relative Survival for Colorectal Carcinoma by Race/Ethnicity, SEER 1992-1999

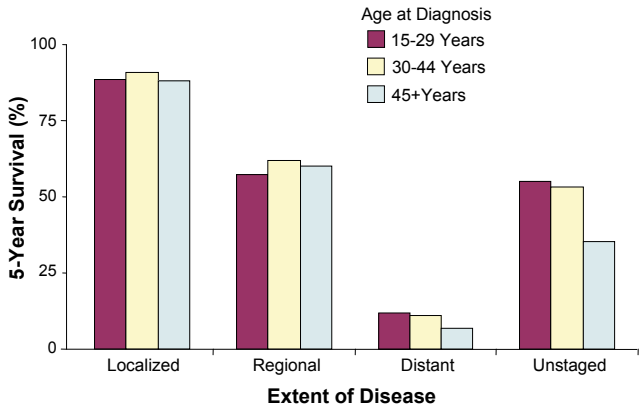

Figure 10.18: 5-Year Survival Rate for Colorectal Cancer by Extent of Disease, SEER 1975-2000

Peutz-Jeghers syndrome,[17] characterized by variable mucocutaneous pigmentation abnormalities and gastrointestinal hamartomas, is also associated with an increased risk of colorectal malignancy. These patients typically present during childhood with recurrent intussusception/bowel obstruction, rectal bleeding, anemia, and rectal prolapse, in some cases before the pigmentary changes classically associated with the disorder are present.[18] Males become symptomatic at an earlier age (peak 5-10 years) than females (peak 10-15 years). Hamartomatous polyps of the small intestine are most common; however, about one-third of patients also have colorectal involvement. Most cases of Peutz-Jeghers syndrome are due to germline mutation of the STK11 gene, which encodes a serine threonine kinase.[19] The transformation from hamartoma to adenocarcinoma in patients with germline STK11 mutations depends on additional somatic mutations.[20] In an analysis of 33 patients with Peutz-Jeghers syndrome, the standardized mortality ratio for gastrointestinal cancer was 24.8.[21]

Adenomatous Polyposis Syndromes

The familial adenomatous polyposis (FAP) syndromes are characterized by the early development of multiple adenomatous colonic polyps. FAP affects about 1 in 7,000 individuals.[9] Virtually all patients with FAP will develop colorectal carcinoma unless a total colectomy is performed prior to the onset of malignancy. FAP is an autosomal dominant trait with high but variable penetrance; 10 to 20% of cases are *de novo* mutations without any apparent family history. Mutations in the APC gene at 5q21 are responsible for the FAP syndrome.[22] The clinical phenotype, including the presence or absence of extracolonic abnormalities, appears to vary according to the exact site of APC gene mutation and the presence of modifying genes.[23,24] Two types of FAP seem to exist, and a relationship between the location of mutations in the gene and the phenotypic expression of FAP has been established:[25] the sparse type, which is characterized by hundreds of polyps, and the profuse type, which presents with thousands of polyps. Patients with the profuse type tend to develop adenocarcinoma at an earlier age. FAP is associated with the development of extracolonic malignancies, including periampullary and thyroid carcinomas and hepatoblastoma.[26,27]

A proportion of FAP patients have Gardner's syndrome,[28] which includes desmoid tumors, cysts of the mandible, fibromas, osteomas, and congenital hypertrophy of the retinal pigment epithelium. Desmoid tumors of the abdominal wall and mesentery occur in a significant proportion of these patients, and are a leading cause of death in post-colectomy patients.

Other syndromes associated with FAP include Turcot's syndrome[29] and Oldfield's syndrome.[30] Patients with Turcot's syndrome manifest multiple pediatric brain tumors (medulloblastoma, gliomas, and others) in conjunction with FAP. Hamilton et al. found that two distinct germline defects, mutation of the APC gene and mutation of a mismatch-repair gene may each give rise to Turcot's syndrome.[31] The type of brain tumor correlates with the mutation, with medulloblastomas characteristic of APC-related mutations and glioblastoma multiforme seen in patients with mismatch-repair gene mutations. Oldfield's syndrome includes FAP in association with multiple sebaceous cysts.

Inflammatory Bowel Disease

Ulcerative colitis is clearly associated with the development of colorectal carcinoma.[32] The age at initial presentation and extent of colonic involvement are strong independent risk factors for subsequent development of colorectal cancer.[33] Patients less than 15 years of age at diagnosis and those with involvement of the entire colon are at the highest risk. The cumulative risk of colorectal carcinoma in individuals less than 40 years of age with pancolitis was 13% at 25 years from diagnosis. Synchronous colorectal tumors are more common in patients with ulcerative colitis than in the remainder of the population with colorectal carcinoma.[34] In a report by Lashner et al.,[35] 11 of 15 ulcerative colitis patients with strictures were found to have carcinomas on biopsy. Thus, patients who develop colonic strictures should be considered to have carcinomas until proven otherwise, and stricture formation is an indication for surgery.

Crohn's disease, when it involves the colon or rectum, is associated with an increased risk of colorectal carcinoma. The relative risk is quite high (20.9 odds ratio) in those in whom the diagnosis is made before the age of 30 years.[36] About one-third of the colorectal carcinomas in patients with Crohn's disease are mucinous adenocarcinoma.[37]

Other Factors Predisposing to Colorectal Carcinoma

Colorectal carcinoma has been reported in patients with Bloom syndrome, a rare autosomal recessive disorder caused by germline mutations of the BLM gene.[38] Gruber et al. showed recently that carriers of BLM mutations are also at increased risk of colorectal carcinoma.[39] About 5% of patients undergoing urinary diversion with ureterosigmoidostomy develop colon cancer, probably due to chronic inflammation caused by the mixture of feces and urine at the implant site.[40]

Colorectal Carcinoma in Childhood Cancer Survivors

Children who receive abdominal or pelvic radiation therapy for the treatment of a malignancy are at increased risk for early development of colorectal cancer in the radiation field.[41,42] This may be particularly problematic in any child who has one of the above genetic predispositions. Overall, however, colorectal cancer is one of the least common second cancers in long-term survivors of childhood cancer.[43-46]

SUMMARY

Colorectal carcinoma accounted for 2.1% of all malignancies in individuals between 15 and 29 years of age, and was the 11th leading cause of cancer in this age group. The average annual incidence of colorectal carcinoma was 7.2 per million in 15- to 29-year-old individuals. The incidence of colorectal carcinoma rose with advancing age, even within the 15- to 29-year age group. Colorectal carcinoma accounted for an increasing proportion of all malignancies with advancing age. While it accounted for only 1% of malignancies in the 15- to 19-year age group, it was responsible for 2.7% of cancers in the 25- to 29-year age group. Colorectal carcinoma was more common in males at all ages over 20 years of age. Although the incidence of colorectal carcinoma has declined over time in individuals over 45 years of age, a similar decline has not been observed in individuals in the 15- to 29-year age group. The small number of patients diagnosed with colorectal carcinoma in this age group makes it difficult to draw conclusions about incidence and outcome data. The average percent annual change in the incidence of colorectal carcinoma increased between 1975 and 2000 among individuals 15 to 29 years of age, and declined in individuals over 30 years of age.

Five-year survival rates for individuals with colorectal carcinoma in the 15- to 29-year age group were similar to those for older individuals. The survival improvements over time observed in individuals over 45 years of age have also been noted in individuals 15 to 29 years of age. Females with colorectal carcinoma had a superior 5-year survival compared to males at virtually all ages; the disparity was particularly marked in individuals younger than 40 years of age.

Risk factors for the development of colorectal carcinoma in childhood and young adulthood include hereditary conditions (polyposis and non-polyposis syndromes), inflammatory bowel disease, and radiation exposure. Hamartomatous polyposis syndromes carry a lower risk of colorectal carcinoma than adenomatous polyposis syndromes. Colorectal carcinoma has also been reported in individuals with Bloom syndrome and in those who have undergone urinary diversion via ureterosigmoidostomy.

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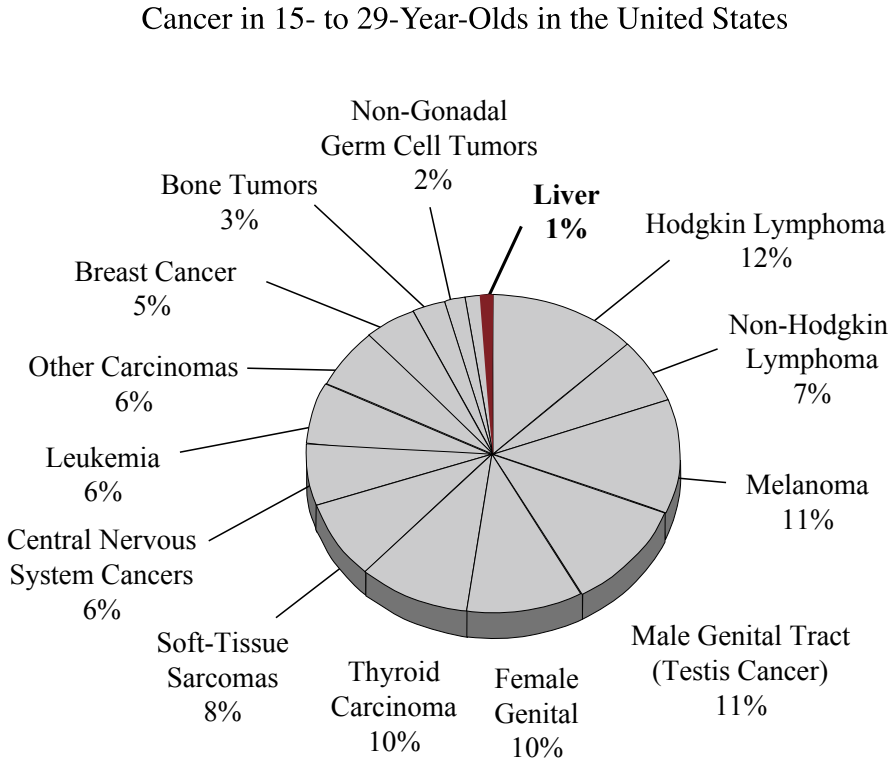
Chapter 11

Liver and Intrahepatic Bile Duct Cancers



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HIGHLIGHTS

Incidence

- Primary neoplasms of the liver are rare in adolescents and young adults. They accounted for 1% of all neoplasms in this age group between 1975 and 2000. Hepatocellular carcinoma was the prominent histologic type.
- The estimated incidence of liver cancer increased with age, from 1.1 per million per year in individuals 15 to 19 years of age to 2.7 per million per year for those 25 to 29 years of age.
- The incidence of liver tumors in males and females younger than 30 years of age was relatively equal. In persons older than age 30, the incidence of liver cancer increased much more rapidly in males than in females.

Mortality & Survival

- Mortality for liver cancer increased with age, especially for males.
- Mortality decreased significantly over time (1975 to 2000) for patients younger than 45 years of age. This progress was most apparent for patients younger than 29 years of age.
- The 5-year survival rate of patients diagnosed with cancer of the liver before age 15 was nearly 60%. For those 15 to 29 years of age it was approximately 16%, and decreased progressively with advancing age.
- These differences in survival rates appear to be due primarily to the fact that hepatoblastoma was the primary cell type in patients younger than 15 years of age whereas hepatocellular carcinoma and other bile duct tumors were most common in older patients.
- Although survival was not different for males younger than 15 years of age compared to females, females had a much better survival rate than males in the 15- to 29-year age group.

Risk Factors

- Known risk factors for hepatoblastoma are familial adenomatous polyposis, Gardner syndrome, Beckwith-Wiedemann syndrome, hemihypertrophy, and low birth weight.
- Hepatocellular carcinomas appear to be a consequence of previous hepatic damage due to metabolic or inflammatory disorders.
- Hepatocellular carcinoma is associated with congenital diseases such as hereditary tyrosinemia, biliary cirrhosis, glycogen storage disease and alpha 1-antitrypsin deficiency.
- Prolonged exposure to anabolic steroids, toxin-contaminated foods (aflatoxin), and potential hepatic carcinogens (pesticides, vinyl chloride, Thorotrast®) have also been associated with the development of hepatocellular carcinoma.

INTRODUCTION

Primary neoplasms of the liver are rare in adolescents and young adults aged 15 to 29 years; they accounted for 1% of all neoplasms in this age group, similar to the proportion in individuals 0 to 14 years of age. However, while hepatoblastomas comprised over two-thirds of the malignant liver tumors in children, most of the tumors seen in adolescents and young adults were hepatocellular carcinomas (HCC).The estimated incidence of liver and intrahepatic bile duct tumors in the U.S. in the year 2000 increased with age, from 1.1 per million in individuals 15 to 19 years of age to 2.7 per million for those 25 to 29 years of age. According to Surveillance, Epidemiology, and End Results (SEER) data, 101 adolescents and young adults in the United States were diagnosed with these tumors in the year 2000 (Table 11.1).

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), hepatic tumors and intrahepatic bile duct cancers are found in category VII. In the ICCC, hepatoblastoma is category VII (a), hepatic carcinoma in the liver or intrahepatic bile duct system is VII(b) and unspecified malignant hepatic and intrahepatic bile duct tumors are VII(c).[1] In the International Classification of Diseases for Oncology (ICD-O), histologies for cholangiocarcinoma, bile duct cystadenocarcinoma, hepatocellular carcinoma, and combinations are listed in categories 8160 to 8180, as follows: hepatocellular carcinoma NOS (8170), fibrolamellar hepatocellular carcinoma (8171), cholangiocarcinoma (8160), bile duct cystadenocarcinoma (8161), Klatskin tumor (8162), and combined hepatocellular carcinoma and cholangiocarcinoma (8180). New hepatocellular histologies in ICD-O-3 are included with hepatocellular carcinoma NOS (8170): scirrhous (8172), hepatocellular carcinoma, spindle cell variant (8173), hepatocellular carcinoma, clear cell type (8174), and hepatocellular carcinoma, pleomorphic type (8175). Hepatoblastoma, ICCC VII(a), corresponds to ICD-O 8970.

In attempting to apply the ICCC and ICD-O systems to hepatic and bile duct tumors in 15- to 29-year-olds, there is evidence that hepatic parenchymal cancers in 15- to 29-year-olds differs from tumors of the same name in younger and older persons. Most of the hepatocellular carcinomas in this age group are not related to pre-existing chronic viral hepatitis and histologically may be "transitional" in nature, with over-expression of beta-catenin.[2] The missing variants of hepatocellular carcinoma described above may also compromise the analysis of 15- to 29-year-old patients who may be at risk of these subtypes.

INCIDENCE

Between 1975 and 2000, the incidence of liver and intrahepatic bile duct tumors in 15- to 29-year-olds in the U.S. SEER sites averaged 1.59 new cases per year per million. The data on liver tumors in adolescents and young adults 15 to 29 years of age were obtained from SEER data collected between 1975 and 2000. Approximately 10,000 individuals in this age group were diagnosed with liver tumors during this period, corresponding to an incidence of 7.4 per million/per year. Although these data include both liver and intrahepatic bile duct tumors, the occurrence of intrahepatic bile duct cancers in individuals younger than 29 years of age was extremely rare, as shown in Figure 11.1.

Age-Specific Incidence

The incidence of liver tumors was relatively constant between 5 and 35 years of age, but increased progressively thereafter (Figure 11.1). The incidence of liver tumors in children under 5 years of age was at least 3 times that observed for individuals 15 to 29 years of age.

Gender-Specific Incidence

The male-to-female incidence ratio for liver tumors was close to 1.1 for individuals 15 to 29 years of age. This is similar to the ratio seen in children younger than 5 years of age. However this ratio increased progressively after the age of 30, as the rate of liver tumors among males increased much more rapidly than among females (Figure 11.2).

Racial/Ethnic Differences in Incidence

Based on the SEER data collected between 1990 and 2000, the incidence of liver and intrahepatic bile duct tumors in adolescents and young adults younger than 25 years of age was too low to determine in all racial/ethnic groups

Table 11.1: *Incidence of Liver and Intrahepatic Bile Duct Cancers in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	4.9	0.7	0.8	1.1	1.5	2.3
Average annual % change in incidence, 1975-2000, SEER	^	^	^	^	1.8	2.6
Estimated incidence per million, year 2000, U.S.	4.9	0.7	0.8	1.1	1.8	2.7
Estimated number of persons diagnosed, year 2000, U.S.	94	15	17	21	33	47

^ Too few for a reliable estimate

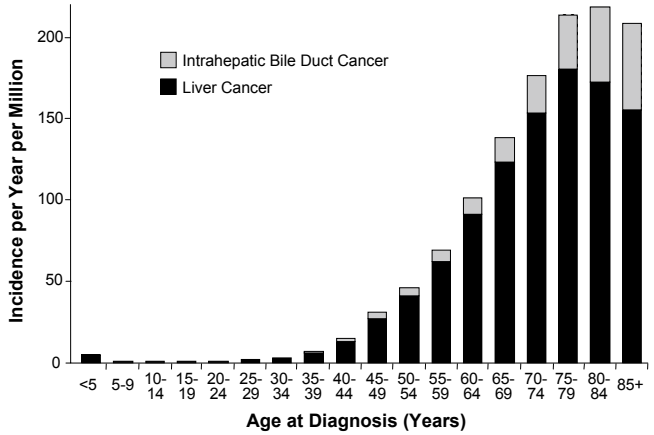

Figure 11.1: Incidence of Liver versus Intrahepatic Bile Duct Cancer, SEER 1975-2000

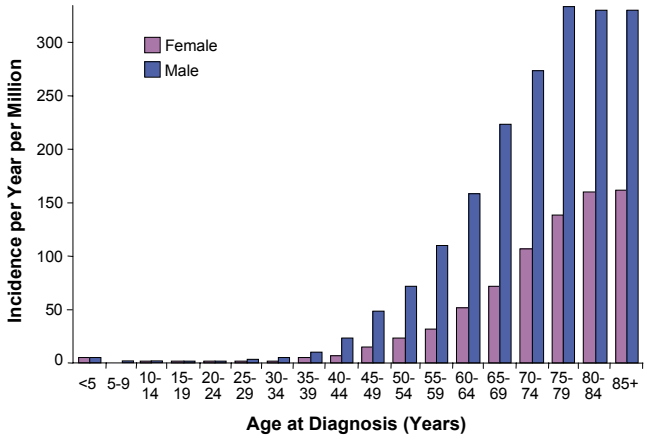

Figure 11.2: Incidence of Liver & Intrahepatic Bile Duct Cancer by Gender, SEER 1975-2000

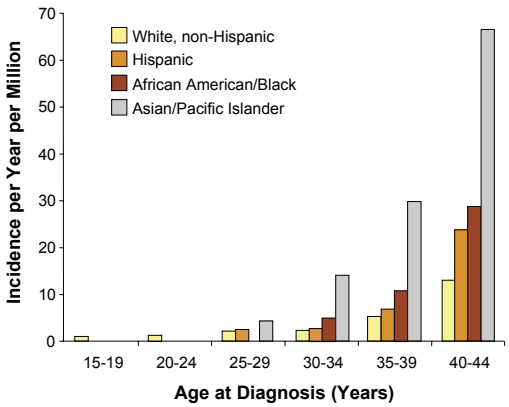

Figure 11.3: Liver & Intrahepatic Bile Duct Cancer Incidence Rate by Race/Ethnicity, U.S., 1990-2000

except white non-Hispanics (Figure 11.3). From age 25 to 45, Asians/Pacific Islanders had a higher incidence than any other racial/ethnic group, likely due to the high incidence of hepatitis B infection in this population.

Trends in Incidence

Figure 11.4 demonstrates the progressive increase in incidence of liver and intrahepatic bile duct tumors between 1975 and 2000. However this increase was more pronounced in patients older than 45 years of age. This increase was seen for all tumor stages, i.e., localized, regional or metastatic (Figure 11.5).

OUTCOME

Mortality

Mortality for liver tumors increased with age, especially for males (Figure 11.6). Mortality decreased significantly over time (1975 to 2000) for patients younger than 30 years of age (Figure 11.7). Above age 30, liver cancer mortality significantly increased (Figure 11.7), consistent with the increase in incidence in this age group (Figure 11.4). In the more recent era, a reduction in mortality was not as apparent for those 15 to 29 years of age. In contrast to the decline in mortality seen previously in this age group, mortality increased during the period 1992 to 2000 (11.7; right panel).

Survival

With the introduction of a multidisciplinary therapeutic approach to liver tumors in the early 1980s, a significant improvement in the survival rates has been noted for individuals younger than 15 years of age. However, progress has been much slower for older individuals, as shown in Figure 11.8. Survival of patients younger than 15 years of age was close to 60%, while for those 15 to 29 years of age it was approximately 16%, and decreased progressively with the advancement of age. This is likely due to the fact that younger patients were diagnosed predominantly with hepatoblastomas, which are more responsive to treatment overall than hepatocellular carcinomas and other bile duct tumors. Although survival was not different for males compared to females younger than 15 years of age, females had much better survival in the 15- to 29-year age group (Figure 11.9).

RISK FACTORS

Hepatoblastoma is rarely seen in adolescents and young adults; it is much more common in younger children. Known risk factors for the development of hepatoblastoma are familial adenomatous polyposis, Gardner syndrome, Beckwith-Wiedemann syndrome, hemihypertrophy, and low birth weight.[3-6] Suggestive but not conclusive factors that may pose a risk for the development of hepatoblastoma are treatment for prematurity; parental exposure to metal, petroleum products, and paint; parental smoking; and genetic susceptibility.[7-13] Single case reports provide limited evidence but have suggested an association between childhood hepatoblastoma and fetal alcohol syndrome, maternal oral contraceptive use during pregnancy, and maternal fertility treatment.[14-16]

Hepatocellular carcinoma is the most prevalent liver tumor in adolescents and young adults (15 to 29 years of age). Hepatocellular carcinomas appear to be a consequence of previous hepatic damage due to metabolic or inflammatory disorders. Infection with hepatitis B or C virus is associated with the development of HCC,[17,18] and chronic infection with hepatitis B virus is the leading cause of HCC in children, adolescents, and young adults in Asian and African countries. However, in Western countries, a cause such as hepatitis or other inflammatory liver disease has been identified in fewer than a third of the adolescent or young adult patients diagnosed with HCC.[19,20] This is in marked contrast to older adults, in whom almost 90% of the cases have been related to cirrhosis secondary to viral infection or alcohol consumption.[21,22] The prevention of a carrier state in children by a universal program of hepatitis B immunization has shown a dramatic decrease in the chronic hepatitis B virus prevalence and a decline in the rates of HCC in Taiwan among children younger than 15 years of age.[23,24]

Less frequently, HCC is associated with congenital diseases such as hereditary tyrosinemia, biliary cirrhosis, glycogen storage disease, α-1 antitrypsin deficiency, and hemochromatosis.[25-29] Prolonged exposure to anabolic steroids, toxin-contaminated foods (aflatoxin), and potential hepatic carcinogens (pesticides, vinyl chloride, Thorotrast®) has also been associated with the development of HCC.[30-32] Polymorphic variation in

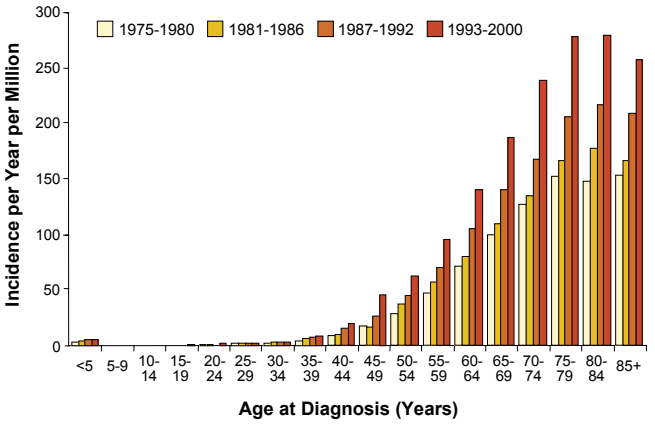

Figure 11.4: Change in Incidence of Liver & Intrahepatic Bile Duct Cancer by Era, SEER 1975-2000

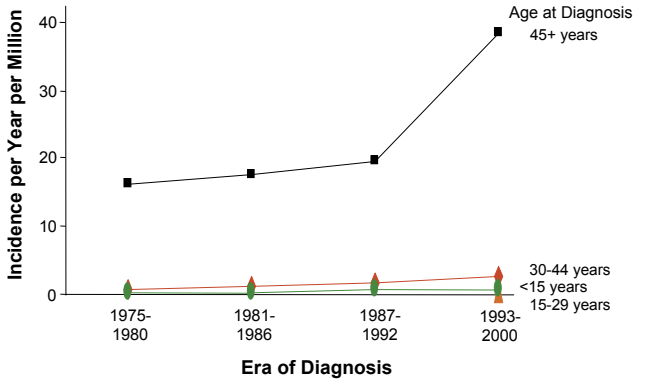

Figure 11.5: Incidence of Liver & Intrahepatic Bile Duct Cancer, Localized Disease, by Era, SEER 1975-2000

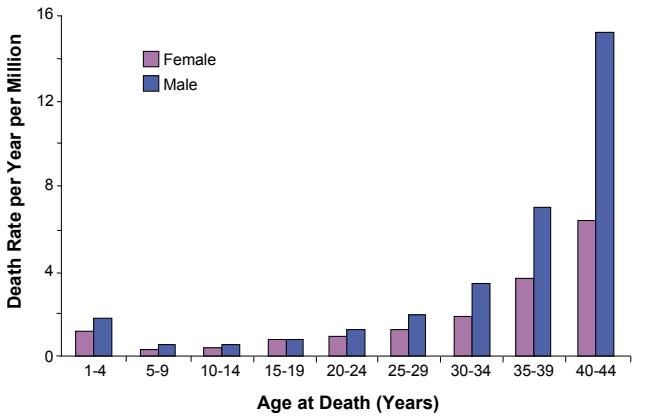

Figure 11.6: Liver & Intrahepatic Bile Duct Cancer, National Mortality by Gender, SEER 1975-2000

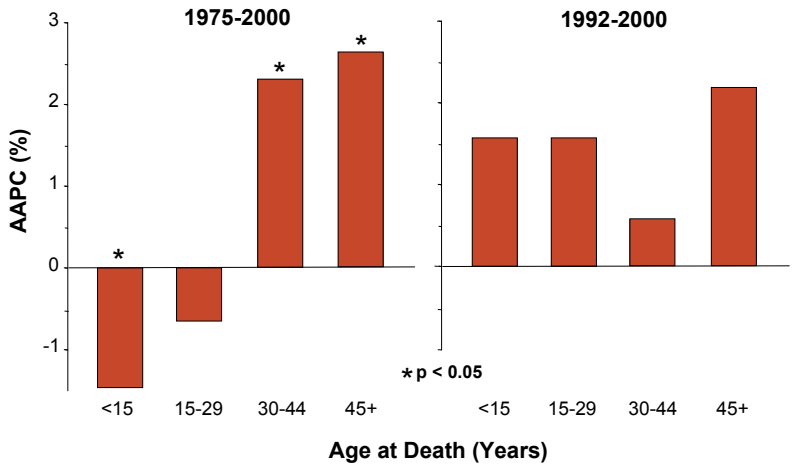

Figure 11.7: Liver & Intrahepatic Bile Duct Cancer, Average Annual Percent Change (AAPC) in National Cancer Mortality

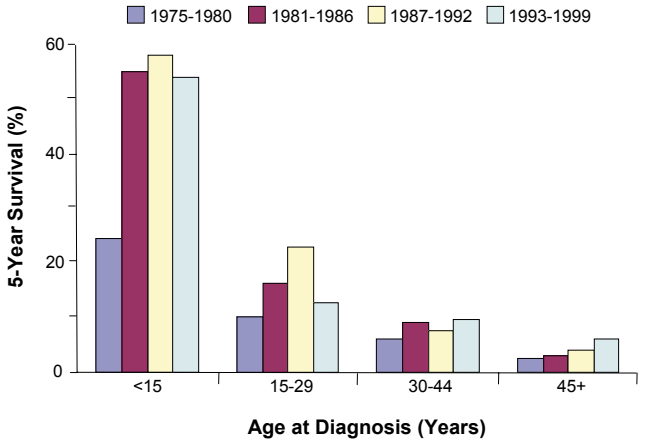

Figure 11.8: Liver & Intrahepatic Bile Duct Cancer 5-Year Survival Rate by Era, SEER 1975-1999

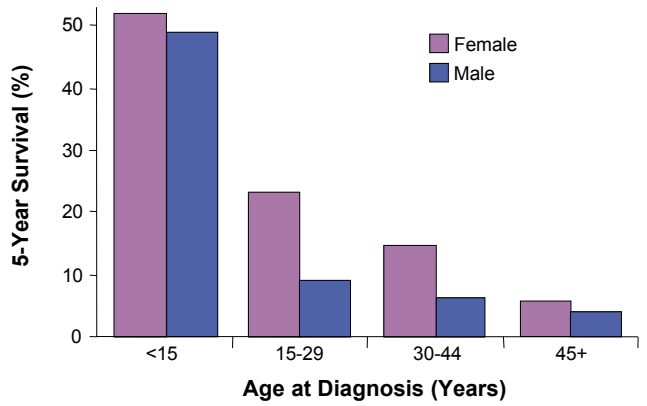

Figure 11.9: Liver & Intrahepatic Bile Duct Cancer, 5-Year Survival Rate by Gender, SEER 1975-1999

xenobiotic metabolism, DNA repair, and immune system genes are all under extensive investigation and have been found to modify the risk of HCC in some studies.[33-35]

SUMMARY

Primary neoplasms of the liver accounted for 1% of all neoplasms in those 15 to 29 years of age, with HCC the most common tumor. The estimated incidence of liver *and* intrahepatic bile duct tumors increased with age, from 2.0 per million in individuals 15 to 19 years of age to 14.6 per million for those 25 to 29 years of age. The incidence of liver tumors was relatively constant between 5 and 35 years of age, but then increased progressively with increasing age. Although there was no gender predilection in the adolescent and young adult age group, male incidence increased more than female incidence with advancing age. Liver tumors were more prevalent in Asians/Pacific Islanders, followed by African Americans/blacks, in comparison to white non-Hispanics and Hispanics. Mortality decreased significantly over time (1975 to 2000) for patients younger than 45 years of age. Survival improved significantly for individuals younger than 15 years of age, but progress has been much slower for older individuals. Chronic infection with hepatitis B virus has been the leading cause of HCC in children, adolescents, and young adults in Asian and African countries. However, the introduction of a universal program of hepatitis B immunization to prevent the carrier state in children has shown a dramatic decrease in chronic hepatitis B virus prevalence and a decline in the rates of HCC.

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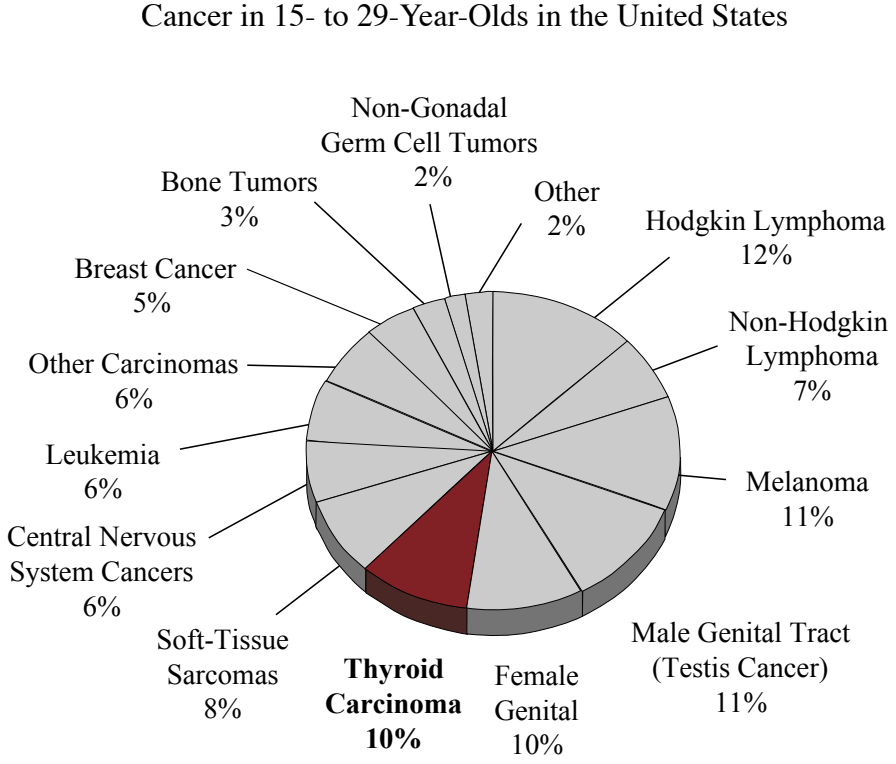
Chapter 12

Thyroid Cancer



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HIGHLIGHTS

Incidence

- In the United States from 1975 to 2000, thyroid cancer accounted for about 10% of all malignancies diagnosed in individuals 15 to 29 years of age and was the 4th most common cancer in this age group.
- Nearly 2,400 individuals 15 to 29 years of age were diagnosed with a malignant thyroid neoplasm in the U.S. during the year 2000.
- Thyroid cancer, as a percentage of all cancer, peaked between 20 and 24 years of age, and represented more than 11% of malignancies in this age group.
- The incidence of thyroid cancer increased rapidly between 15 and 29 years of age, and reached a plateau by the 5th to 6th decades.
- Differentiated thyroid cancer (papillary and follicular carcinoma – PTC and FTC) accounted for the vast majority of cases occurring before 30 years of age, and medullary thyroid carcinoma (MTC) accounted for most of the rest.
- More than 80% of the cases of thyroid cancer occurred in females.
- Between 1975 and 2000 the incidence of thyroid cancer increased steadily, at a statistically significant rate. Most of the increase occurred during the 1990s.
- The increase in incidence occurred in localized and regional—but not distant—presentations of disease.

Mortality & Survival

- The mortality rate of thyroid cancer increased above age 10, and continued to rise as a function of age.
- Thyroid cancer has been one of the most curable malignancies, with 5-year survival rates exceeding 99% in 15- to 29-year-olds. This holds true even in patients with disseminated disease at diagnosis.
- Patients with MTC have not fared as well as those with PTC and FTC.
- Although the survival difference between males and females was small, males had a consistently lower survival rate than females.

Risk Factors

- Appreciating the major histologic distinction between PTC and MTC is fundamental to understanding the differences in the biologic behavior and treatment applicable to these very different thyroid cancers.
- The major established environmental risk factor for the development of malignant thyroid neoplasms, particularly PTC, is ionizing radiation. This can result from exposure to both external beam radiotherapy and internal radiation as delivered by the ingestion of radioiodine.
- The *RET* proto-oncogene is implicated in the development of PTC.
- Most young individuals diagnosed with MTC have one of three hereditary cancer syndromes: familial MTC, multiple endocrine neoplasia type 2A, or multiple endocrine neoplasia type 2B.
- MTC in the context of a familial syndrome is caused by germline mutations in the *RET* proto-oncogene.
- Sporadic MTC is rare in the adolescent and young adult population.

INTRODUCTION

Although uncommon, thyroid carcinoma is not an unusual finding in the adolescent and young adult population. Between 1975 and 2000, it represented approximately 7.8% of all cancers diagnosed in the 15- to 19-year age group, 11.5% in patients 20 to 24 years old, and 10.1% in individuals from ages 25 to 29 (Figure 12.1). In children younger than 15 years of age it is very rare, with very few cases diagnosed before 10 years of age. Fortunately, the long-term prognosis is excellent for most

children and young adults diagnosed with thyroid carcinoma. Due to the limited number of cases diagnosed each year and because of the extended follow-up needed to obtain meaningful outcome data, thyroid carcinoma in the adolescent and young adult population remains a poorly studied disease. In contrast to thyroid cancer in older individuals, thyroid carcinomas in patients younger than 30 years of age have notable differences in tumor biology and clinical presentation. Despite the likelihood of having more widespread disease at presentation, adolescents and young adult patients with thyroid cancer typically have a better outcome than older adults who present with a similar extent of disease.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

Thyroid cancer is classified in the International Classification of Childhood Cancer (ICCC) in category XI(b) as Thyroid Carcinoma, a category within Carcinomas and Other Epithelial Neoplasms (X). The ICCC thyroid category specifies that thyroid carcinoma includes International Classification of Disease for Oncology (ICD-O) categories 8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8573. These categories include general carcinomas and adenocarcinomas and specific cancers of the thyroid. ICCC group XI(b) also includes follicular carcinomas (8330-8350) of any cancer site.

Three major types of thyroid cancer exist in the adolescent and young adult population. The differentiated thyroid carcinomas (DTC)—papillary thyroid carcinoma (PTC) (ICD-O categories 8050, 8260, 8340) and follicular thyroid carcinoma (FTC) (ICD-O categories 8330-8334)—arise from the thyroid follicular epithelium. In contrast, medullary thyroid carcinoma (MTC) (ICD-O category 8510) arises from the parafollicular C cell, which has a distinct embryologic origin from neural crest cells.

The diagnosis of PTC and FTC is based upon histopathological features that are unique to each type of carcinoma. Within the broader classification of PTC and FTC, there are subtypes of each. Follicular cell, tall cell, diffuse sclerosing, columnar cell, and encapsulated are variants of PTC whereas subtypes of FTC include Hürthle-cell (oncocytic), clear cell, and insular carcinoma. Certain tumor subtypes, such as follicular and diffuse sclerosing variants of PTC, are more common in children and young adults as compared to older individuals.[1] Furthermore, in contrast to the classical type of PTC identified in older individuals, childhood PTC, particularly in the very young, may: 1) be unencapsulated and widely invasive throughout the gland and 2) have a solid and follicular architecture with unique nuclear features and abundant psammoma bodies.[2,3]

In general, MTC accounts for approximately 7-10% of all thyroid malignancies in the general population. PTC represents about 80% and follicular thyroid carcinoma accounts for approximately 20% of the differentiated thyroid carcinomas.[2,4,5] PTC and FTC account for the vast majority of cases before 30 years of age, and MTC accounts for almost all of the rest.

In contrast to DTC, MTC is often an inherited disease in the pediatric and young adult population, resulting from gain-of-function mutations in the rearranged during transfection (RET) proto-oncogene.[6] Sporadic cases of MTC are less common in the AYA age group. In patients with heritable disease, the MTC is virtually always bilateral, multicentric and located at the junction of the upper one-third and lower two-thirds of the thyroid lobes, which is where the greatest concentration of C cells exists. In contrast, only one thyroid lobe is typically involved in patients with sporadic tumors. In individuals with a familial form of MTC, clusters of C cells (C-cell hyperplasia) are routinely identified pathologically. This C-cell hyperplasia is believed to be one of the initial stages in the development and progression of MTC.[7]

Poorly differentiated and frankly anaplastic thyroid carcinomas arise from the differentiated thyroid carcinomas. Although they can occur in the adolescent and young adult population, they are exceedingly rare. Therefore, the main focus of this chapter will be the major categories of thyroid carcinoma identified in the adolescent and young adult age group: PTC, FTC, and MTC.

As explained in the Methods chapter, data are presented for 15- to 29-year-olds with comparisons to the age

Table 12.1: *Incidence of Thyroid Cancer in Persons Younger Than 30 Years of Age, U.S, 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	0	1.0	4.2	15.4	37.2	54.8
Average annual % change in incidence, 1975-2000, SEER	^	^	^	1.23	1.32	1.42
Estimated incidence per million, year 2000, U.S.	0	1.0	4.3	17.6	43.3	63.0
Estimated number of persons diagnosed, year 2000, U.S.	0	20	89	355	820	1,222

^ Too few for a reliable estimate

groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

INCIDENCE

Age-Specific Incidence

Based on incidence data collected from 1975 to 2000 in the United States, approximately 2,400 persons between 15 and 29 years of age were diagnosed each year with thyroid cancer (Table 12.1); this represents about 10% of all such cancers. More than half of these patients were 25 to 29 years of age. Over this same time period, more than 350 older adolescents in the 15- to 19-year age group were diagnosed annually to have thyroid cancer (Table 12.1).

Thyroid cancer as a percentage of all cancer reached a peak in those 20 to 24 years of age, and represented 11.5% of all malignancies in this age group. For those younger than age 10, it represented less than 1% of all cancers and for those 40 years and older, it represented 4% of all cancers (Figure 12.1).

DTC, MTC and other types of thyroid cancer peaked in incidence at 50, 70 and after 80 years of age, respectively, with DTC predominant at all ages (Figure 12.2). The incidence of DTC increased 3.5-fold from age 15 to 19 years to 25 to 29 years (Figure 12.3). In contrast, the incidence of MTC rose gradually over the life span, and there was no dramatic increase in the rate of diagnosis in the young adult population (Figure 12.4). In adolescents and young adults, MTC was an uncommon disease with an incidence of less than 1 case/million/year. Since PTC and FTC represented the vast majority of thyroid cancer cases, it is not surprising that the incidence of thyroid carcinomas as a whole (Figure 12.2) was parallel to that of DTC (Figure 12.3).

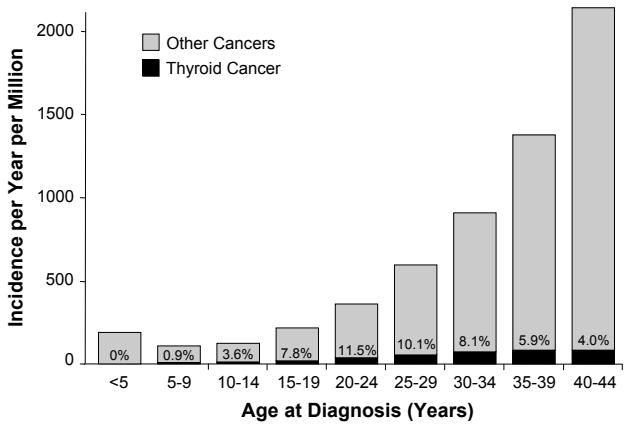

Figure 12.1: Incidence of Thyroid Cancer Relative to All Cancer, SEER 1975-2000

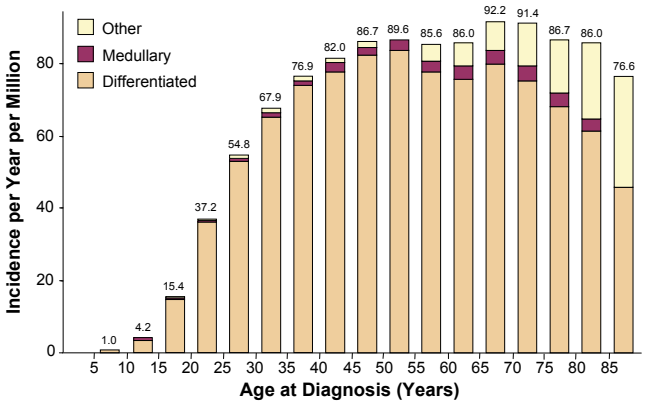

Figure 12.2: Incidence of Thyroid Cancer by Histology, SEER 1975-2000

Gender-Specific Incidence

Most cases of thyroid cancer occurred in females; peak incidence was between 45 and 50 years of age (Figure 12.5). In males, the peak incidence occurred at a much older age. The ratio of females to males with thyroid cancer was as high as 5-fold, and the maximum ratio was seen in the adolescent and young adult age group (Figure 12.5). This gender difference was not pronounced in children younger than 10 years of age.

When the types of thyroid cancer were reviewed by major subtype, the gender-specific incidence for DTC (Figure 12.6) was similar to that of the total group (Figure 12.5). However, MTC did not have as striking a difference in the female-to-male incidence ratio (Figure 12.7). Because MTC is frequently heritable via an autosomal dominant mode of transmission (see *Risk Factors and Etiology*), it is not surprising that the female-to-male ratio approximates one in many age groups.

Racial/Ethnic Differences in Incidence

Between 15 and 45 years of age, white non-Hispanics and Asians/Pacific Islanders were at highest risk of developing thyroid cancer, and African Americans/blacks and American Indians/Alaska Natives were at lowest risk (Figure 12.8). Among 15- to 29-year-olds in the U.S., African Americans/blacks were least affected, with an incidence less than one-half that of the other racial/ethnic groups. Hispanic persons had an intermediate incidence of thyroid cancer (Figure 12.8). Female-to-male ratios in the adolescent and young adult population were similar among the various racial/ethnic groups: 5.1 in African Americans/blacks; 5.4 in white non-Hispanics; 5.8 in Asians/Pacific Islanders; and 6.7 in Hispanics. The female-to-male ratio is not known for American Indians/Alaska Natives due to too few cases reported in males.

Trends In Incidence

Between 1975 and 2000, thyroid cancer increased steadily in all adolescent and young adult age groups, with a noticeable increase occurring in the 25- to 29-year-old and older age groups (Table 12.1, Figure 12.9). Most of the increase occurred during the 1990s (Figure 12.9). Overall, the most significant increase in incidence was observed in those individuals 45 years of age and older, but in all age groups these changes were statistically significant.

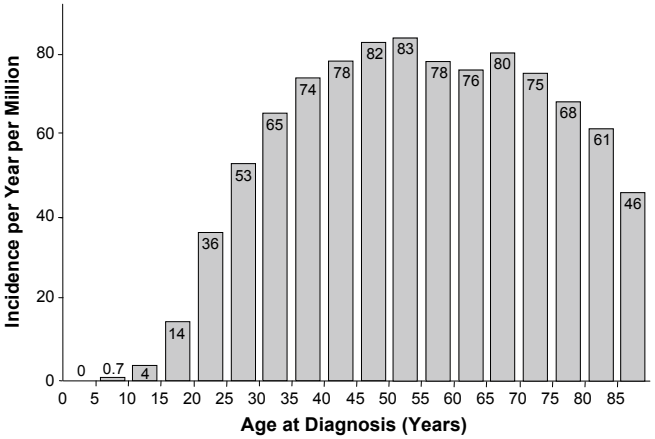

Figure 12.3: Incidence of Differentiated (Papillary and Follicular) Thyroid Cancer, SEER 1975-2000

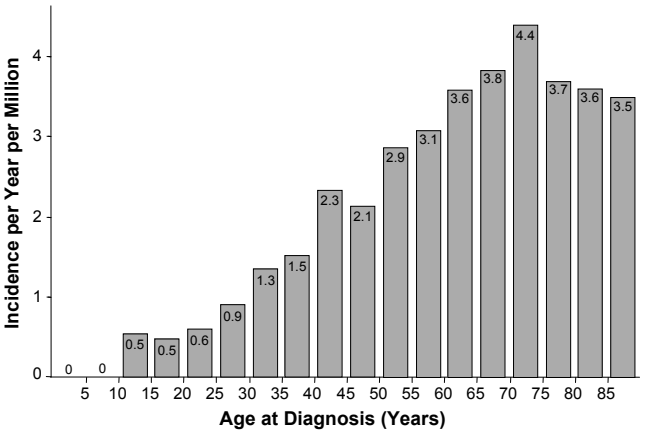

Figure 12.4: Incidence of Medullary Thyroid Cancer, SEER 1975-2000

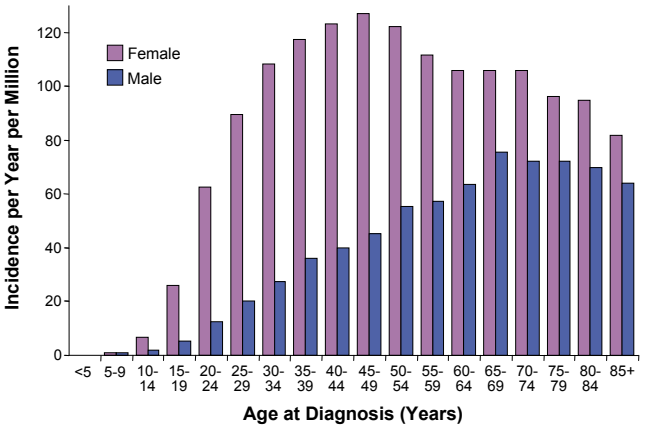

Figure 12.5: Incidence of Thyroid Cancer by Gender, SEER 1975-2000

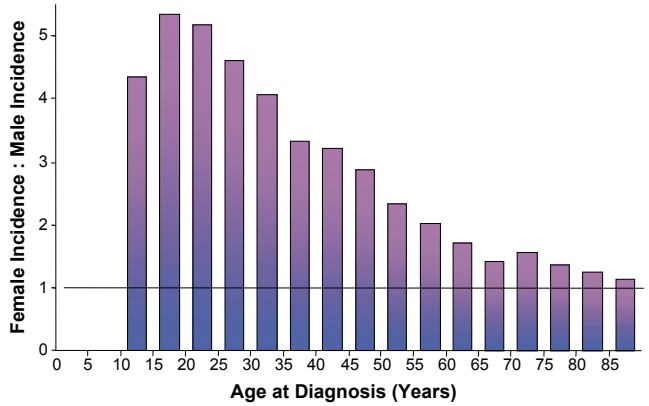

Figure 12.6: Ratio of Female to Male Incidence of Differentiated (Papillary and Follicular) Thyroid Cancer, SEER 1975-2000

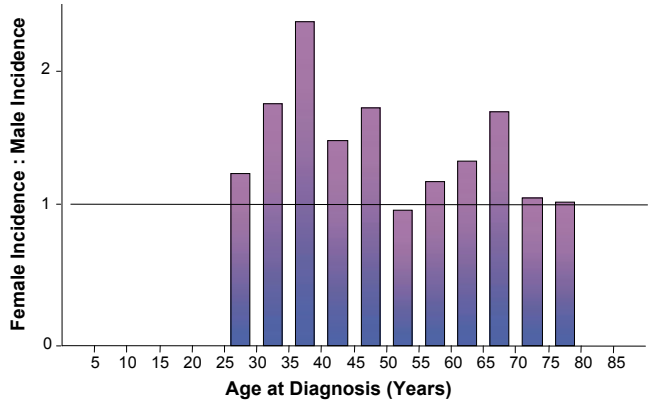

Figure 12.7: Ratio of Female-to-male Incidence of Medullary Thyroid Cancer, SEER 1975-2000

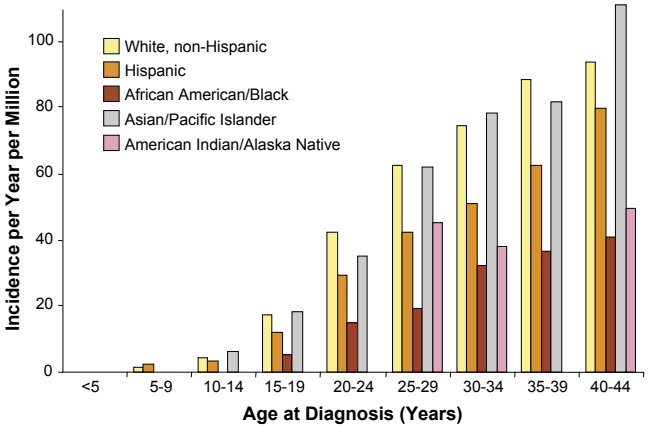

Figure 12.8: Incidence of Thyroid Cancer by Race/Ethnicity, SEER 1990-2000

Reasons for the significant changes in the incidence of thyroid cancer are unknown, but may include the increased use of diagnostic imaging, heightened awareness of cancer screening, or an environmental factor such as radiation (see *Risk Factors and Etiology*), to which the population as a whole has had increased exposure. There was an obvious increase in incidence of thyroid cancer in females (Figure 12.10) but not in males (Figure 12.11).

The increase in incidence was greater in regional presentations of disease than in either localized presentations or those with distant metastases (Figure 12.12). This may be a partial artifact due to better imaging and more complete lymph node dissections, which detect regional disease at a higher rate than in prior eras.

OUTCOME

Mortality

Overall, mortality for thyroid cancer remains low, since most cases in the adolescent and young adult population are cured after initial therapies or have an indolent clinical course. The death rate for those 15 to 24 years of age was 0.1 per year per million, and continued to rise as a function of age (Figure 12.13). The overall prognosis of DTC in young children, adolescents and young adults is favorable, even for patients with disseminated disease at diagnosis.[5,8] However some of these individuals may succumb to their disease or die from treatment-related complications decades after diagnosis, which underscores the importance of life-long follow up.[8]

Despite the remarkably higher incidence of thyroid cancer in females (Figure 12.5), mortality in females and males was essentially identical in the adolescent and young adult age group (Figure 12.14).

Mortality from thyroid cancer has not declined in the 15- to 29-year age group during the past quarter century, probably because of the high survival rates (see *Survival*). However, it has declined in older patients, probably representing an improvement in the diagnosis and treatment of these patients (Figure 12.15).

Survival

Thyroid cancer is one of the most curable of malignancies, particularly if identified early and treated appropriately. For all thyroid cancers, 5-year survival rates were 99% or greater in 15- to 29-year-olds (Figure 12.16). Although children diagnosed prior to age 10 had 5-year survival rates approaching 100% in the U.S (Figure 12.16), some still die from their disease many years to decades after diagnosis.[2,9]

It is known that MTC has a biological behavior that is more aggressive than PTC or FTC, but less aggressive than anaplastic or poorly differentiated thyroid carcinoma. Therefore patients with MTC have not fared as well as those with DTC, particularly those 15 to 24 years of age (Figure 12.17). Nonetheless, between 1975 and 2000, 5-year survival rates for MTC were still good overall, ranging between 85% and 95% among patients 10 to 44 years of age (Figure 12.17). For patients with MTC not diagnosed early, incurable yet indolent disease is often the norm. The biological aggressiveness of MTC also depends on the genetic background in which it develops. As compared to MEN2A and familial MTC (FMTC), MTC arising in the setting of MEN2B is more aggressive, presenting at a very early age in most cases. FMTC usually has a more benign clinical course, whereas MTC within MEN2A is somewhat capricious, following an indolent course in most patients but progressing rapidly in others. The reasons for this variable biological behavior of MTC in these different clinical entities are unknown. In adolescents and young adults it is difficult to assess the behavior of MTC in sporadic compared to familial cases.

Although the survival difference between males and females was small, males had a consistently lower survival rate than females (Figure 12.18).

Several prognostic scoring systems (AMES, MACIS, AGES, etc.) have been described for the thyroid carcinomas, chiefly PTC, but a thorough review of these is beyond the scope of the current discussion. The pathological TNM classification is used as an international reference staging system. Given that it takes into account the prognostic effects of lymph node metastases at presentation, it may be superior to the others, at least in PTC.[10] By definition, and reflecting the good prognosis in

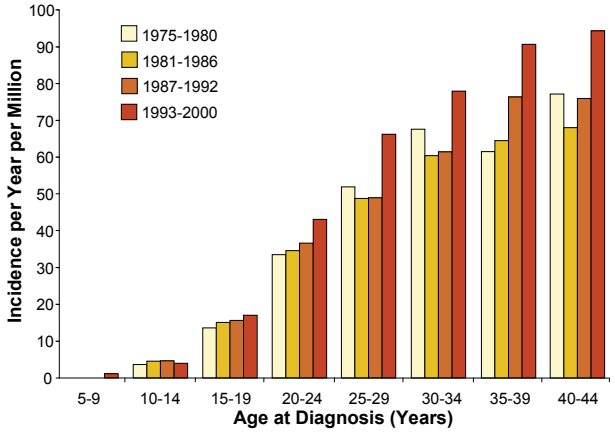

Figure 12.9: Incidence of Thyroid Cancer by Era, SEER 1975-2000

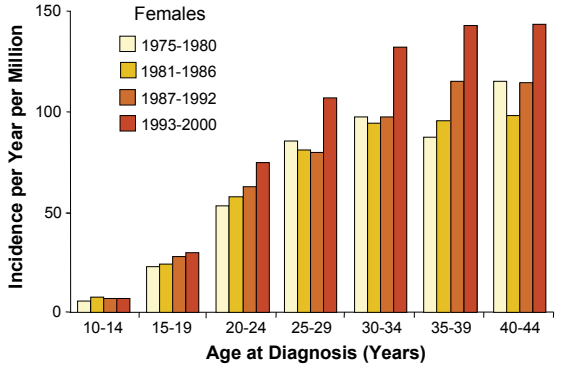

Figure 12.10: Change in Incidence of Thyroid Cancer in Females, by Era, SEER 1975-2000

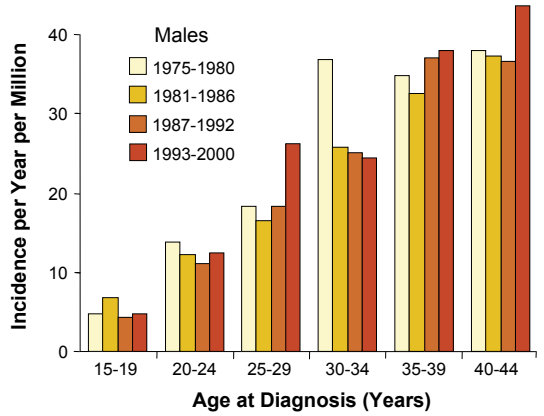

Figure 12.11: Change in Incidence of Thyroid Cancer in Males, by Era, SEER 1975-2000

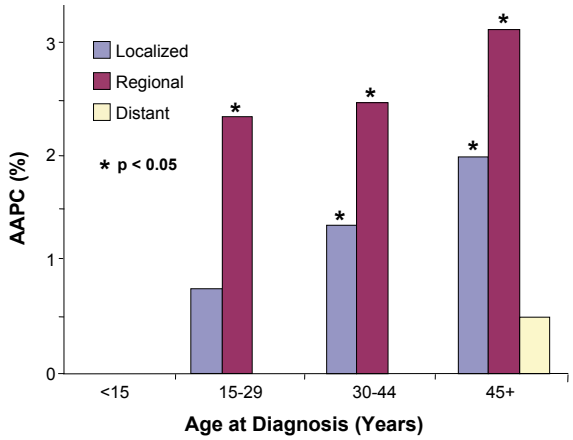

Figure 12.12: Average Annual Percent Change (AAPC) in Incidence of Thyroid Cancer by Extent of Disease, All Sites, SEER 1975-2000

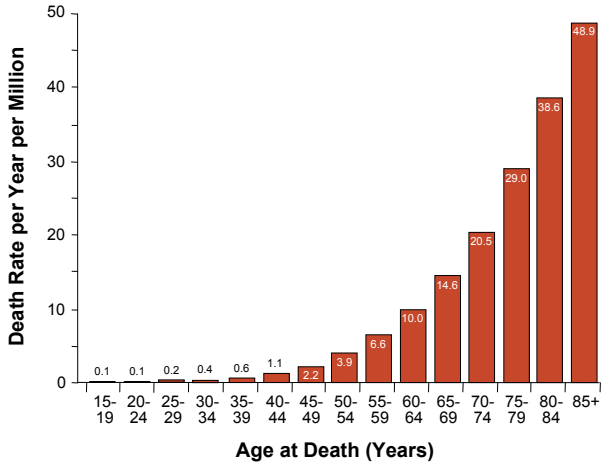

Figure 12.13: National Thyroid Cancer Mortality, U.S., 1975-2000

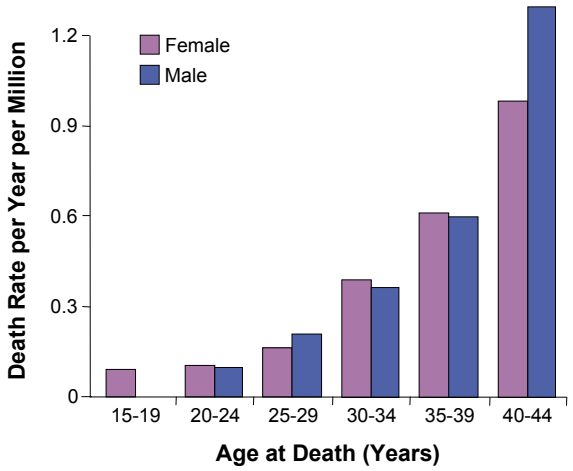

Figure 12.14: National Mortality for Thyroid Cancer by Gender, U.S., 1975-2000

adolescents and young adults, the highest TNM stage that anyone younger than age 45 can achieve is stage II, even with distant metastases. Therefore, utilizing the TNM staging system as a predictor of outcome or a determinant of treatment aggressiveness is not necessarily useful in children and young adults with thyroid cancer

RISK FACTORS AND ETIOLOGY

Differentiated Thyroid Carcinoma

The major established environmental risk factor for thyroid neoplasms, particularly PTC, is radiation exposure to the thyroid.[11,12] Younger individuals, particularly those under 5 years of age, are much more sensitive to the tumorigenic effects of irradiation.[12,13] In part, this may be due to the higher rate of thyroid cell replication in children as compared to adults.[1,14,15] Because children are no longer treated with external beam radiation therapy for benign conditions such as tonsillar hypertrophy, thymic enlargement, or acne, there are currently fewer adolescent and young adult thyroid cancer patients with this well-established risk factor. However the use of radiotherapy to treat malignancies (chiefly Hodgkin and non-Hodgkin lymphomas) remains a significant risk for thyroid carcinoma development, even many years after the completion of therapy.[16] Although there are some conflicting data, it appears that radiation-induced thyroid carcinoma is not more clinically aggressive as compared to sporadic, non-radiation induced tumors.[16,17]

Another well-documented risk factor for the development of PTC is internal ionizing radiation, such as occurred with the large environmental exposure to radioactive iodines from the Chernobyl nuclear accident.[18,19] The risk of thyroid cancer secondary to radioiodine is significantly higher the younger the age at the time of exposure, perhaps because the thyroid gland in younger children is better equipped to transport iodine as compared to older children.[15] The risk of thyroid cancer from the Chernobyl disaster has been demonstrated to be linearly correlated with radiation doses up to 1.5-2 Gy.[18] The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas than elsewhere. Administration of iodine as a dietary supplement reduced this risk of radiation-related thyroid cancer by a factor of 3, for consumption of

potassium iodide versus no consumption.[18] Fortunately, the doses of radioactive iodine used in diagnostic thyroid scans appear not to increase the rate of tumorigenesis.[11]

Researchers are beginning to understand the genetic and molecular basis of the differentiated thyroid carcinomas. One of the major early somatic events that is associated with the development of PTC is a chromosomal rearrangement linking the promotor region of an unrelated gene(s) (named "*PTC*") to the carboxyl terminus of the *RET* (rearranged during transfection) proto-oncogene.[1,6,14,19] Although it is widely believed that *RET/PTC* rearrangements are critical for the development of pediatric and radiation-induced PTC,[20-26] some recent reports have challenged these conclusions.[27] Mutational activation of the BRAF oncogene is commonly found in adult PTC. In children and young adults, mutations in BRAF do not occur frequently, although the prevalence of this genetic alteration appears to increase with age.[28-30]

Although PTC does not usually present as a familial disease, approximately 3-5% of patients with PTC do have a positive family history.[31] Having familial PTC may portend a worse prognosis, given previous data suggesting that these cases may have more aggressive disease with shorter disease-free intervals after initial therapy.[31,32] To date, the genetic basis for dominantly inherited non-medullary thyroid carcinoma has not been elucidated. Other familial tumor syndromes in which there is an increased risk of DTC include the Carney complex, Cowden disease, and familial adenomatous polyposis (Gardner syndrome).[1]

Figure 12.15: National Mortality for Thyroid Cancer by Era, U.S., 1975-2000

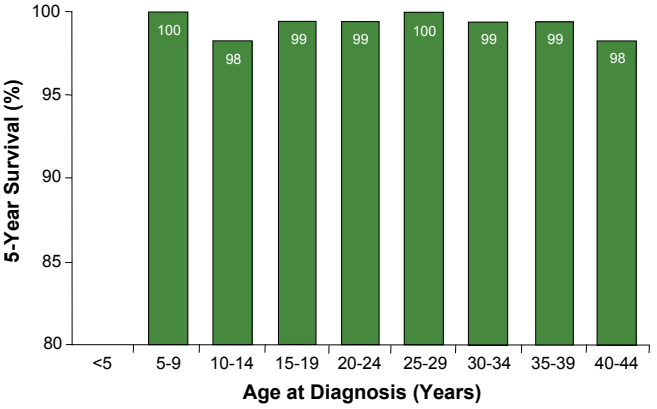

Figure 12.16: 5-year Survival Rate for Thyroid Cancer, SEER 1975-1999

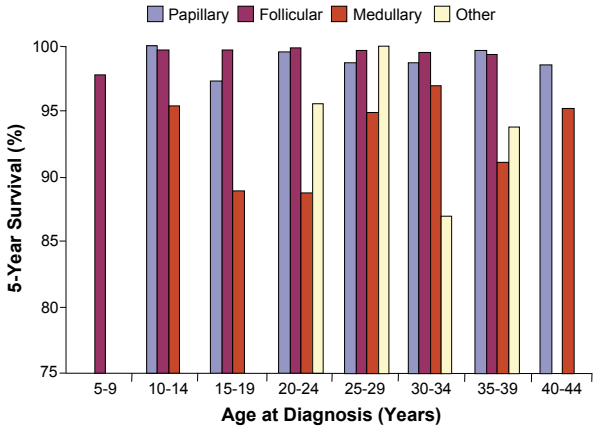

Figure 12.17: 5-year Survival Rate for Thyroid Cancer by Histologic Type, SEER 1975-1999

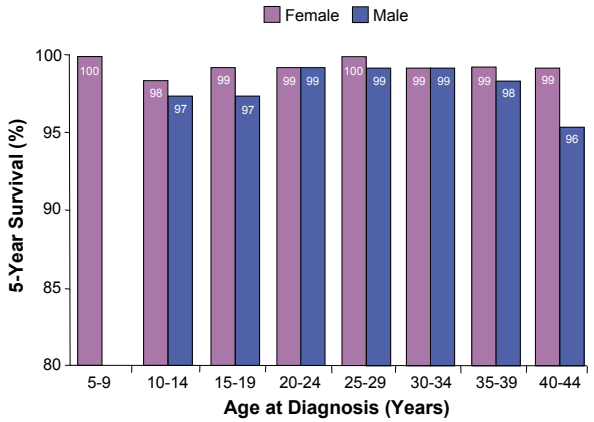

Figure 12.18: 5-year Survival Rate for Thyroid Cancer by Gender, SEER 1975-1999

Medullary Thyroid Carcinoma

Unlike PTC, medullary thyroid carcinoma does not have clearly identified environmental risk factors. On the other hand, the molecular basis of MTC in the context of the familial syndromes (see below) is very well understood. The development of MTC in this setting is also particularly relevant in young children because, with current methods of diagnosis and treatment, MTC is one of the few malignancies that can be prevented or cured (via total thyroidectomy) before it becomes clinically manifest. In the adolescent and young adult population, it is fair to say that the vast majority of cases of MTC will have a genetic basis, i.e. germline mutations in the *RET* proto-oncogene. Although sporadic (non-heritable) MTC can be seen in this age group, such cases are rare. Therefore, the focus of the subsequent discussion is on familial MTC, which is inherited in an autosomal dominant fashion.

Most children and young adults with MTC are afflicted with one of three hereditary cancer syndromes: FMTC, MEN2A, or MEN2B. Medullary thyroid carcinoma occurs in almost all patients with these familial syndromes, and it is the most common cause of death in affected individuals. Patients with FMTC only develop MTC. In MEN2A and MEN2B, 50% of patients develop pheochromocytoma; up to 20% of MEN2A patients develop hyperparathyroidism.[33] Individuals with MEN2A may also develop a pruritic cutaneous lesion on the upper back, termed "cutaneous lichen amyloidosis."[34] Other MEN2A kindreds can have associated Hirschsprung's disease.[35,36] All patients with MEN2B develop a generalized ganglioneuromatosis, manifested most obviously by the presence of oral mucosal neuromas. These individuals also manifest a Marfanoid body habitus and a characteristic facial appearance.

The exact etiology of sporadic MTC is unknown, although it too may have a genetic basis. After the discovery that germline mutations in the *RET* proto-oncogene cause heritable MTC, it was identified that somatic mutations in *RET* can be found in over 40% of sporadic cases of MTC.[37] However, due to the rarity of sporadic MTC in those younger than 30 years of age, it is unknown if this holds true for this age group.

SUMMARY

Malignant neoplasms of the thyroid were the fourth most commonly diagnosed cancer in the 15- to 29-year age group between 1975 and 2000. In the year 2000, nearly 2,400 individuals 15 to 29 years of age were diagnosed with a malignant thyroid neoplasm in the U.S., representing approximately 10% of all thyroid cancer cases. The incidence of thyroid carcinoma increased rapidly between 15 and 29 years of age and reached a plateau by the 5th—6th decades of life. Differentiated thyroid cancer (PTC and FTC) accounted for the vast majority of cases diagnosed before 30 years of age, and MTC accounted for almost all of the rest. Females were much more likely to develop thyroid cancer than males.

Between 1975 and 2000, the incidence of thyroid cancer rose steadily in all age groups between 15 and 30 years. In adolescent and young adult females this occurred at a statistically significant rate. Most of the increase in incidence occurred during the 1990s. The increase occurred in localized and regional, but not distant, presentations of disease, which may reflect changes in imaging modalities and surgical approaches to these diseases.

Overall, mortality from thyroid carcinoma was low, although it increased as a function of age. Despite the remarkably higher incidence of thyroid cancer in females, mortality for females and males was essentially identical and declined steadily during the past quarter century. Although the survival difference between males and females was small, males had a consistently lower survival rate than females. Thyroid cancer is one of the most curable malignancies, with 5-year survival rates exceeding 99% in the adolescent and young adult population, even in patients with disseminated disease at diagnosis. Patients with MTC have not fared as well as those with DTC, particularly those in the 15- to 24-year-old age group.

The major established environmental risk factor for the development of benign and malignant thyroid neoplasms, particularly PTC, is ionizing radiation exposure to the thyroid, whether from external (cancer radiotherapy) or internal (radioiodine exposure) sources. The genetic causes of DTC are now coming to light. Most adolescents and young adults with MTC are afflicted with one of three hereditary cancer syndromes—FMTC, MEN2A, or MEN2B—that are caused by activating mutations of the *RET* proto-oncogene.

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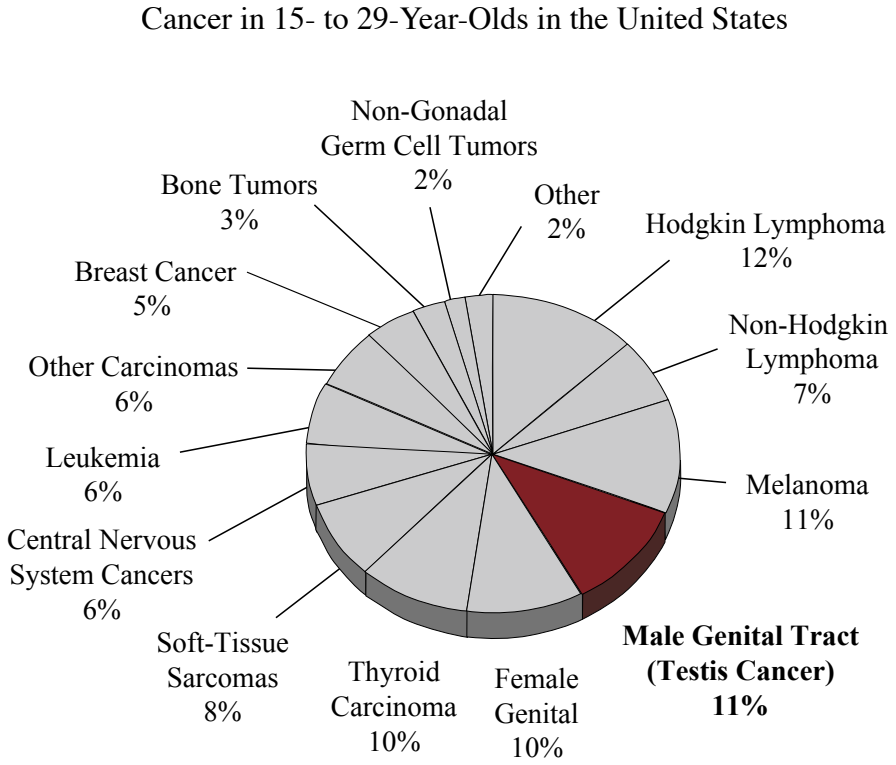
Chapter 13

Male Genital Tract Cancer



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HIGHLIGHTS

Incidence

- Male genital tract or testicular tumors accounted for 21% of all neoplasms in *male* adolescents and young adults from 1975 to 2000, and were the most common solid cancer diagnosis in this age group.
- Testicular cancer accounted for 11% of all cancers occurring in *all* individuals in the 15- to 29-year age group.
- In the year 2000, 2,500 individuals 15 to 29 years old were diagnosed with testicular cancer in the U.S.
- The incidence of testicular cancer peaked in the age ranges 25 to 29 and 30 to 34, and then declined thereafter.
- At its peak, the incidence of testicular cancer was in excess of 120 per year, per million population.
- There were profound racial/ethnic differences in the incidence of testicular cancer. The incidence in white non-Hispanics was 4-fold that in African Americans/blacks.
- Since 1975, the incidence of testicular cancer has increased at an annual rate of 0.97% for individuals aged 15 to 29 years.

Mortality and Survival

- National mortality has decreased from 1975 to 2000 for individuals in all age groups.
- The 5-year survival rate in all age groups was in excess of 90%.
- Testicular cancer survival rates were very histology-specific. The 5-year survival rate varied from 95% for seminoma in 25- to 29-year-olds, to less than 70% for 15- to 19-year-olds with choriocarcinoma or other non-seminomatous histologies.

Risk Factors

- Cryptorchidism is an established risk factor for testicular cancer (a 2.5- to 11-fold increased risk).
- The cause of the vast majority of cases of testicular cancer is unknown.

INTRODUCTION

Almost all male genital tract tumors affecting 15- to 29-year-olds occur in the testis (Figure 13.1). From 1975 to 2000, testicular tumors accounted for 21.4% of all neoplasms in male adolescents and young adults in the U.S., and were the most common solid tumors in males in this age group.[1-8] This is in contrast to children 0 to 14 years of age, in whom testicular tumors accounted for only 2% of all neoplasms, and to individuals 30 to 44 years of age in whom testicular tumors accounted for 7% of all neoplasms. In the U.S., 2,500 adolescents and young adults 15 to 29 years of age were diagnosed with testicular cancer in the year 2000 (Table 13.1).

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer

Table 13.1: *Incidence of Male Genital Tract Cancer in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	9.587	10.274	10.264	10.109	9.482	9.690
Average incidence per million, 1975-2000, SEER	7.8	3.9	4.7	28.3	82.4	117.7
Average annual % change in incidence, 1975-2000, SEER	-0.4%	^	^	1.5%	0.5%	1.6%
Estimated incidence per million, year 2000, U.S.	4.4	3.9	4.7	32.6	87.1	136.5
Estimated number of persons diagnosed, year 2000, U.S.	42	40	48	329	826	1,323

^ Too few for a reliable estimate

(ICCC), malignant germ cell tumors are described in category IX as *Germ-Cell, Trophoblastic and other Gonadal Neoplasms*. Within this classification, there is no distinction between those germ cell tumors that occur in males versus those that develop in females. (The ICCC group also includes intracranial and intraspinal germ-cell tumors [category IX(a)].) Hence for male genital tract tumors, the ICCC was not used and the analysis is based on the topography and morphology information from the International Classification of Diseases for Oncology (ICD-O). Almost all of the cancers of the male genital tract in 15- to 29-year-olds are in the testis, and therefore this chapter is limited to testicular cancer.

The male genital tract includes the tract and associated glands within the testis and prostate. The tract begins in the seminiferous tubules of the testis and ends at the ampulla and ejaculatory duct of the vas deferens. Within the ICD-O, the topographic sites of the male genital tract are the testis (C62.0-C62.1, C62.9), epididymus (C63.0), spermatic cord (C63.1), scrotum (C63.2), seminal vesicle (C63.7), tunica vaginalis (C63.7), overlapping lesions and those not otherwise specified (NOS) (C63.8-C63.9), the prostate (C61.9), and penis (C60.0-C60.9). The ICD-O categories include carcinomas and adenocarcinomas (8010-8041, 8140, many others), malignant Leydig and Sertoli cell tumors (8640-8650, 8631), androblastoma (8630), and germ-cell neoplasms. The latter span categories 9060 to 9085 and include seminoma (9061-9063), dysgerminoma (9060), germinoma (9064), embryonal carcinoma (9070), endodermal sinus (yolk sac) tumor (9071), polyembryoma (9072), teratoma/teratocarcinoma (9080-83), and mixed germ cell tumor (9085).

Since 15- to 29-year-old males rarely have malignant tumors in the male genital tract at sites other than the testis, non-testicular primary sites were excluded from the analyses. The vast majority of the testicular neoplasms are seminomas and non-seminomas. This chapter covers the carcinomas, Leydig/Sertoli cell tumors, seminomas, and germ cell cancers of the testis, including embryonal cell, yolk sac, teratoma and mixed histologies.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate.

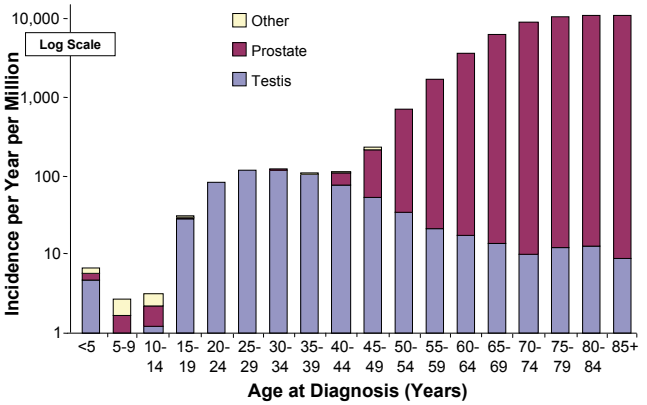

Figure 13.1: Incidence of Genital Tract Cancers in Males, SEER 1975-2000

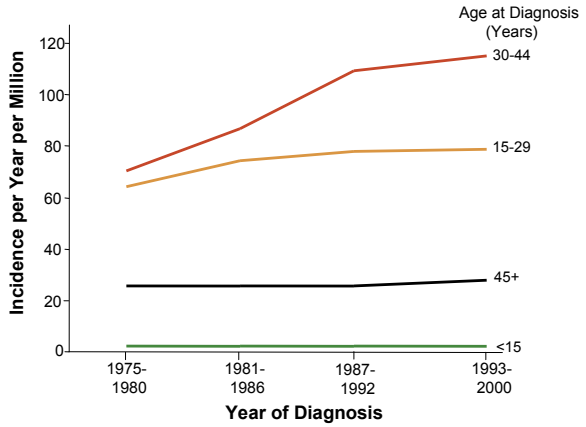

Figure 13.2: Incidence of Testicular Cancer in Males by Era, SEER 1975-2000

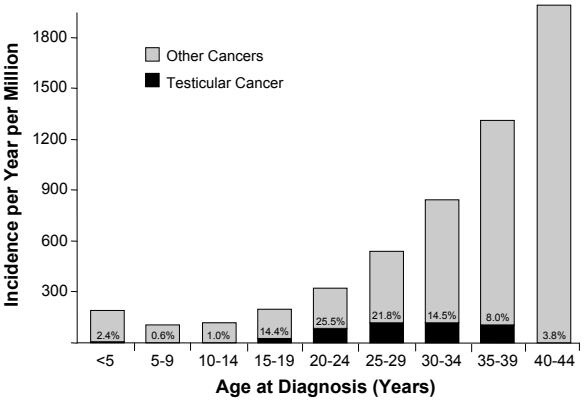

Figure 13.3: Incidence of Testicular Cancer in Males < Age 45 Relative to All Cancers in Males < Age 45, SEER 1975-2000

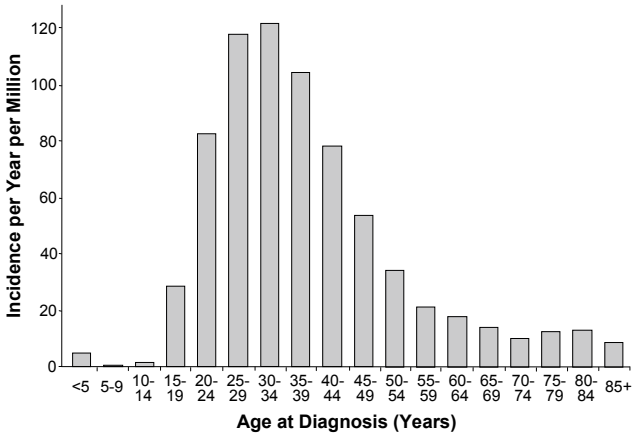

Figure 13.4: Incidence of Testicular Cancer in Males, All Ages, SEER 1975-2000

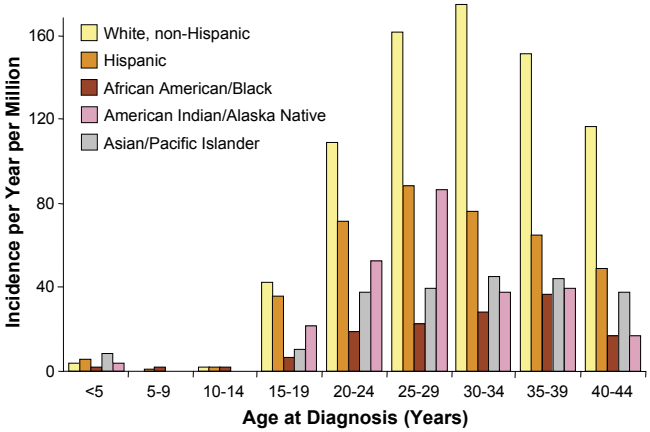

Figure 13.5: Incidence of Testicular Cancer in Males by Race/Ethnicity, SEER 1990-2000

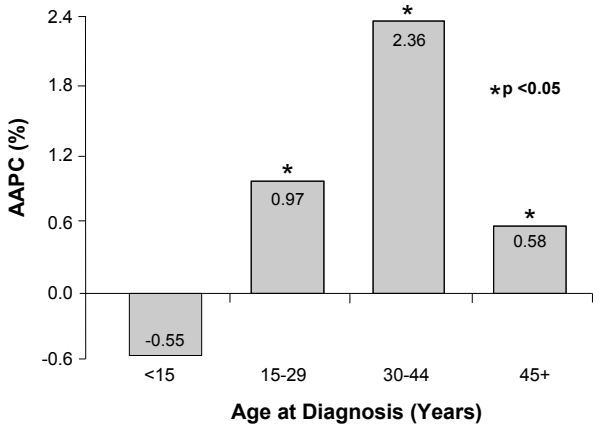

Figure 13.6: Average Annual Percent Change (AAPC) in Incidence for Testicular Cancer in Males, SEER 1975-2000

For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

Since the ICCC was set up as a classification for childhood cancer, it does not have a separate category for testicular cancer alone. Topography and histology from ICD-O can be used to examine differences among very young testicular cancer patients compared to older patients, but it does not capture the molecular biology of testicular cancer. Males aged 15 to 29 are at a transition point from pediatric to adult biologic characteristics of testicular neoplasms. For example, the isochromosome of the short arm of chromosome 12, i(12p) is a specific genetic marker of all histologies of germ cell tumor in adults. This marker is rarely found in children or young adolescents with germ cell cancer.

INCIDENCE

The incidence of testicular cancer rose slowly in the 15- to 29-year age group during the observation period 1975 to 2000 (Figure 13.2). By comparison, there was a substantial increase in incidence for individuals 30 to 44 years of age.

Age-Specific Incidence

The incidence of testicular cancer as a function of age at diagnosis over the period 1975 to 2000 is presented in Figure 13.3. Relative to other tumors, the proportion of testicular cancers increased from 1% of all cancers in 10- to 14-year-old individuals to 21.8% of cancers diagnosed in the 25- to 29-year age group. There was an increase in all tumors combined in this older group, but the main contribution for the increase was the greater number of testicular cancers diagnosed (Figure 13.4). The incidence of testicular cancer peaked in the 25- to 29- and 30- to 34-year age groups, then decreased in successive 5-year age groups. At its peak, the annual incidence of testicular cancer exceeded 120 per million males.

Racial/Ethnic Differences in Incidence

At all adolescent and adult ages, the incidence of testicular cancer was highest in non-Hispanic whites and lowest in African Americans/blacks (Figure 13.5). Between 25 and 45 years of age, the incidence in non-Hispanic whites was more that 2-fold greater than in all other race/ethnicity groups.

Trends in Incidence

Figure 13.2 displays the trend in testicular cancer incidence by age group. The average annual percent change (AAPC) in incidence is portrayed in Figure 13.6. There were significant increases in the AAPC in incidence for all age groups above age 15. Change in incidence from 1975 to 2000, by age group, is depicted in Figure 13.7.

OUTCOME

Mortality

Trends in mortality data for U.S. males from 1975 to 2000 are shown in Figure 13.8. Over the entire interval of 1975 to 2000, men diagnosed with testicular carcinoma in the 15- to 29-year age group had an average percent reduction in cancer mortality of 6.04% (Figure 13.8, left panel). During the last 9 years of this interval, from 1992 to 2000, the average reduction rate declined to 3.97% per year (Figure 13.8, right panel). The AAPC in mortality for men in the 30- to 44-year age group was -2.46% for the period 1975 to 2000, changing to 0.15% for the more recent period, indicating that 15- to 29-year-olds had a greater rate of mortality reduction. In contrast to younger men, those diagnosed with testis cancer after age 45 had a significant acceleration in mortality reduction over the same intervals, with an AAPC of 0.27% from 1975 to 2000 and an AAPC of -3.38% in the period 1992 to 2000. Since the incidence of testicular cancer in older men increased at a statistically significant, average rate of 0.58 % per year (Figure 13.6), the decline in mortality in this age group is all the more impressive. The likely explanation is that advances in testicular cancer therapy pioneered in young men have subsequently been successfully applied to older men.

Racial/Ethnic Differences in Mortality

U.S. national testicular cancer mortality data for race/ethnicity are depicted in Figure 13.9. The number of evaluable Asians/Pacific Islanders and American Indians/Alaska Natives were too low to reliably include in racial/ethnicity comparisons. Non-Hispanic whites had the highest testis cancer mortality among those above age 25, in part due to the higher incidence in this racial group (Figure 13.5). African Americans/blacks had a lower testis cancer death rate in comparison to both non-Hispanic whites and Hispanics (Figure 13.5). When compared directly to the

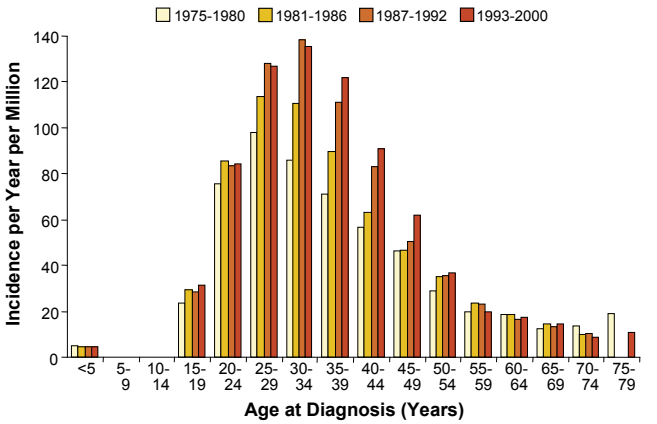

Figure 13.7: Change in Incidence for Testicular Cancer in Males by Era, SEER

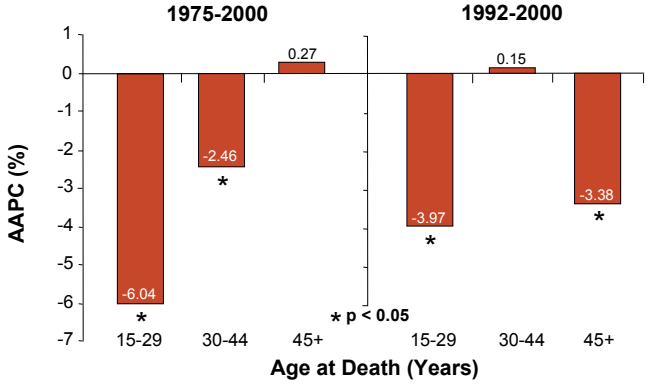

Figure 13.8: Average Annual Percent Change (AAPC) in Testicular Cancer Mortality for Males, SEER 1975-2000

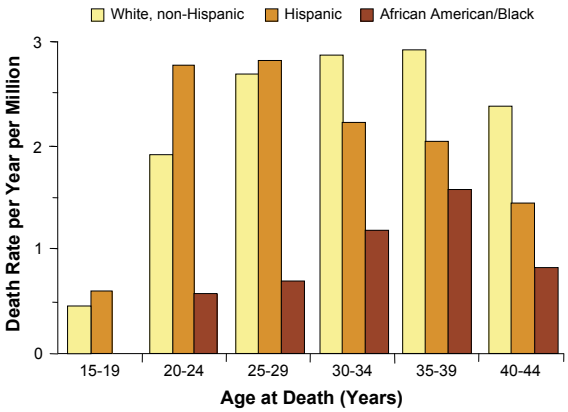

Figure 13.9: Testicular Cancer Mortality in Males by Race/Ethnicity, U.S., SEER 1975-2000

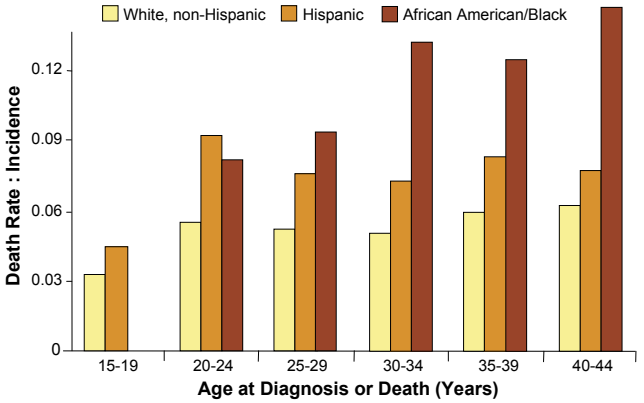

Figure 13.10: Ratio of National Death Rate to SEER Incidence by Race/Ethnicity, Testis Cancer in Males, 1975-2000

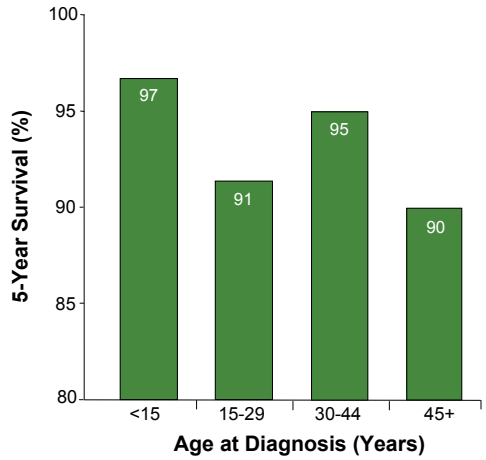

Figure 13.11: 5-Year Survival Rate for Testicular Cancer in Males, SEER 1975-1999

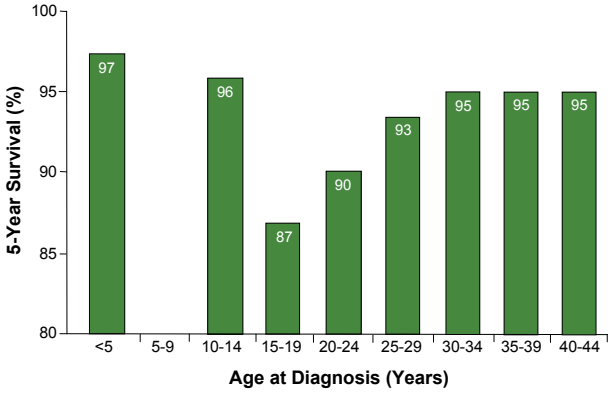

Figure 13.12: 5-Year Survival Rate for Testicular Cancer in Males, SEER 1975-1999

incidence pattern, however, African Americans/blacks 25 years of age and older had higher testis cancer mortality than either of the other races/ethnicities (Figure 13.10). The worse prognosis for young African Americans/blacks with cancer is consistent with several other cancers reviewed in this monograph, and is likely attributable to a variety of factors, including delayed diagnosis, differences in access to care and other social inequities, and possible biologic differences in the cancer and host responses to therapy.

Survival

The survival of patients with testicular cancer has improved substantially from 1975 to 2000. This is due primarily to improvements in chemotherapy and to the education of oncologists in new treatment approaches. The 5-year survival rates for individuals with testicular cancer from 1975 to 1999 are shown in Figures 13.11 and 13.12. A 5-year survival rate of 91% was observed in the 15- to 29- year age group. When examined by 5-year age intervals (Figure 13.12) the 15- to 19- and 20- to 24-year age groups had the lowest survival rates—87% and 90%, respectively.

The trends in testicular cancer survival during the years 1975 to 2000 are presented in Figures 13.13 and 13.14. All age groups experienced improvements in survival during this observation period. Individuals 15 to 29 and 20 to 24 years of age demonstrated the largest increases in 5-year survival rates from 1975 to 1980 and 1993 to 2000. Furthermore, the relatively poor survival rates for those 15 to 19 and 20 to 24 years of age reflect in large part the results reported from 1975 to 1980 (Figure 13.14).

The histology of testicular cancer had a profound effect on 5-year survival rates (Figure 13.15). This was observed across all three adolescent and young adult 5-year age intervals presented (Figure 13.16), and varied from 66% for non-seminomatous tumors (choriocarcinoma, yolk sac, etc.) in 15- to 19-year-olds, to greater than 95% for 25- to 29-year-old individuals with seminoma.

RISK FACTORS

The SEER Pediatric Monograph on cancer incidence and survival reviewed the data on proven and suspected risk factors for germ cell tumors.[1,9] These risk factors are presented below in modified form as they apply to testicular cancer.

Cryptorchidism is a proven risk factor for testicular cancer. This occurs on both the ipsilateral and contralateral sides, and increases the risk by 2.5- to 11-fold.[1,10,11] Suggestive evidence for testicular cancer etiology has been reported for the following: hernia, trauma, family history of germ cell tumor, and high maternal hormone levels during pregnancy.[1,10,12-14] Factors such as viral infection, parental occupation, x-ray exposure, or genetic chromosomal syndromes such as Klinefelter's have not been shown convincingly to cause testicular cancer.[1,10,15-18] Review of these data on risk factors for testicular cancer suggests that an extremely small minority of these cancers may be attributable to environmental factors, thus the opportunity for prevention of male germ cell cancers is minimal.

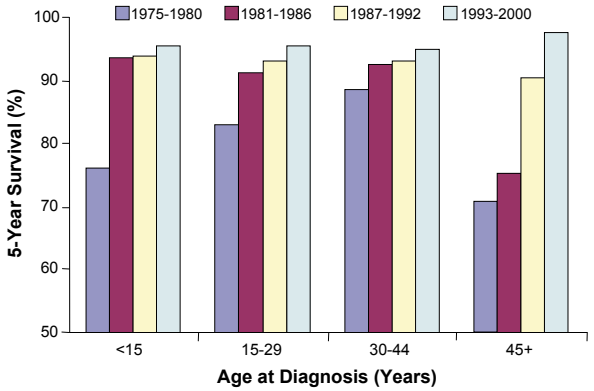

Figure 13.13: 5-Year Survival Rate for Testicular Cancer in Males by Era, SEER

SUMMARY

Testicular cancers, or tumors of the male genital tract, accounted for 21% of all neoplasms diagnosed in males 15 to 29 years of age, and were the most common solid tumors diagnosed in this age group. The incidence of testicular cancer reached its maximum in the age groups 24 to 29 years and 30 to 34 years. At its peak, the incidence of testicular cancer in males exceeded 120 per year per million. In adolescents and young adults, the incidence of testicular cancer has increased in the time period 1975 to 2000.

Testicular cancer mortality for U.S. males aged 15 to 29 years decreased from 1975 to 2000, by an average annual rate of 6%. There have been corresponding increases in 5-year survival rates observed among all age groups.

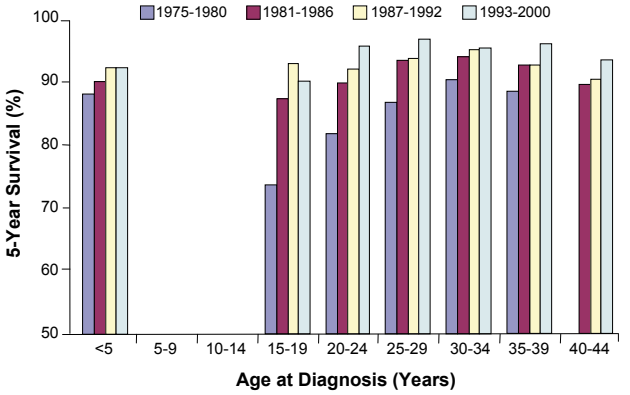

Figure 13.14: 5-Year Survival Rate for Testicular Cancer in Males by Era, SEER

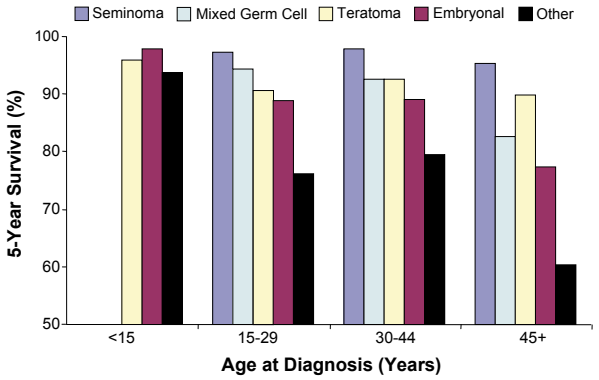

Figure 13.15: 5-Year Survival Rate for Testicular Cancer in Males by Histology, SEER 1975-1999

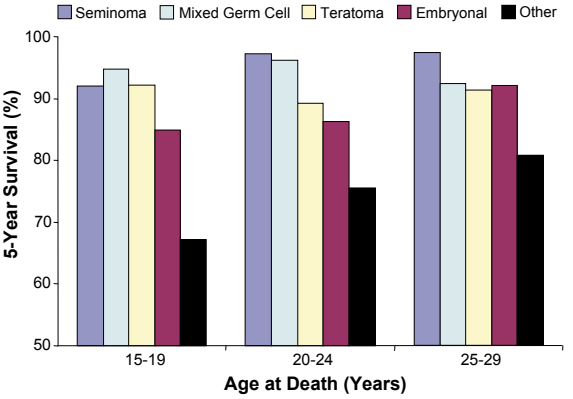

Figure 13.16: 5-Year Survival Rate for Testicular Cancer in Males by Histology, SEER 1975-1999

The survival from testicular cancer was histology specific, ranging from 90-95% survival for seminoma to 60-80% survival for choriocarcinoma and others.

Epidemiologic studies have demonstrated that cryptorchidism is the only proven risk factor for testicular cancer. Other factors and environmental exposures have been suggested but have not been consistently associated with an increased risk of testicular cancer.

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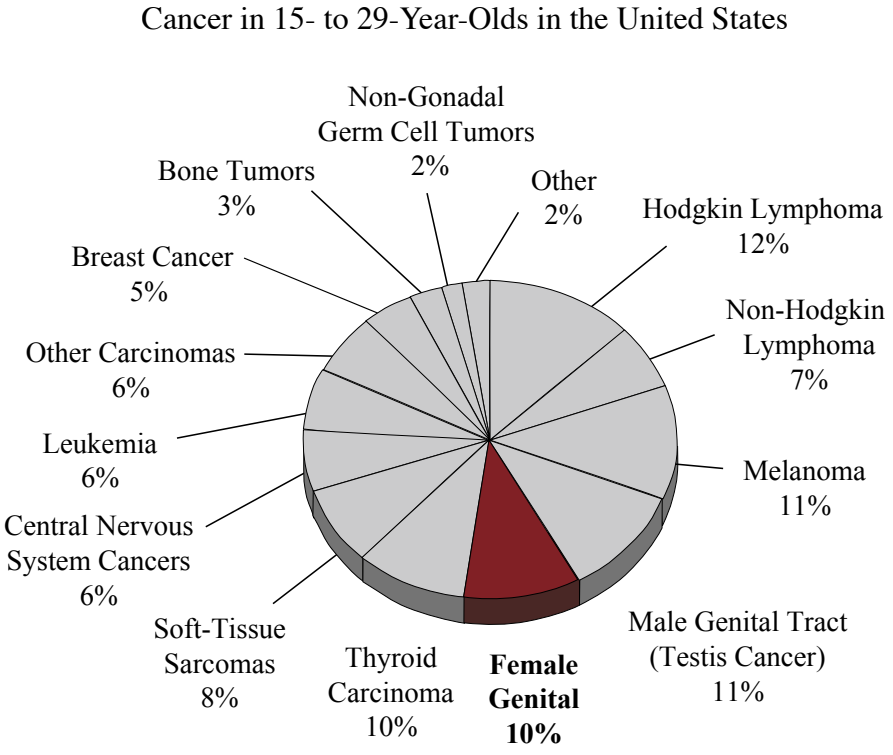
Chapter 14

Female Genital Tract Cancer



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HIGHLIGHTS

Incidence

- The vast majority of genital tract tumors diagnosed in women 15 to 29 years of age are carcinomas of the cervix and corpus uteri, and carcinomas and germ cell tumors of the ovary.
- In the period 1975 to 2000, this group of cancers accounted for 13% of all malignancies in 15- to 19-year-old females, 17% in 20- to 24-year-old females, and 23% of all malignancies in 25- to 29-year-old females.
- Cervical carcinoma in 15- to 29-year-olds decreased in incidence over time from 1975 to 2000.
- The incidence of cervical cancer in 15- to 29-year-olds was higher in white non-Hispanic, Hispanic, and African American/black females than it was in other races/ethnicities.
- Cancer of the ovary occurs most frequently in Asian/Pacific lslander females and is least common in American Indian/Alaska Native females.

Mortality & Survival

- The 5-year survival rate for cancer of the cervix has not improved in 15- to 29-year-olds during the past quarter century.
- The 5-year survival rate for ovarian cancer has not improved in 15- to 29-year-olds during the past quarter century, in contradistinction to that for women over age 30 when diagnosed.
- In 15- to 29-year-olds, cancer of the cervix had a higher mortality rate for African Americans/blacks than for white non-Hispanics, Hispanics, or Asians/Pacific Islanders.

Risk Factors

- Cervical cancer in females occurs most often in those infected with human papillomavirus types 16, 18, 31, and 45.
- These malignancies are also more common in women of increased parity, those who engage in early sexual activity, have many sexual partners, use oral contraceptives, smoke, or are of lower socioeconomic status.
- The lack of adequate screening programs and poor compliance among 15- to 29-year-old women is a serious concern.
- Future use of vaccines for human papillomavirus may prevent the development of invasive cervical cancer.

INTRODUCTION

Among 15- to 29-year-old females, carcinomas of the uterine cervix are the most common cancer of the female genital tract, followed by ovarian cancer. Nearly all genital system tumors are carcinomas of the cervix, germ cell tumors of the ovary, and carcinomas of the ovary. Most cervical carcinomas are thought to be caused by human papillomaviruses as a result of sexual contact. With the advent of a vaccine that is highly preventive of the strains of human papillomavirus mediated by sexual contact, there is now a distinct possibility that cervical carcinoma can be largely prevented. This chapter reviews the epidemiology of cervical carcinoma and ovarian cancers in 15- to 29-year-olds in the United States, and compares the findings with those in younger and older women.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), malignant germ cell tumors are described in category IX as *Germ-Cell, Trophoblastic and other Gonadal Neoplasms*. Within this classification, there is no distinction between those germ cell tumors that occur in males versus those that develop in females. (The ICCC group also includes intracranial and intraspinal germ-cell tumors (category IX(a)].) Hence for female genital tract tumors, the ICCC was not used and the analysis is based on the topography and morphology information from the International Classification of Diseases for Oncology (ICD-O).

The female genital tract includes the ovaries, fallopian tubes, uterus (body/corpus and cervix), vagina and vulva.

Within the ICD-O, the topographic sites of the female genital tract are the vulva (C51.0-C51.9), vagina (C52.9), cervix uteri (C53.0-C53.9), corpus uteri (C54.0-C54.9), uterus NOS (C55.9), ovary (C56.9), fallopian tube (C57.0), and other specified and unspecified sites of female genital tract (C57.1-C57.9). The ICD-O morphology categories include carcinomas and adenocarcinomas (8010-8041, 8140, many others). Also included are malignant gonadal neoplasms [malignant thecomas (8600), malignant granulosa cell tumors (8620), malignant androblastomas (8630), Sertoli cell carcinoma (8640, and malignant Leydig cell tumor (8650)]. The germ cell neoplasms span categories 9060 to 9085 and include dysgerminoma (9060-9063), germinoma (9064), embryonal carcinoma (9070), endodermal sinus (yolk sac) tumor (9071), polyembryoma (9072), and teratoma/teratocarcinoma (9080-9083), and mixed germ cell tumor (9085).

Most cancers of the genital tract in 15- to 29-year-old females occur within the ovary and uterine cervix. Hence, this chapter focuses on cancer at these two sites. As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

Since the ICCC was set up as a classification for childhood cancer, it does not have a separate category for female genital cancer or for specific sites such as ovary and cervix uteri. Topography and histology from ICD-O can be used to examine differences among young females with cancer of the genital tract compared to older patients, but it is not expected to capture the intermediate biology of these cancers in females aged 15 to 29, which is at a transition point from pediatric to adult features.

INCIDENCE

In the United States, genital tract tumors accounted for 17.8% of all invasive cancers in females 15 to 29 years of age who were diagnosed between 1975 and 2000 at SEER sites (Figure 14.1). In the year 2000, approximately 1,700 U.S. women aged 15 to 29 years were diagnosed to have a genital tract cancer (Table 14.1). Among 15- to 19-year-old females, the proportion of all invasive cancers that were genital tract tumors was 11.9%. Among 20- to 24-year-olds, the proportion was 15.4%, and among 25- to 29-year-olds it was 21.4% (Figure 14.2).

Age-Specific Incidence

The most common cancers in females 10 to 44 years of age are shown in Figure 14.3, each as a proportion of all cancers that occurred in women during 1975 to 2000. In 25- to 29-year-olds, genital tract tumors peaked as a proportion of all cancer and accounted for more cancers than any other category. In the 15- to 24-year age group, the genital-tract-cancer proportion was third to melanoma and thyroid malignancies.

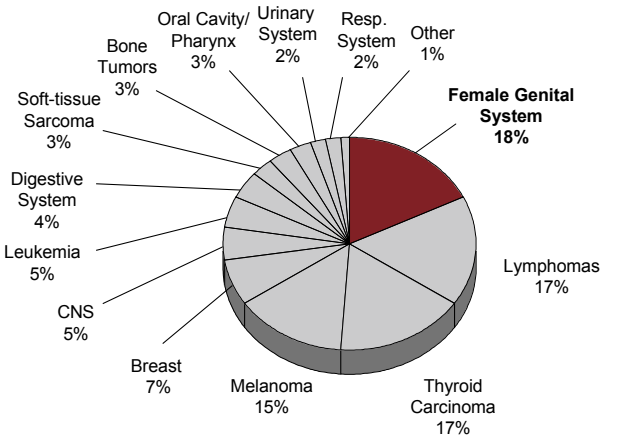

Figure 14.1: Cancer Incidence in 15- to 29-Year-Old Females

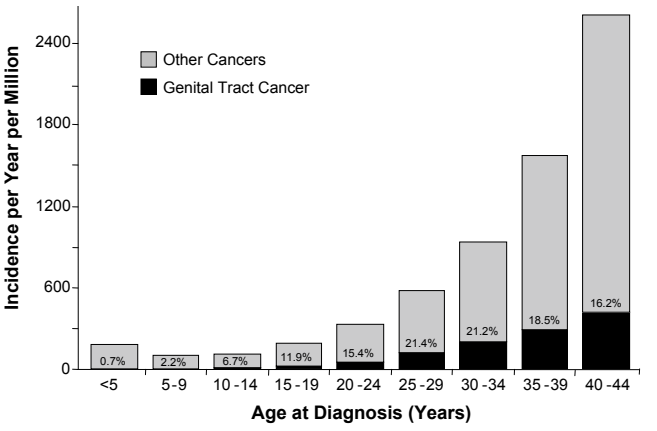

Figure 14.2: Incidence of Genital Tract Cancer Relative to All Cancer in Females, U.S., SEER 1975-2000

The most common genital tract tumor occurring in females 15 to 29 years of age was carcinoma of the uterine cervix. Cancer of the ovary (germ cell tumors and carcinoma) was second in incidence in this age group, in contrast to being the most predominant genital tract tumor, by far, among 5- to 14-year-olds (primarily germ cell type) (Figure 14.4).

From 1975 to 2000, cervical carcinoma accounted for 22% of the genital tract tumors in females 15 to 29 years of age (Figure 14.4). Ovarian tumors accounted for 18% of the genital tract tumors in adolescent and young adult females during this same era (Figure 14.4). In the year 2000, nearly 800 U.S. women 15 to 29 years of age were diagnosed to have a cervical carcinoma, and approximately 525 were diagnosed to have cancer of the ovary (Table 14.1).

Gender-Specific Incidence

The age dependence of genital tract malignancies in females contrasts sharply with that of males. This is dramatically apparent when the incidence of genital tract tumors in one gender is compared with the other, as in Figure 14.5. In the 15- to 29-year age group, genital tract cancer incidence was higher in males than females. From ages 30 to 50, however, there was a strikingly higher female:male ratio of genital tract tumors that peaked at 3.7 between 40 and 45 years of age. Under age 30 and over age 50, there was a higher male:female ratio, primarily due to testicular cancer in young males and prostate cancer in older males. In the 15- to 29-year age group, testicular cancer accounted for 11% of all invasive cancers, which is similar to the corresponding value of 10% for female genital tract cancer.

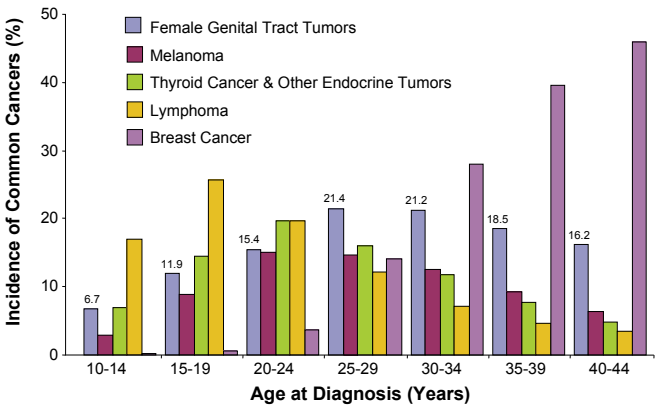

Figure 14.3: Common Cancers in 10- to 44-Year-Old Females as a Proportion of All Cancer, SEER 1975-2000

Table 14.1: *Incidence of Female Genital Tract Cancer in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions), females	9.365	10.026	10.008	9.829	9.276	9.583
ALL FEMALE GENITAL TRACT CANCER						
Average incidence per million, 1975-2000, SEER	1.0	2.1	7.3	22.7	50.4	122.6
Average annual % change in incidence, 1975-2000, SEER	^	^	0.2%	-0.3%	-1.9%	-1.0%
Estimated incidence per million, year 2000, U.S.	1.1	1.0	7.4	16.5	50.1	111.1
Estimated number of persons diagnosed, year 2000, U.S.	10	11	74	162	465	1064
CARCINOMA OF THE UTERINE CERVIX						
Average incidence per million, 1975-2000, SEER	0	0.1	0.3	3.3	23.2	78.0
Average annual % change in incidence, 1975-2000, SEER	^	^	^	^	-1.9%	-1.0%
Estimated incidence per million, year 2000 , U.S.	0	0	0	2.2	14.8	66.0
Estimated number of persons diagnosed, year 2000, U.S.	0	0	0	22	137	632
CANCER OF THE OVARY						
Average incidence per million, 1975-2000, SEER	0.2	1.8	6.4	15.3	19.0	27.0
Average annual % change in incidence, 1975-2000, SEER	^	^	0.3%	-0.1%	-1.7%	-1.7%
Estimate incidence per million, year 2000, U.S.	0	1.0	7.4	13.2	26.2	15.7
Estimated number of persons diagnosed, year 2000, U.S.	0	11	74	130	243	151

^ Too few for a reliable estimate

Racial/Ethnic Differences in Incidence

In 15- to 29-year-olds, the incidence of cervical cancer during 1992 to 2002 was higher in white non-Hispanic, Hispanic, and African American/black females than it was in females of other races/ethnicities (Figure 14.6). Among females over 30 years of age, however, Hispanics had the highest incidence of cervical cancer (Figure 14.6), a pattern that became more prominent with increasing age (data not shown).

Cancer of the ovary, however, occurred most frequently in Asian/Pacific lslander females and was distinctly less common in American Indian/Alaska Native females (Figure 14.7). Among females over 30 years of age, however, non-Hispanic whites had the highest incidence of ovarian cancer, a difference that became more prominent with increasing age (data not shown).

Trends in Incidence

The incidence of cancer of the cervix was 33.6 per year per million in 15- to 29-year-olds; this increased dramatically for those over 30 years of age (Figure 14.8). Over time, however, the incidence of cervical cancer declined slightly in the 20- to 24-year-old group (Figure 14.9), a trend that was also noted in older age groups. This reduction in incidence is attributable to a decline in the incidence of squamous cell carcinoma of the cervix, although the incidence of adeoncarcinoma of the cervix actually increased.[1]

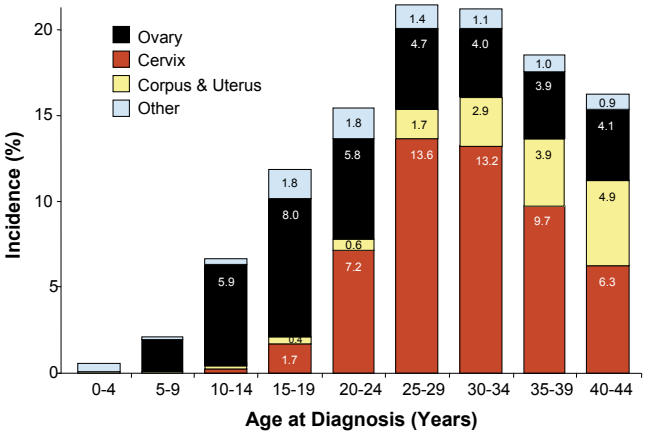

Figure 14.4: Incidence of Female Genital Tract Tumors as a Proportion of All Cancer, by Age and Tumor Type, SEER 1975-2000

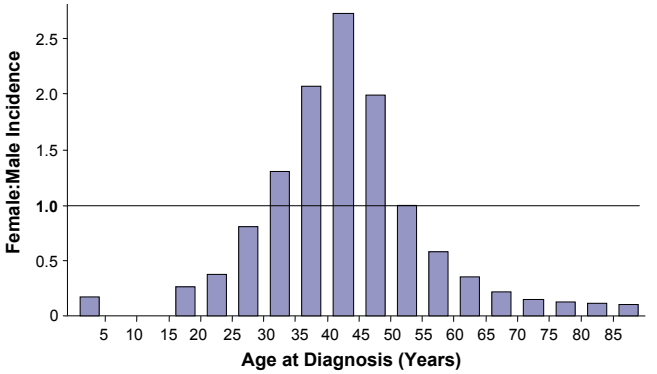

Figure 14.5: Incidence of Genital Tract Cancer, Female:Male Ratio, SEER 1975-2000

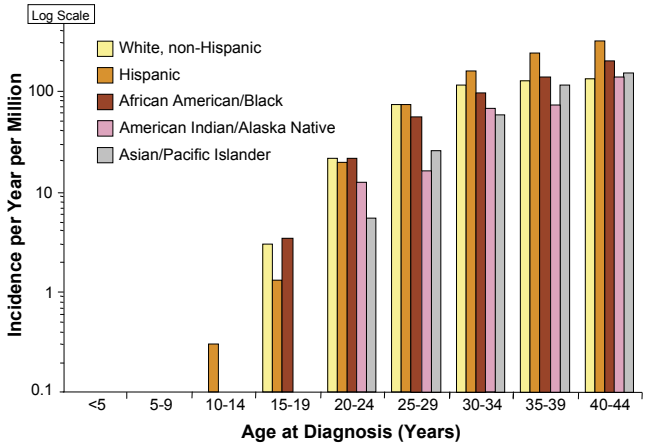

Figure 14.6: Incidence of Cervical Cancer in Females by Race/Ethnicity, SEER 1992-2002

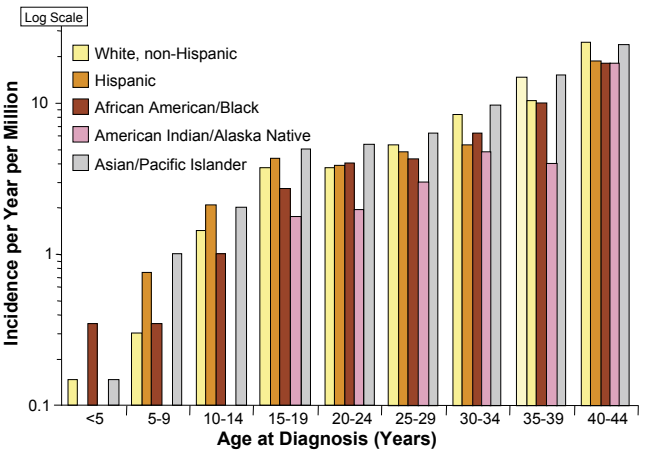

Figure 14.7: Incidence of Ovarian Cancer in Females by Race/Ethnicity, SEER 1992-2002

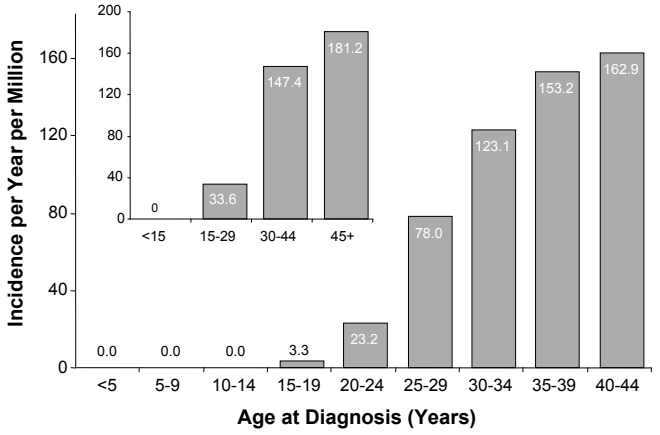

Figure 14.8: Incidence of Cervical Cancer, SEER 1975-2000

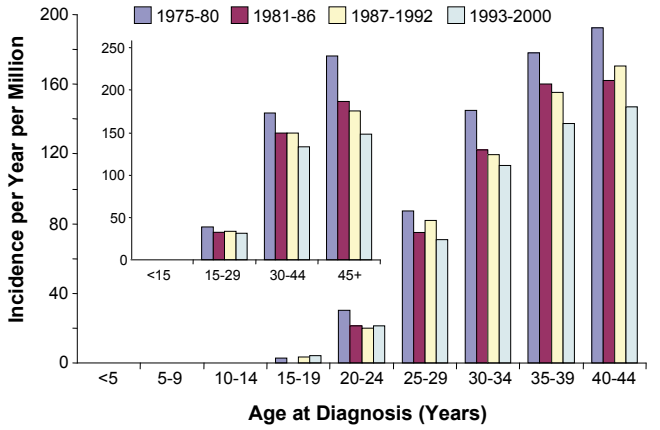

Figure 14.9: Incidence of Cervical Cancer by Era, SEER

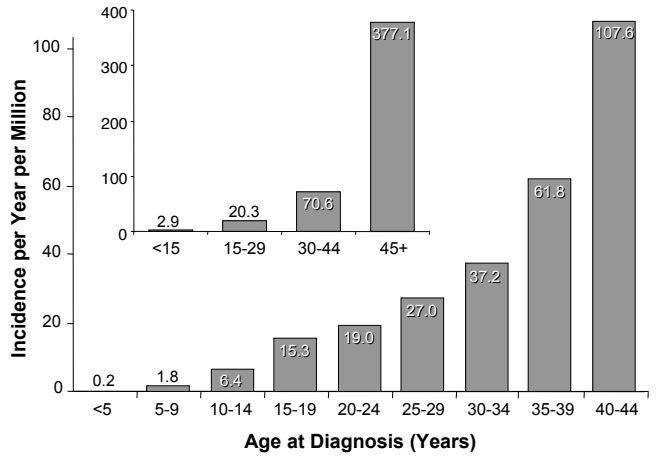

Figure 14.10: Incidence of Ovarian Cancer, Excluding Borderline Histology, SEER 1975-1999

The incidence of cancer of the ovary is depicted in Figure 14.10. In 15- to 29-year-olds the incidence was 20.3 per year per million, but this increased dramatically to 377 per year per million in adults over 45 years of age.

OUTCOME

Mortality

The U.S. mortality for cervical carcinoma from 1975 to 2000 is shown in Figure 14.11. In the 15- to 19-year age group, the death rate was 0.1 deaths/year/million; in 20- to 24-year-olds the rate was 1.9 deaths/year/million, and in 25- to 29-year-olds it was 8.4 deaths/year/million, reflecting increasing incidence. The African American/black population had the highest mortality for cervical carcinoma at all ages (Figures 14.12 and 14.13). Among 15- to 29-year-olds, Asians/Pacific Islanders had the lowest mortality (Figure 14.13). The mortality differential in African Americans/blacks, relative to other races/ethnicities, was greater than the corresponding difference in incidence.

Mortality for cancer of the ovary in persons younger than age 45 is shown in Figure 14.14. The pattern reflects the incidence-versus-age profile. Mortality according to race/ethnicity (Figure 14.15) was generally similar among adolescents and young adults and reflective of the incidence patterns. American Indians/Alaska Natives were an exception, in that 20- to 39-year-olds had a disproportionately higher death rate in comparison to incidence (Figure 14.7).

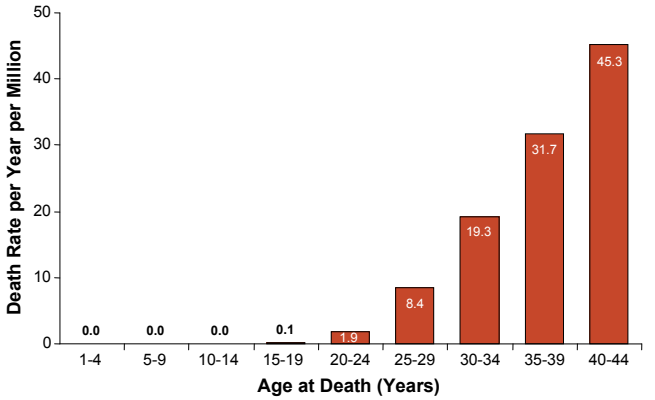

Figure 14.11: National Mortality for Cervical Carcinoma, U.S., 1975-2000

Survival

The 5-year survival rate of women diagnosed between 1975 and 2000 with cervical carcinoma was 91% in 15- to 19-year-olds, 89% in 20- to 24-year-olds, and 87% in 25- to 29-year-olds (Figure 14.16). The survival rate in older patients plummeted as a function of age.

The 5-year survival rate of women diagnosed between 1975 and 2000 with cancer of the ovary was between 83% and 87% for the 5-year age intervals between 15- and 29-years of age (Figure 14.17). In older patients, the survival rate declined dramatically as a function of age, and at a steeper slope than that of cervical carcinoma.

Trends in Survival

Figure 14.18 depicts the change in 5-year survival rates for carcinoma of the cervix as a function of era, from 1975 to 1998. According to these data, there was no improvement in survival over the last quarter century among 15- to 29-year-olds with cervical carcinoma. Figure 14.19 shows analogous data for ovarian cancer, and similarly indicates that there was no improvement in the 5-year survival rate among 15- to 29-year-olds with ovarian cancer, in contradistinction to the improvement in survival noted for women older than 30 years when diagnosed with ovarian cancer.

RISK FACTORS

The risk of developing ovarian carcinoma is influenced by genetic, hormonal, and environmental factors.

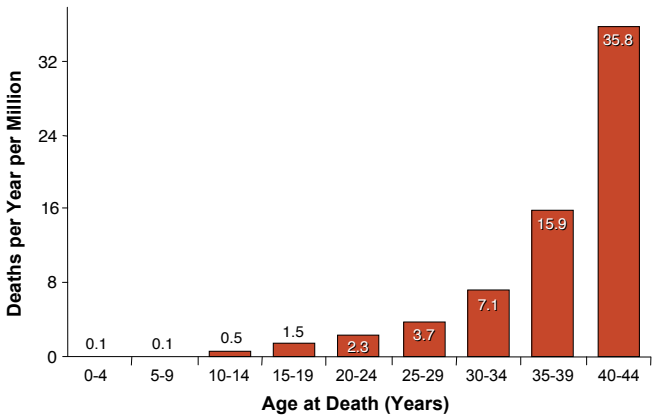

Figure 14.14: National Mortality for Ovarian Cancer, U.S., 1975-2000

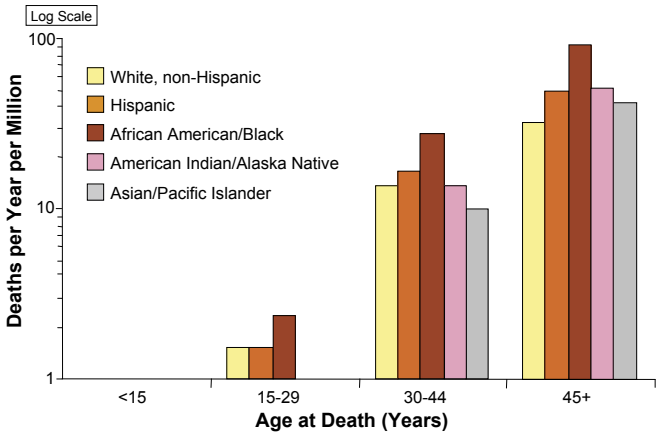

Figure 14.12: National Mortality for Cervical Carcinoma in Females, by Race/Ethnicity, SEER 1992-2002

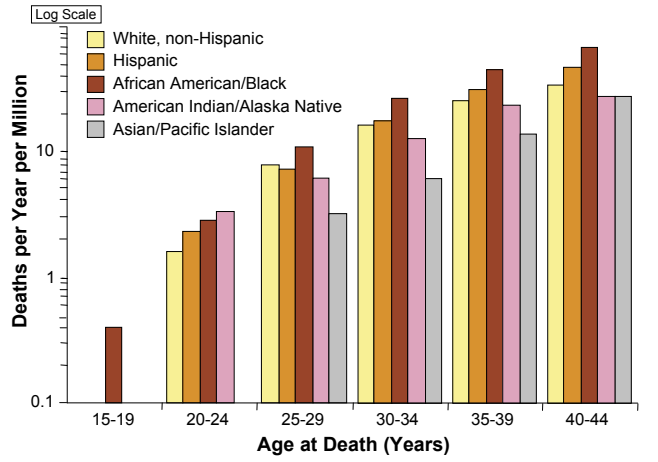

Figure 14.13: National Mortality for Cervical Carcinoma by Race/Ethnicity, U.S., 1975-2000

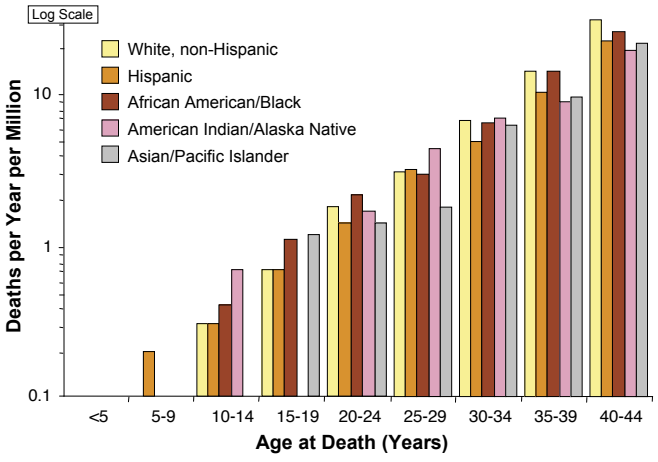

Figure 14.15: National Mortality for Ovarian Cancer by Race/Ethnicity, U.S., 1990-2000

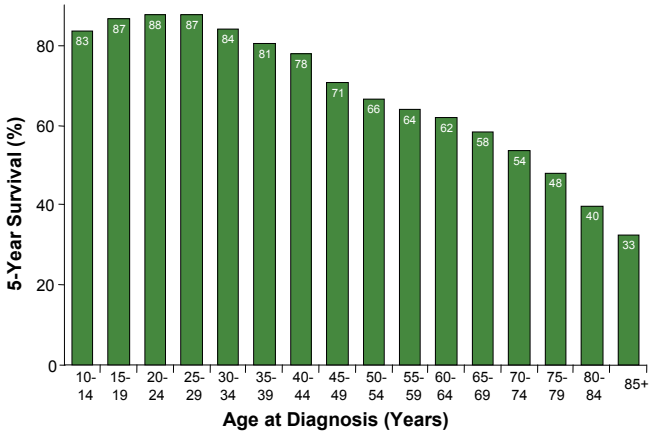

Figure 14.16: 5-Year Survival for Cervical Carcinoma, SEER 1975-2000

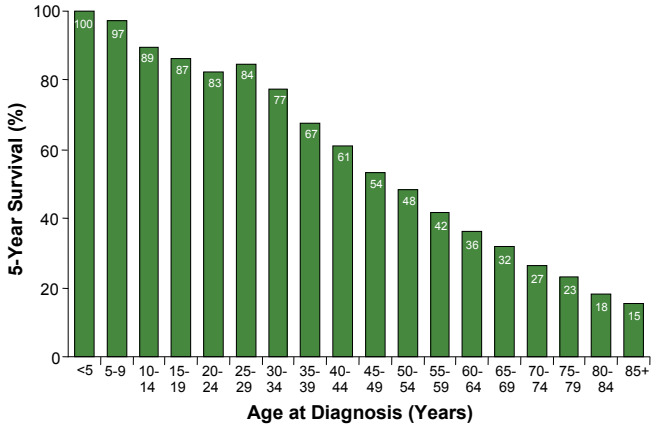

Figure 14.17: 5-Year Survival for Ovarian Cancer, SEER 1975-2000

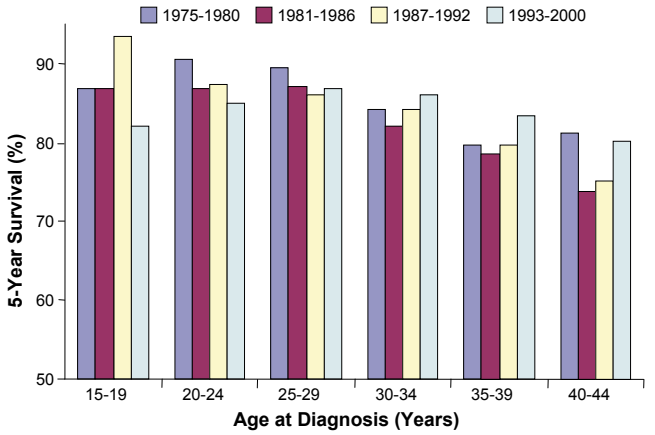

Figure 14.18: 5-Year Survival for Cervical Carcinoma by Era, SEER

Approximately 5-10% of women have a genetically acquired risk of ovarian cancer due to inherited mutations in the BRCA1 or BRCA2 tumor suppressor genes; there is an increased incidence of these mutations in the Ashkenazi Jewish population.[2,3] The overall risk of developing ovarian carcinoma for those with BRCA1 mutations is 20-60% and for those with BRCA2 mutations, 10-35%.[2] Several studies have reported that women with ovarian cancer and BRCA mutations may survive longer than women with sporadic ovarian cancer,[2,4,5] possibly due to an improved tumor response to platinum-based chemotherapy.[4]

Over the last 30 years, the highest incidence of ovarian carcinoma has occurred in Norway, Sweden and Israel.[6] Studies have linked this higher incidence with occupational/environmental exposures, increased body mass index and low physical activity, and BRCA mutations.[7-9]

Conditions that delay or suspend ovulation—such as oral contraceptive use, pregnancy, and lactation—reduce the risk of ovarian cancer.[2,10,11]

The most important risk factor for cervical cancer is human papilloma virus (HPV) infection; HPV DNA can be found in 95-100% of cervical cancers. HPV has multiple types, both oncogenic and non-oncogenic, and many cervical cancers reveal multiple HPV types.[12] HPV types 16, 18, 31, 33 and 45 are those most associated with invasive cervical cancers; these strains take longer to clear than other non-pathogenic strains.[13-15] Recent vaccines have been developed for types 16 and 18, which account for approximately 70% of HPV cases associated with cervical cancer.[16] Since peak infection occurs in the adolescent and young adult years, clinical trials are ongoing to determine the efficacy of these vaccines when initiated in adolescence. Other preventative methods such as screening programs for older women should also lower the risk of developing invasive cervical cancer.[17]

Co-risk factors for cervical carcinoma include sexual activity at an early age, multiple sexual partners, sexually transmitted disease, high parity, smoking, long-term oral contraceptive use, and low socioeconomic status.[14,15,18-25] Human immunodeficiency virus is felt to affect the disease progression of HPV and the incidence of cervical carcinoma.[12,25] When at-risk populations are adequately

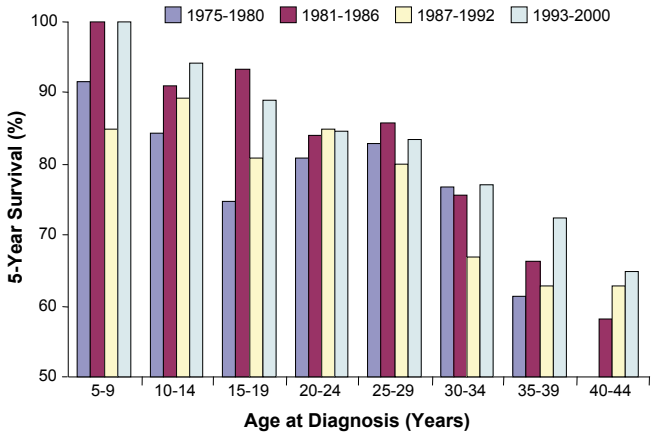

Figure 14.19: 5-Year Survival for Ovarian Cancer by Era, SEER

monitored with available and accepted screening programs, favorable changes in incidence have been noted.[12]

There is preliminary evidence that male circumcision may decrease the incidence of HPV infection as well as the incidence of cervical carcinoma in female partners.[21,22] Those with strict religious beliefs governing sexual behavior have a lower incidence of HPV infection and a lower incidence of cervical carcinoma.[12]

SUMMARY

Genital tract tumors account for nearly one-fourth of invasive cancers in adolescent and young adult females.[26] The ratio of male-to-female cancer also changes within this age group. Under age 30, testicular cancer in males exceeds the incidence of gynecological cancer in females. After age 50, the high incidence of prostate cancer increases the ratio of male-to-female genital tract tumors.

The predominant genital tract cancers in 15- to 29-year-old females are carcinomas of the cervix and carcinomas and germ cell tumors of the ovary. Within the classification of cervical carcinoma, the incidence of squamous cell carcinoma has decreased since 1975 in this age group, but especially in 25- to 29-year-olds, whereas the incidence of adenocarcinoma has increased.

Cervical carcinoma is one of the few cancers than can be successfully identified at a pre-invasive stage in the 15- to 29-year age group by the use of screening methods (Pap smears). Yet there is little evidence, in contradistinction to older patients, that survival from cervical carcinoma has improved in young adults during the past quarter century. The recent development of vaccines for two of the most common HPV types offers reason to hope that cervical cancer can be successfully prevented in the majority of women. In the near term, screening programs help identify cervical dysplasia so treatment can be initiated prior to the development of invasive disease. Such screening programs should be made accessible to all women, and at-risk groups should be educated about their use. With such programs and the eventual vaccination of adolescents, invasive cervical cancer may become a disease of the past.

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Chapter 15

Highlights and Challenges

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HIGHLIGHTS AND CHALLENGES

Summary

- Cancer patients diagnosed when 15 to 29 years of age are at the interface of pediatric and young adult oncology.
- In this age group, cancer is unique in the distribution of the types that occur; at no other age is the distribution similar.
- Cancer occurring at 15 to 29 years of age accounts for only 2 to 3 percent of all invasive cancer, but is nearly three times more frequent in incidence than cancer during the first 15 years of life.
- In the 15- to 29-year age group, males are at higher risk than females of developing cancer and have a lower likelihood of survival, with the risks directly proportional to age.
- Over a span of just 15 years, from age 15 to 29, the frequency distribution of cancer types changes substantively, such that the pattern at the youngest age does not resemble the one at the oldest.
- The vast majority of cases of cancer diagnosed before age 30 appear to be spontaneous and unrelated to either carcinogens in the environment or inherited factors. Exceptions are those melanomas due to ultraviolet light, cervical carcinoma caused by the human papillomavirus infection, Kaposi sarcoma and certain non-Hodgkin lymphoma related to the human immunodeficiency virus; and Hodgkin and Burkitt lymphomas associated with the Epstein-Barr virus.
- Hodgkin lymphoma, Ewing sarcoma, osteosarcoma, and testis cancer peak in incidence within this age range. Melanoma, female genital tract malignancies, thyroid cancer, soft-tissue sarcomas, non-Hodgkin lymphoma, leukemia, central nervous system tumors, breast cancer, and non-gonadal germ cell tumors account for 95% of the remaining cancers in this age group.
- Among the races/ethnicities evaluated, the incidence of cancer in this age group is highest among non-Hispanic whites and lowest in Asians, American Indians and Alaska Natives. Survival has been worse among African Americans/blacks, American Indians, and Alaska Natives than among the other races and ethnicities.
- The incidence of cancer in the 15- to 29-year age group increased steadily during the past quarter century. The rate of increase is now slowing, and at the older end of the age range the overall incidence appears to be returning to the incidence of the 1970s. Reasons for these changes remain speculative.
- At the beginning of the last quarter century, the diagnosis of cancer in 15- to 29-year-olds carried a more favorable prognosis, on the average, relative to cancer at other ages. Since then, there has been a lack of progress in survival improvement in adolescents and young adults relative to all other ages.
- Survival improvement trends portend a worse prognosis for young adults diagnosed with cancer today than 25 years ago, and the deficit is increasing with longer follow-up.
- The deficit in survival improvement is not limited to the United States; it appears to be a global problem.

Challenges

- Adolescent and young adult oncology patients belong to a distinct age group and, like pediatric, adult, and geriatric patients, have unique medical and psychosocial needs.
- Challenges in treating the 15- to 29-year age group include understanding the complex psychosocial environment of this age group, particularly during diagnosis and treatment, managing chronic and delayed adverse sequelae, overcoming a lack of progress in prolonging survival, improving the quality of survival, and addressing the economic costs associated with diagnosis, treatment and long-term follow-up.
- The single greatest current challenge in young adults and older adolescents with cancer is to overcome the lack of progress in their survival improvement, a deficit that has spanned nearly a quarter of a century.
- There are multiple reasons for the lack of progress. These may be categorized into personal/patient (older adolescents and young adults), family/community (family members, colleagues/friends, educators, employers, politicians, legislators, knowledge workers), health professional (physicians, nurses, allied health professionals), and societal/cultural (healthcare system) factors.

- The features common to the above factors are lack of awareness, inadequate health insurance coverage, lack of clinical trial participation, and a deficit in translational research of the cancers in older adolescents and young adults.
- Solutions to the survival deficit include raising awareness about the problem, improving healthcare access and insurance, enhancing understanding of the biology of cancers that occur in this age group, developing national and international organizations to address the deficits, and ultimately, creating a formal discipline of adolescent/young adult oncology.
- In particular, resources should be devoted to educating the public, health professionals, insurers, and legislators about cancer during this phase of life and about the special needs of these patients.
- Specific attention should be paid to longer delays in diagnosis that occur in older adolescents and young adults relative to younger patients. These are correlated with the quality of health insurance coverage.
- Also of special importance is the facility where diagnosis and treatment take place. For several of the pediatric type of malignancies (acute lymphoblastic leukemia, acute myelogenous leukemia, Ewing sarcoma, rhabdomyosarcoma), there is evidence that the therapeutic approach taken by pediatric oncologists has led to better survival rates than those applied by medical oncologists and hematologists.
- Meanwhile, older adolescents and young adults with cancer should be encouraged to report symptoms without delay, to seek care at a comprehensive health care center, to not "age out" of insurance, to understand that what is done at the time of diagnosis is most important, and to ask about and find clinical trials for their age.

INTRODUCTION

Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000 includes 15 chapters contributed and reviewed by more than 50 authors, editors and reviewers from a wide variety of disciplines across the spectrum of pediatric and adult oncology. In this chapter, the senior editors offer their perspectives on the monograph's highlights, elucidate challenges, and offer recommendations for the future. The opinions expressed by the editors are theirs alone, and do not officially represent the opinions of any of the chapter authors per se, nor of their organizations, including the U.S. government, the National Cancer Institute, or the National Institutes of Health.

CURRENT STATUS

Despite the well-known and characterized childhood cancer incidence peak, malignant disease diagnosed from 15 to 29 years of age is nearly three times more frequent in the U.S. and Canada than cancer during the first 15 years of life. It is nonetheless uncommon, relative to cancer at older ages, and accounts for just 2% of all invasive cancer. The vast majority of cases of cancer diagnosed before age 30 appear to be spontaneous and unrelated to either carcinogens in the environment or inherited factors. Exceptions are melanoma induced by ultraviolet light, cervical carcinoma ascribed to human papillomavirus, Kaposi sarcoma and non-Hodgkin lymphoma related to human immunodeficiency virus, and Hodgkin and Burkitt lymphomas associated with Epstein-Barr virus. These six cancers account for the vast majority of malignancies known to be environmentally-induced in this age group. In aggregate, they represent more than one-third of cases, with the remainder not known to be either caused by environmental agents or inherited (familial) factors.

In this age group, cancer is unique in the distribution of the types that occur—at no other age is the distribution similar. 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 non-gonadal germ cell tumors account for 95% of the cancers in 15- to 29-year-olds. Over a span of just 15 years—from age 15 through 29—the frequency distribution of cancer types changes dramatically, such that the pattern at the youngest age does not resemble that at the oldest. The incidence of cancer in the 15- to 29-year age group increased steadily during the past

quarter century. However, the rate of increase is slowing and at the older end of the age range the overall incidence appears to be returning to the rate of the 1970s. Compared to females, males in the 15- to 29-year age group are at higher risk of developing cancer and have a lower likelihood of survival, with the risks directly proportional to age. Among the races/ethnicities evaluated, the incidence of cancer in this age group is highest among non-Hispanic whites and lowest in Asians, Pacific Islanders, American Indians and Alaska Natives. Survival has been worse among African Americans/blacks, American Indians, and Alaska Natives than among the other races and ethnicities.

At the beginning of the last quarter century, the diagnosis of cancer in 15- to 29-year-olds carried a more favorable prognosis, on the average, compared to a cancer diagnosis at other ages. Since then, there has been a relative lack of progress in survival improvement among older adolescents and young adults. In the U.S., the 15- to 19-year age group showed some progress in the early 1980s, but progress has remained relatively static since 1986 (Figure 15.1, upper panel). In the 20- to 24-year age group, there has been no improvement since 1980 (Figure 15.1, middle panel). The 25- to 29-year age group actually had a decline in the overall survival rate in the mid- to late 1980s, likely due to HIV-related cancers, primarily Kaposi sarcoma and non-Hodgkin lymphoma (Figure 15.1; lower panel). In the latter age group, the decrease abated as HIV-induced cancers were prevented during the 1990s; there is evidence that a modicum of overall survival improvement has been achieved subsequently (Figure 15.1; lower panel).

Paramount among other challenges is improving the quality of survival of cancer patients in this age group. This includes enhancing the psychosocial environment during diagnosis and treatment, reducing and preventing acute, chronic and delayed adverse sequelae, and abrogating the financial costs associated with diagnosis, treatment and long-term follow-up.

REASONS FOR LACK OF PROGRESS

The relative lack of survival improvement for older adolescent and young adult cancer patients is a complex issue. In this section, probable explanations and contributing factors are specified and potential solutions are suggested. Contributing factors were derived from workshops and discussion groups hosted by the U.S. National Cancer Institute (NCI),[1] the Children's Oncology Group (COG), the International Society of Pediatric Oncology (SIOP),[2] and from preliminary studies in the U.S. Proposed explanations were categorized according to whether they applied to individuals (potential patients or patients diagnosed to have cancer), family/community members, the health care profession or society/culture in general.[3] In turn, each category was subdivided into factors that were likely (primary determinants) or unlikely (secondary determinants) to explain the survival deficit (Table 15.1).

Personal/Patient

The personal/patient category includes the individual adolescent and young adult before, during and after a cancer diagnosis. Importantly, it includes persons before they are diagnosed with cancer—because of the importance of early diagnosis in an age group for which prevention is largely ineffective. Factors within this category can be further subdivided into those that are biologic/physical, psychologic/emotional/spiritual, economic/financial, and social. Biologic factors include the unique physiologic and pharmacologic characteristics of adolescent and young adult patients and their cancers, many of which are unique to their age group.

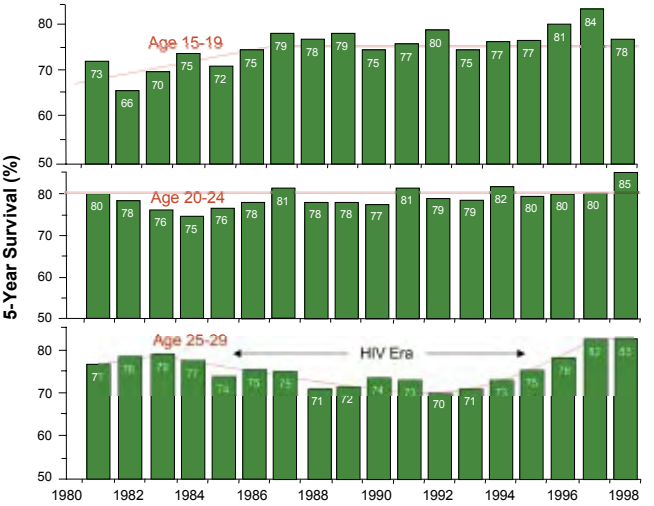

Figure 15.1: 5-Year Survival Rate for All Invasive Cancer Since 1980 by Age Group, U.S., SEER

A primary factor in the personal/patient category is the overarching goal for those in this age group to learn how to become independent and autonomous. To a large extent, making one's way in the world does not lend itself to concern about the risk of cancer. The individual is much more challenged by tasks of daily living and the immediate future. Another factor is the characteristic, age-specific feeling of immortality and invulnerability, which at no other time in life is more prominent. It is striking how few adolescents and young adults are aware that cancer can and does occur in their age group, or that the risk of developing cancer increases exponentially with age.

Adherence to treatment regimens is another major factor, both in terms of an intrinsic antagonism towards compliance (as a result of the need to become autonomous) and external pressures that mitigate adherence. The former has been well characterized in adolescents, not only with respect to expectations but also with regard to compliance with chemotherapy.[4-7] Once in college or in the workforce, many young adults face restrictions about taking time for medical concerns. Having to attend class, complete homework, or be on the job make it difficult to adhere to the rigors of diagnosis and treatment, especially when teachers, school administrators and employers are not aware of, or won't accommodate, their student's or employee's needs with respect to cancer management (see *Family/ Community* section below).

Also important is the frequent lack of, or utilization of, health insurance in adolescents and young adults. As described below, this is more problematic in this age

Table 15.1: *Factors Likely (Primary) or Unlikely (Secondary) to Explain the Survival Deficit*

GENERAL CATEGORY	PRIMARY FACTORS*	SECONDARY FACTORS
Personal/Patient (older adolescents and young adults)	Independence/Autonomy Feelings of Invincibility Under-utilization of Healthcare Services *Awareness* *Delays in Diagnosis* *Health Insurance* Adherence Financial Limitations *Participation in Clinical Trials* *Tumor Specimens* *Translational Research*	Embarrassment Psychosomatic Emphasis Transportation Limitations Psychosocial Environment during Diagnosis and Treatment Pharmacokinetic Differences
Family/Community (family members, colleagues/friends, educators, employers, politicians, legislators, knowledge workers)	*Awareness* Lack of Education Lack of Guidance Inadequate Community Resources	Constituency Influence
Health Professional (physicians, nurses, allied health professionals)	*Awareness* *Delays in Diagnosis* Healthcare Teams Education/Training Reimbursement *Health Insurance* *Participation in Clinical Trials* *Tumor Specimens* *Translational Research* Lack of Specialty/Discipline	Communication Skills Facilities Turf Conflicts Lack of Dedicated Researchers
Societal/Cultural (healthcare system)	*Awareness* (by Employers, School Personnel, Associates, Neighbors, Community) *Health Insurance* *Delays in Diagnosis*	Focus on Young and Middle Age Competing Challenges

*Items in italics appear in multiple categories

group than in any other. In the U.S., 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) on the one hand, and the coverage supplied by a full-time, secure job on the other. Nearly one-third of all 18- to 24-year-olds in the United States are uninsured, and more than 40% are either uninsured (Figure 15.2) or have Medicaid (state government) assistance (Figure 15.3).[8] More than twice as many 18- to 24-year-olds are uninsured or underinsured as 45- to 54-year-olds (Figures 15.2 and 15.3).

Young adults and older adolescents also have the lowest rate of primary care use of any age group in the United States.[9] 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 with knowledge of the patient's baseline heath status, the symptoms of cancer can be missed.

Cancer patients in the 15- to 29-year age group are at the interface between pediatric and adult oncology (Figure 15.4). They have cancers that peak in incidence within their age range (Figure 15.4) and a mix of tumor types (Figure 15.5) unique to their age. As a result, patients in the 15- to 29-year age group present a special challenge to those trained to care for younger and older persons (see *Health Professional* factors below).

Family/Community

The family/community category includes family members, colleagues/friends, educators, employers, politicians and knowledge workers, who in general also lack awareness of the cancer problem in the adolescent and young adult group. Despite often being the first source of information and guidance for a young person, they almost always lack education and guidance themselves. Patient navigator programs conducted by community volunteers and cancer survivors—for prostate, lung, breast or colorectal cancer, for example—have been formed in many communities because of this need. However, such programs, when they do exist, are rarely applicable to adolescents or young adults. Community resources that exist at the local level are generally devoted to younger and older patients.

Health Professional

Health professional factors include a lack of awareness about cancer in the adolescent and young adult, in part due to a lack of training and in part to the absence of continuing medical education programs on the topic. Oncology specialists and allied health professionals have less knowledge about treating this age group than children or adults with cancer. Approximately one half of the cancers in the 20- to 29-year age group constitute those ordinarily treated by adult oncologists (medical, radiation, gynecologic, surgical); the other half are more familiar to pediatric oncologists and their specialized pediatric diagnostic, therapeutic and supportive care teams (oncology nurses, radiologists, pathologists, infectious disease specialists, endocrinologists, nephrologists, psychologists,

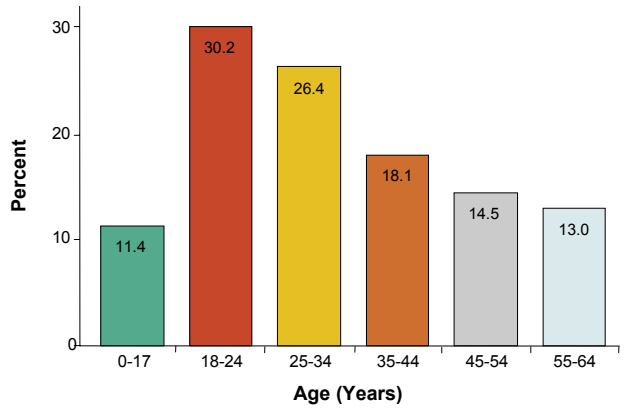

Figure 15.2: Percent without Health Insurance, Under 65 Years of Age, U.S., 2003

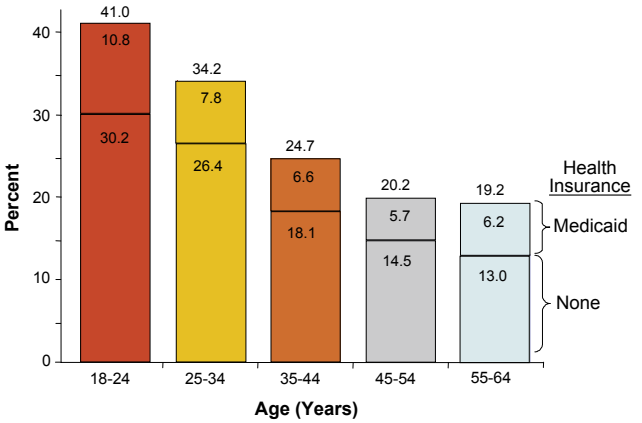

Figure 15.3: Percent without Health Insurance, 18 to 65 Years of Age, U.S., 2003

psychiatrists, and social workers) (Figure 15.5; lower pie diagram). The pediatric approach is favored for 15- to 19-year-olds, because two-thirds to three-fourths of the malignancies that occur in this age group are well known by the pediatric oncology team (Figure 15.5; upper pie diagram).

In contrast to the breadth of the pediatric oncology team, healthcare teams available to the young adult patient in an adult care program pale by comparison. It is rare that an adult patient has access to the services provided to a patient at a pediatric cancer center (Figure 15.6).

In general, specific communication skills are needed to relate to adolescents. Neither adult nor pediatric oncologists are trained with these skills, and difficult topics of conversation, such as sexuality and fertility, are often not addressed.

There is no other patient age group for which the time period to diagnosis is longer, clinical trial participation is lower,[10] and fewer tumor specimens are available for translational research (Figure 15.7). The lack of clinical trial participation is particularly problematic. Only one to two percent of all 20- to 29-year-olds with cancer can be identified as participating in a therapeutic clinical trial sometime during their cancer experience. A correlation exists between the level of clinical trial activity and improvement in survival prolongation and mortality reduction.[11-13] These factors explain much of the deficit in translational research and the lack of tumor specimens available for studies assessing molecular and cellular mechanisms of cancer in this age group. There is also a shortage of laboratory-based and clinical researchers dedicated to the study of cancers in the adolescent and young adult age group.

Patterns of care delivered to adolescents and young adults differ from those delivered to younger and older patients. Children are treated almost always in pediatric facilities where the specialists are familiar with their diseases, where they receive age-appropriate therapy, and where they are frequently enrolled in clinical trials.[14-16] By contrast, some adolescents receive care in adult facilities where certain diagnostic and treatment events take longer to accomplish than in

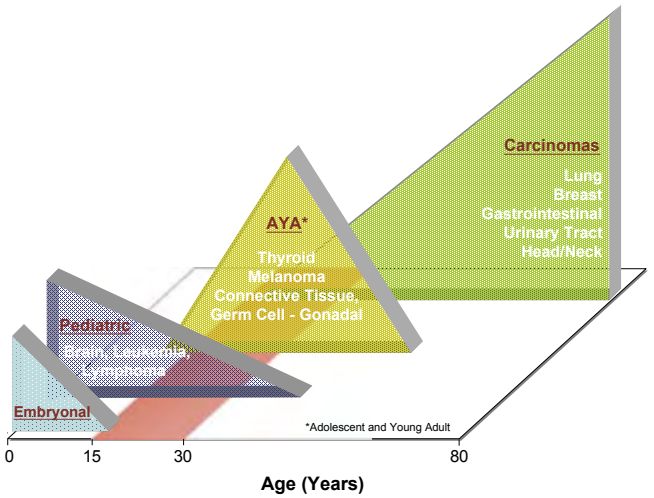

Figure 15.4: The Interface Between Pediatric and Adult Oncology

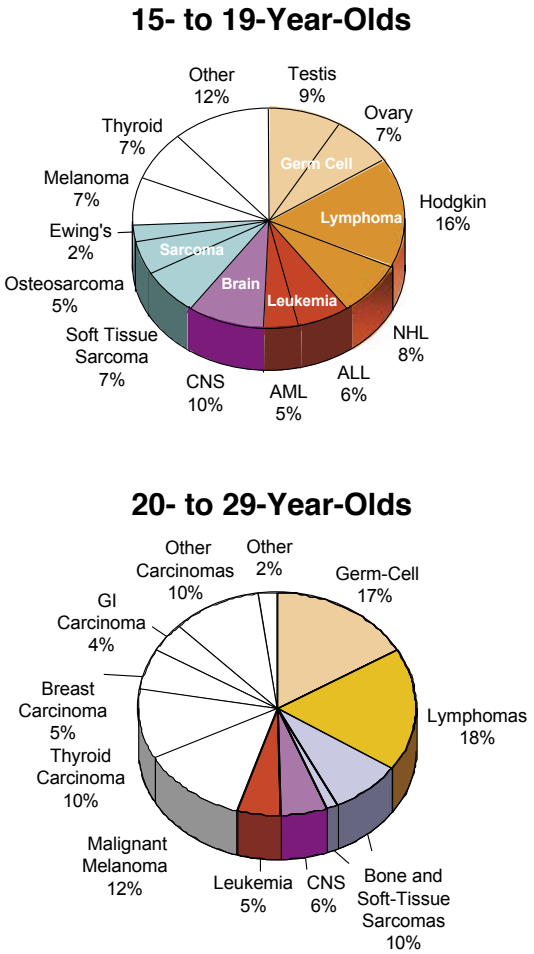

Figure 15.5: Cancers in 15- to 29-Year-Olds, U.S. SEER, 1975-2001

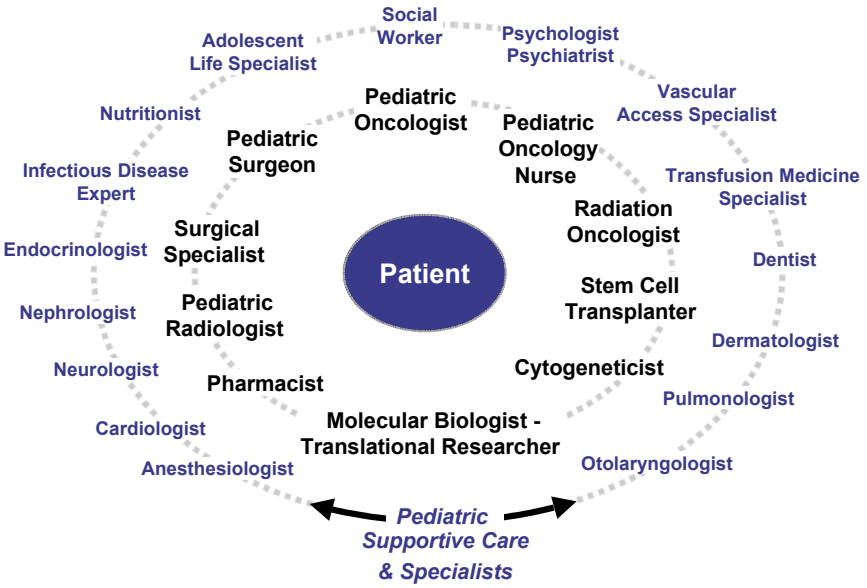

Figure 15.6: Pediatric Oncology Team

pediatric centers.[17] Also, adolescents are more likely to delay contact with the health care system, behavior likely related to their increasing autonomy.[18-20] Finally, types of cancer differ between children and adolescents, and the two groups have different tolerances for therapy.[21,22] These factors, taken together, contribute to delays in diagnosis and treatment for adolescents and young adults with cancer. When their care is managed less efficiently and effectively than that of other age groups, decreased survival is the likely outcome.

As alluded to above, few—if any—health care centers have dedicated units for adolescents and young adults. One of the most frequent complaints from patients in this age group is that they have little in common with other patients in the waiting room, outpatient clinic, or hospital environment.

Reimbursement is a factor for both pediatric and adult oncology treatment teams. The lower rate of health insurance coverage in young adults lowers the reimbursement rate of services rendered and tends to diminish incentives for providers and limit diagnostic evaluation, treatment interventions, and supportive care.

That patients in the adolescent and young adult age group are at the interface between pediatric and adult medicine may lead to uncoordinated care, to uncertainties about who is responsible for their management, and, in worse case scenarios, to conflicts of turf.

Societal/Cultural

The societal/cultural category consists of the challenges societies face in providing for the healthcare needs of older adolescents and young adults. The general public is largely unaware of cancer as a significant health care problem among young adults in the U.S. Even healthcare providers at universities and colleges do not have cancer in their curricula. High schools and universities do not have cancer awareness as an essential educational or health evaluation component. It is not surprising, therefore, that the time to diagnosis in older adolescent and young adult patients is not only delayed relative to the time to diagnosis in younger patients, but that it is also correlated with health insurance status, as discussed below.

PRIORITIZATION OF CHALLENGES AND POTENTIAL SOLUTIONS

Primary factors (Table 15.1) contributing to the deficit in survival for older adolescents and young adults should be prioritized over secondary factors, and those factors that appear in more than one category are likely to be more important targets for change. *Lack of awareness*, for example, appears in all of the four major categories.

Inadequate health insurance coverage appears in three categories, as does *low participation in clinical trials*. A *deficit in translational research* and *lack of tumor specimens for research* appear in two categories. These four factors—*awareness, health insurance, participation in clinical trials, and translational research*—may be regarded as paramount and are emphasized in the prioritization review below.

Personal/Patient

Awareness is a primary goal. Older adolescents and young adults not only believe they are immune to the risks of disease and accident, they do not realize the risk of cancer is one in 210 for those between 15 and 29 years of age in the U.S. Overcoming ideation of invincibility will require local and national educational efforts. The importance of healthcare availability and healthcare insurance coverage will also need more emphasis, while the availability and goals of clinical trials will require particular attention. Moreover, the approaches used to educate and recruit adolescent and young adult cancer patients to clinical trials and translational research efforts will likely need to be quite different from those utilized for older adults.

Family/Community

Those who associate with older adolescents or young adults should be aware that cancer occurs in this age group and be able to advise and encourage a medical evaluation for symptoms and signs of malignant disease. This applies to family members, friends, neighbors, classmates, teachers, fellow employees, employers, and clergy.

Health Professional

Health professionals must become more aware of cancer occurring during early adulthood, and professional training and continuing education should emphasize the risk of cancer and its common symptoms and signs. Health professionals should become advocates for affordable health insurance. Oncologists should become more cognizant of the gaps in clinical trial activity and translational research in the adolescent and young adult group. They should make available more clinical trials for the adolescent and young adult population and seek ways to increase clinical trial participation specific to this age group.

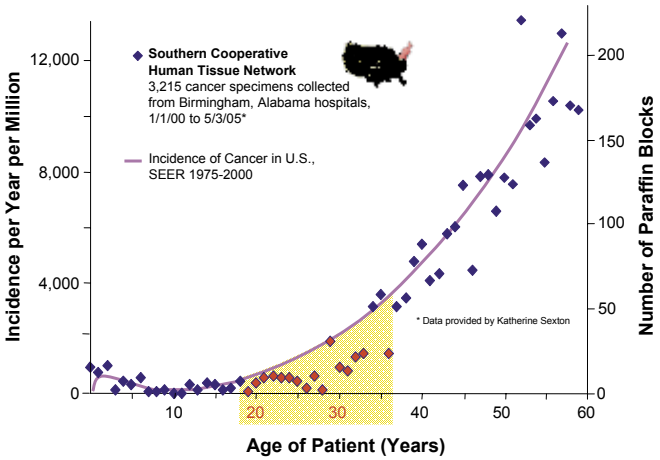

Figure 15.7: Number of Tumor Bank Specimens Compared with Incidence of Cancer by Age

Societal/Cultural

The lack of awareness of the adolescent and young adult cancer problem should be overcome with public information and education programs. Legislators, health policy administrators, insurance company directors, national medical organization leaders, and leaders of institutions of higher learning should be particularly informed and educated. The role of healthcare insurance should be emphasized, as should the risk of cancer in educational curricula. In the U.S., cancer organizations such as the American Society of Clinical Oncology, the American Cancer Society, the National Cancer Institute, the National Comprehensive Cancer Network, C-Change, and the national cancer cooperative groups should make adolescent and young adult oncology a priority. They should be joined in this effort by private cancer foundations that have a responsibility for young adults or older adolescents, such as Planet Cancer, Fertile Hope, Young Survival Coalition, and The Leukemia and Lymphoma Society (see *Appendix I*). Ideally, universal healthcare insurance should be available to all persons in the 18- to 29-year age range, until private insurance is provided by an employer or young people can afford or supplement it on their own.

In summary, *improving awareness of the cancer problem, providing better healthcare insurance coverage and access to healthcare services, and increasing clinical and translational research on cancer in older adolescents and young adults* are challenges that would benefit patients in

this age group. This is not to say that challenges such as psychosocial supportive care and dedicated healthcare facilities are not important. On the contrary, they are crucial. But tackling problems of highest priority is likely to have downstream effects that will alleviate many of the other problems listed in Table 15.1. The solutions will take a coordinated effort at local, regional, national and international levels. Four additional challenges are discussed in further detail below.

Time to Diagnosis is Longer in Adolescents and Young Adults than in Children

The interval from the onset of the first cancer-specific symptom to the first anti-cancer treatment, known as the *waiting time*, has been shown to be longer in adolescents than in children.[23-26] Young children (younger than 5 years of age) have been observed to have the shortest waiting times.[27] The waiting time may be influenced by factors related to the individual, to the health care system, and/or to the disease. Variation in waiting times among children has been shown to be due primarily to the type of disease, and secondarily to age. The time from onset of symptoms to initial health care contact is influenced by individual and health care system factors; the time from initial contact to assessment by treating oncologist or surgeon is most likely affected by health care system factors; and the time between that assessment and date of first anti-cancer treatment most likely reflects disease-related factors.[28-30]

The interval from onset of the first cancer-specific symptom to the day of cancer diagnosis is referred to as the *lagtime*. Studies in the United States, Canada, Scotland, and Mexico have demonstrated that lagtimes are longer in adolescents than in children.[31-35] In these studies it is unclear whether the longer lagtime experienced by adolescents—in comparison with younger children—are related to the types of cancers they develop or to other factors related to their age.[36]

In the U.S., health insurance coverage is a major determinant of lagtimes in patients 15 to 29 years of age.[37] The lagtimes in this age group are more closely correlated with health insurance status than race, ethnicity, gender, marital status, religion, urban versus rural home residence, or median household income of the zipcode of residence.[3,37] The issue of health insurance coverage is likely a greater factor in 18- to 29-year-olds than in any other age group, since this is the age in the U.S. at which health insurance coverage is the lowest. Countries with national health insurance are also likely affected by this determinant, since health insurance utilization is lower in the young adult age range than in younger or older persons despite the universal availability of health insurance.

Place of Diagnosis and Treatment: Pediatric versus Adult Care Specialists and Facilities

A central, complex issue is the choice of the most appropriate specialist who will manage care for the older adolescent and young adult cancer patient—a pediatric oncologist or an adult oncologist (medical, radiation, surgical or gynecologic oncologist). For older adolescents, the site of diagnosis and treatment may be problematic since, at least in theory, these patients could be treated at either a pediatric or adult care facility. Leonard and his colleagues in the United Kingdom have pointed out that 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." Simultaneously, they have emphasized that pediatric oncologists "have little to no experience in epithelial tumours or some of the other tumours common in late adolescence."[38] In 1997, the (admittedly biased) American Academy of Pediatrics issued a consensus statement 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.[39] 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."[40] However, neither of these statements defines an age cutoff in the recommendations.

Currently, the choice of specialist is made haphazardly and most often depends upon the decision of the referring physician. Younger children primarily obtain care

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.[41] And when the referral of a young adult or adolescent patient is made to an oncologist, it may be to a medical, radiation, surgical, gynecologic, or other oncologic specialist.

The switch from predominantly pediatric to adult medical management tends to occur not at age 21 or even at age 18, as might be expected, but closer to age 15. The majority of 15- to 19-year-olds diagnosed with cancer are treated at adult facilities. A cancer registry review in the state of Utah, which has only one pediatric oncology treatment facility, revealed that only 36% of oncology patients 15 to 19 years of age were ever seen at the pediatric hospital.[42] In Canada, only 30% of cancer patients in this age group are managed at pediatric centers.[17] A study of the National Cancer Data Base found that, for nearly 20,000 cases of cancer in adolescents aged 15 to 19 years, only 34% were treated at centers that had National Cancer Institute (NCI) pediatric cooperative group affiliation.[43]

In the end, the healthcare facility 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 next weigh into the decision. For some diseases, data support a particular site or specialist. In North America, a comparison of 16- to 21-year-olds with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) showed that the outcome was superior for patients treated on cooperative group trials than for those not entered.[44] In France, Holland and North America, older adolescents with ALL treated on pediatric clinical trials have fared considerably better than those treated on adult leukemia trials.[45-47] In Germany, older adolescents with Ewing sarcoma who were treated at pediatric cancer centers had a better outcome than those treated at other centers.[48] In Italy, young adults with rhabdomyosarcoma fared better if they were treated according to pediatric standards of therapy than when treated ad hoc or on an adult sarcoma regimen.[49] At the University of Texas M.D. Anderson Cancer Center, results of treatment for ALL in adults improved substantively after treatment derived from pediatric trials was introduced into the institution's trials.[50] The analysis of data from the U.S. National Cancer Data Base revealed that adolescents 15 to 19 years of age with non-Hodgkin lymphoma, leukemia, liver cancer, and bone tumors had a survival advantage if treated at an NCI pediatric group institution.[43] Thus, for these *pediatric* types of cancer, the pediatric specialist/facility is favored.

For other cancers, adult-treating medical/surgical/gynecologic/radiation oncologists are more appropriate providers. Adolescent and young adult patients with melanoma, colorectal carcinoma, breast cancer or epithelial neoplasm of the ovary may be better served under the care of physicians who are more familiar with these malignancies, such as medical oncologists or gynecologic oncologists. Until pediatric oncologists demonstrate that they have the expertise to treat these relatively non-pediatric cancers, this referral direction should be a first consideration.

The alternative is for adult care specialists/facilities to adopt a pediatric approach, which may be difficult for a variety of historical, socio-political, economic and infrastructure reasons. For example, two adult cooperative groups in the U.S. (Cancer and Acute Leukemia Group B, and Southwest Oncology Group) are starting a trial of a pediatric regimen taken directly from the Children's Oncology Group which will treat 15- to 29-year-old patients with ALL. A number of obstacles have been encountered in planning this approach, including differences in treatment philosophy (e.g. when to resume therapy after myelosuppression relative to the platelet and absolute phagocyte counts, and when to transfuse platelets and red cells), health insurance coverage, adherence of patients to treatment schedules and regimens, and the availability of supportive care and allied health professionals. Nonetheless, these obstacles are expected to be surmounted and the outcomes of young adult patients improved in the process.

Determining which specialist/facility is most appropriate certainly will vary from cancer to cancer and 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 18 years of age—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 individually determined. Pediatric oncologists may be less adept at a non-paternalistic 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 aggressive with chemotherapy dosing than the pediatric oncologist, whose younger patients can tolerate higher doses. The ultimate challenge would be to develop centers and oncologists devoted solely to the care of this group of patients. Such a dedicated program has been championed in the United Kingdom, at least for older adolescents. A number of unique "teenage cancer units" have been established, staffed by physicians and nurses with expertise in adolescent and young adult cancer patient management.[51] This provides the older adolescent with age-specific nursing care, recreation therapy, and peer companionship. Eventually, there could be a *discipline* of adolescent and young adult oncology with its own training programs, science, translational research, clinical trials and national and international organizations.

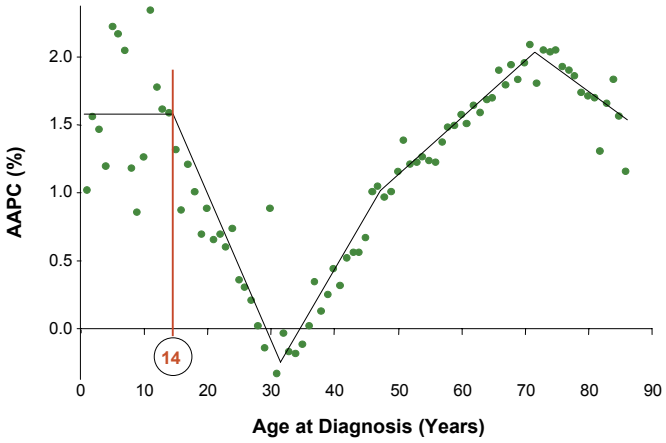

Figure 15.8: Average Annual Percent Change (AAPC) in 5-Year Relative Survival for All Invasive Cancer, U.S. SEER, 1975-1997

IMPLICATIONS FOR OTHER AGE GROUPS

When the average annual percent change in 5-year survival is expressed as a function of specific year of age at diagnosis, the age range affected by adverse trends can be identified more precisely. Such an analysis suggests that the decline in lack of progress versus age over the past quarter century in the United States is linear over the 15- to 29-year age span, with inflections at age 14 and 31 (Figure 15.8). This suggests that the factors that account for the lack of improvement for the adolescent and young adult group relative to children start at age 15, and are increasingly more problematic up to age 30. Between 31 and 47 years of age, the trend is reversed with an analogous, nearly mirror-image linear improvement (Figure 15.8). This observation indicates that the next oldest 15-year age span (30- to 44-years) should be evaluated in a fashion similar to that undertaken for older adolescents and young adults. This analysis also suggests that the greatest progress in prolonging survival from cancer during the past quarter century in the United States has been in the 60- to 80-year age group, with a peak improvement at age 70 (Figure 15.8).

GLOBAL CHALLENGE

The SEER data in this monograph are from the United States, and most of the conclusions herein are derived from these SEER data. Nonetheless, most if not all of the observations are applicable to other countries. Certainly, there is a worldwide lack of awareness about cancer in young adults and older adolescents relative to the recognition of cancer in children and older adults. And it is safe to claim that the deficits in clinical trial participation as well as translational research in early adulthood are universal.

The national survival data for Australia show patterns of outcome similar to those observed in the United States (Figure 15.9; Australian data kindly provided by Stevenson C, Australian Institute of Health and Welfare). During the years 1982 to 1997, 15- to 29-year-old Australians with cancer had the least progress in survival improvement, in comparison with other 15-year groups at younger or older ages. This is consistent with—albeit not as dramatic as—the age pattern in the United States (Figure 15.9). That Australians enjoy universal health insurance—as do most inhabitants of socio-economically

advantaged countries of the world—suggests that lack of national health insurance in the United States does not alone explain the deficit in America. On the other hand, universal health insurance in Australia does not guarantee access to or use of health care services, and is clearly not universally utilized in the young adult age group. Indeed, longer times to a diagnosis of cancer occur in this age group in countries with and without national health insurance, as described above. Most likely, lack of health insurance and of utilization of health care services are global problems in young adults and older adolescents.

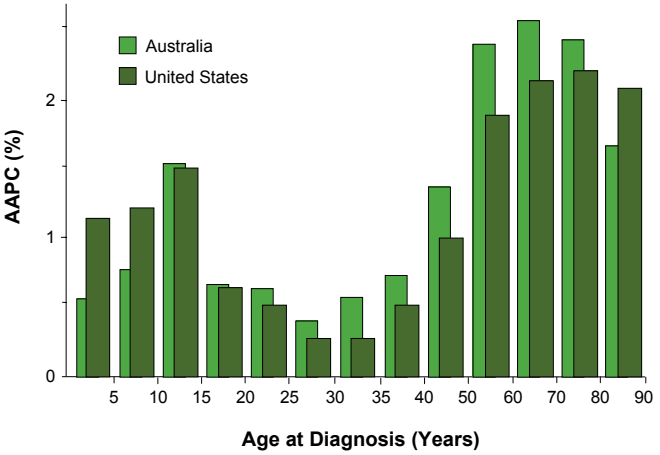

Figure 15.9: Average Annual Percent Change (AAPC) in 5-Year Relative Survival Rate for All Invasive Cancer, by Age, 1982 to 1997

FUTURE DIRECTIONS AND INTERIM SOLUTIONS

In North America and Australia, the Children's Oncology Group (COG) has taken a leadership role in meeting the challenges described in this chapter. 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 specifically designed for patients in this age group. The COG Adolescent and Young Adult Committee was formed in 2000 to research the obstacles faced by older adolescents and young adult patients, with the disease focus on sarcomas. The Southwest Oncology Group (for adult patients) subsequently opened the COG trial for metastatic Ewing sarcoma, and thereafter hosted the development of an intergroup sarcoma committee—the Intergroup Consortium Against Sarcoma (ICAS)—with formal representation from all the adult cooperative groups as well as the National Cancer Institute of Canada.

Evidence for improvement in the accruals to NCI-sponsored national sarcoma treatment trials is shown in Table 15.2. The proportion of American sarcoma patients younger than age 40 entered onto the trials has nearly doubled—from 5.1% to 9.8%—during the past five years.

Table 15.2: *Accruals to National Cancer Treatment Trials during the Era of National Collaboration to Augment Sarcoma Clinical Trial Development and Participation**

	AGE	1998-9	2000-1	2002-3
All Cancer	All Ages	48,225	57,033	54,717
	<20	9,094	7,791	6,070
	20-39	3,488	3,752	3,411
	40-59	17,403	22,025	22,556
Sarcomas	<40	637	888	929
% of all Entries		5.1%	7.7%	9.8%
Other Cancers	<40	11,945	10,655	8,552

*Clinical trial accrual data from the Cancer Therapy Evaluation Program, National Cancer Institute, courtesy of Michael Montello and Troy Budd

In contrast, and as a control for this observation, the other cancers that occur in this age group (and that have not yet been addressed) showed a decline in patient accrual.

Another initiative in the United States is the formation of a consortium of all the organizations devoted to assisting adolescents and young adults with cancer. Known as the LIVE**STRONG**™ Young Adult Alliance, this organization is dedicated to improving survival rates and the quality of life of young adults living with cancer by promoting relevant research and the delivery of patient care, generating awareness of the issue, being a voice for young adults with cancer, and advancing helpful community-based programs and services (see *Appendix I*). The Alliance will bring together for the first time key voices in the cancer community to improve results for young adults.

In parallel, the U.S. National Cancer Institute has initiated a Progress Review Group (PRG) to evaluate the national status of young adult cancer outcomes and needs. This PRG will assess the deficits and scientific issues described in this chapter and address others identified by a panel of experts in a year-long process. Specific recommendations for national implementation are expected to be presented in late 2006.

Meanwhile, several practical suggestions should facilitate early detection of cancer in adolescents and young adults and promote referral to a cancer center where clinical trials are a priority (Table 15.3).

CONCLUSIONS

The medical literature on cancer during the first 15 years of life—in infants, children, and young adolescents—is vast and burgeoning. This monograph essentially represents the first treatise on cancer during the subsequent 15 years of life. The contrast in available information for each group symbolizes the difficulties that older adolescents and young adults face when they are diagnosed with cancer. With national and international focus on younger and older patients during the past half-century, young adults and older adolescents are orphans, lacking the overall progress made in cancer prevention, diagnosis and treatment. Solutions include raising awareness of the problem, improving healthcare access and insurance, enhancing understanding of the biology of the cancers that occur in the age group, and developing national and international organizations to address the deficits. Ultimately, a formal discipline of adolescent/young adult oncology, dedicated to scientific investigation and replete with training programs, should be developed to address the interface between pediatric and adult oncology. Meanwhile, older adolescents and young adults with cancer should be encouraged to address symptoms, to seek care at a comprehensive healthcare center, to maintain health insurance, to understand that optimal cancer management starts at diagnosis, and to ask about and find clinical trials suitable for them.

Surviving adolescence and young adulthood is difficult enough when all is well and health is robust. Cancer

Table 15.3: *Practical Suggestions to Enhance Early Detection of Cancer and Clinical Trial Participation in Older Adolescents and Young Adults*

- Appreciate that cancer occurs in one in every 200 older adolescents and young adults and that everyone is at risk.
- Be aware that young adults often deny symptoms, are too embarrassed to report them, or attribute them to psychosomatic manifestations.
- Encourage and assist young adults to seek care at a comprehensive healthcare center.
- Realize that young adults are least likely to have adequate health insurance, and that they should not allow themselves to "age out" of insurance.
- Know that there are very few known causes of cancer during early adulthood, and that "it just happens," regardless of the health of the person.
- Convey that what is done at the time of the cancer diagnosis is important and that the best outcome is determined by the initial evaluation and therapy. Optimal cancer management means doing it right from the start!
- Once diagnosed with cancer, suggest that young adults ask about clinical trials. If none are available on site, help them find centers that participate in clinical trials suitable for their age.
- Once enrolled on a clinical trial, the adolescent and young adult cancer patient needs understanding and support in order to best adhere to the trial's requisites.

makes this phase of life extraordinarily more challenging and demanding. Medical professionals should pay special attention to the unique transitions faced by these patients—at diagnosis, through the process of informed consent, at initiation of therapy, during school and employment re-entrance, at completion of therapy, during post-treatment follow-up, and when switching from pediatric to adult care. Ideally, specialized adolescent and young adult cancer units should be developed with the anticipation that centralization of care and availability of age-targeted clinical trials will lead to improved treatment, survival, and quality of life.

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 survival outcomes for this group have lagged behind those of others and identify the efforts–including better clinical trial accrual—that might remedy the disparity. Lastly, more scholarly and focused attention on the unique psychosocial needs of this population will improve the quality of their cancer care and of their survival. At the very least, those at the interface deserve the same attention and progress that has been achieved in younger and older persons.

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NATIONAL CANCER INSTITUTE

www.cancer.gov/

The National Cancer Institute (NCI) is a component of the National Institutes of Health (NIH), one of eight agencies that compose the Public Health Service (PHS) in the Department of Health and Human Services (DHHS). The NCI is the Federal Government's principal agency for cancer research and training and coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients.

The NCI's Web site provides accurate, up-to-date information on many types of cancer, information on clinical trials, resources for people dealing with cancer, and information for researchers and health professionals. Many of the NCI's cancer information resources are accessible through the cancer information page on www.cancer.gov/. NCI's Web site has many resources available in Spanish

For a quick overview of cancer resources and links to additional NCI sites, go to: cis.nci.nih.gov/resources/resources.html

RESOURCES AVAILABLE ON THE NCI WEB SITE:

PDQ® (Physician Data Query)
www.cancer.gov/cancer_information/doc.aspx?viewid=9D617786-179B-4DB7-8664-885DD33E7D51
NCI's comprehensive cancer database includes summaries on cancer treatment, screening, prevention, genetics, and supportive care, and information on ongoing clinical trials. Some PDQ information is available in Spanish.

NCI Cancer Facts cis.nci.nih.gov/fact/index.htm
A collection of fact sheets that address a variety of cancer topics. Fact sheets are frequently updated and revised in accordance with the latest cancer research.

What You Need to Know About™. . .
www.cancer.gov/cancer_information/doc.aspx?viewid=920AFA90-5547-4739-8D2D-89968F77A87D
A publication series that provides information on many types of cancer. Each publication includes information about symptoms, diagnosis, treatment, emotional issues, and questions to ask your doctor.

Publications Locator and Catalog https://cissecure.nci.nih.gov/ncipubs/
National Cancer Institute publications and materials may be ordered or viewed online at this Web site. Also, a catalog and order form may be viewed or downloaded.

OTHER NCI RESOURCES:

International Resources cis.nci.nih.gov/resources/international.htm
A list of cancer resources that may be particularly helpful to information seekers living outside the United States.

National Institutes of Health Resources cis.nci.nih.gov/resources/nci.htm
A compendium of cancer-related information available from other NIH institutes, offices, and online resources.

Additional Resources cis.nci.nih.gov/resources/additional_resources.htm
Information about general cancer, clinical trials, cancer drugs, smoking cessation, and additional government resources.

Cancer Information Service (CIS) cis.nci.nih.gov/
(1-800-4-CANCER (1-800-422-6237)
The National Cancer Institute's Cancer Information Service (CIS) provides the latest and most accurate cancer information to patients, their families, the public, and health professionals. The CIS is a free public service of the National Cancer Institute, and serves those in the United States, Puerto Rico, the U.S. Virgin Islands, and the Pacific Islands.

The CIS provides personalized, confidential responses to specific questions about cancer.

- By telephone: U.S. residents may call the CIS toll free at 1–800–4–CANCER (1–800–422–6237). CIS information specialists answer calls Monday through Friday from 9:00 a.m. to 4:30 p.m. (caller's local time), in English or Spanish. Callers with TTY equipment may call 1–800–332–8615. Callers also have the option of listening to recorded information about cancer 24 hours a day, 7 days a week.
- Online: CIS information specialists also offer online assistance in English Monday through Friday from 9:00 a.m. to 11:00 p.m. Eastern Time through the LiveHelp link at www.cancer.gov on the Internet.

The CIS provides assistance to smokers who want to quit.

- By telephone: U.S residents may call NCI's Smoking Quitline toll free at 1–877–44U–QUIT between 9:00 a.m. and 4:30 p.m. (caller's local time).
- Online: Information specialists also offer online assistance to smokers in English Monday through Friday from 9:00 a.m. to 11:00 p.m. Eastern Time through the LiveHelp link at www.cancer.gov on the Internet.

NCI publications on adolescent and young adult cancer:

- Childhood Cancers Homepage www.cancer.gov/cancerinformation/cancertype/childhood/
  A collection of information sheets about types of childhood cancer, cancer screening and detection, treatment, clinical trials, and cancer literature.

- NCI Research on Childhood Cancers cis.nci.nih.gov/fact/6_40.htm
  General facts about childhood cancer and research endeavors.

- Young People with Cancer: A Handbook for Parents www.cancer.gov/cancertopics/youngpeople
  An overview of childhood cancer diagnosis, treatment, topics of concern and additional information for parents.

- Care for Children and Adolescents With Cancer: Questions and Answers cis.nci.nih.gov/fact/1_21.htm
  A fact sheet detailing questions and answers about childhood cancer, childhood cancer centers, and research about treatment for childhood cancers.

ADDITIONAL RESOURCES

Information about Clinical Trials clinicaltrials.gov/
ClinicalTrials.gov provides regularly updated information about federally and privately supported clinical research in human volunteers. This site includes information about a trial's purpose, who may participate, locations, and phone numbers for more details.

MEDLINEplus www.nlm.nih.gov/medlineplus/

The National Library of Medicine's MEDLINEplus Web site includes links to health topics, drug information, a medical encyclopedia, a medical dictionary, health news, directories of doctors, dentists, and hospitals, and other resources and health organizations, including MEDLINE/PubMed. MEDLINE/PubMed is the National Library of Medicine's database of references to more than 14 million articles published in 4,800 biomedical journals.

NCI's Office of Liaison Activities la.cancer.gov/index.html

NCI's Liaison Activities support the Institute's research and related programs by fostering strong communications and relationships with the cancer advocacy community, professional societies, scientific organizations, and Federal agencies.

- CARRA: Consumer Advocates in Research and Related Activities la.cancer.gov/carra/

  In order to encourage people affected by cancer to provide their viewpoints and ideas directly to NCI staff, NCI created the CARRA program. Members of the CARRA Program play a critical role in communicating these cancer advocacy viewpoints to NCI staff, so that the NCI can incorporate this perspective into NCI programs and activities.

- DCLG: Director's Consumer Liaison Group deainfo.nci.nih.gov/advisory/dclg/dclg.htm

  The Office of Liaison Activities supports and coordinates the NCI Director's Consumer Liaison Group (DCLG), NCI's all-consumer advisory committee. The DCLG advises and makes recommendations to the Director of NCI from the consumer advocate perspective on a wide variety of issues, programs, and research priorities. The DCLG, in working with NCI, has become a model for increasing consumer involvement in NCI.

- NCI Listens and Learns ncilistens.cancer.gov/

  The National Cancer Institute (NCI) and the NCI's Director's Consumer Liaison Group (DCLG) have developed a Web site to enhance collaboration and communication between NCI and the cancer advocacy community. NCI Listens and Learns is an online forum designed to facilitate dialogue between NCI and two segments of the community: cancer advocacy organizations and members of the general public. The Web site will address a variety of issues related to NCI's strategic plans and initiatives.

Office of Education and Special Initiatives (OESI) www.cancer.gov/aboutnci/oesi

The OESI develops, implements, and evaluates education programs across the cancer continuum. OESI also manages NCI initiatives and programs that focus upon NCI special priorities in cancer research and treatment in addition to cancer education models that best target these areas.

President's Cancer Panel pcp.cancer.gov

The President's Cancer Panel, established by the National Cancer Act of 1971 (P.L. 92-218), is charged with identifying barriers to the optimal development and implementation of all aspects of the National Cancer Program. The Panel raises questions and explores issues chiefly, though not solely, by soliciting testimony from leaders in cancer-related medicine, academic research, industry, the advocacy community, and the public. At least annually, the Panel reports to the President its recommendations for removing identified barriers and addressing identified needs.

Living Beyond Cancer: Finding a New Balance deainfo.nci.nih.gov/ADVISORY/pcp/pcp03-04rpt/Survivorship.pdf

This report of the President's Cancer Panel, a Presidential advisory committee charged with overseeing the development and execution of the National Cancer Program, is the first to take a life span approach to describing cancer survivorship issues, focusing particularly on the post-treatment period. In addition to identifying issues common to people regardless of their age at diagnosis, it enumerates challenges specific to those diagnosed as children (ages 0-14 years), adolescents and young adults (ages 15-29 years), adults (30-59 years of age), and older adults (ages 60 and older). The findings and 17 recommendations

are drawn from testimony received at five meetings conducted between May 2003 and January 2004, as well as additional data gathering. The nearly 200 meeting participants included survivors, caregivers, health care providers, advocates, and others who candidly described their experiences of life after cancer and the issues of providing care and support. Testimony was provided both in formal hearings and at evening Town Hall meetings.

SEER: Surveillance, Epidemiology, and End Results — seer.cancer.gov/

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. The SEER Program currently collects and publishes cancer incidence and survival data from 14 population-based cancer registries and three supplemental registries covering approximately 26 percent of the US population. Information on more than 3 million in situ and invasive cancer cases is included in the SEER database, and approximately 170,000 new cases are added each year within the SEER coverage areas. The SEER Registries routinely collect data on patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. The SEER Program is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and survival rates within each stage. The mortality data reported by SEER are provided by the National Center for Health Statistics.

The Cancer Statistics Branch (CSB) manages the Surveillance, Epidemiology, and End Results (SEER) program, and conducts research and developmental activities related to the surveillance of cancer patterns in the United States and monitoring progress against cancer. This monograph and other SEER publications/monographs can be viewed at seer.cancer.gov/ under Publications.

The SEER Cancer Statistics Review (CSR), a report of the most recent cancer incidence, mortality, survival, prevalence, and lifetime risk statistics, is published annually by the Cancer Statistics Branch of the NCI.

CANQUES Cancer Query Systems — seer.cancer.gov/canques/

The Cancer Query Systems (CANQUES) are data retrieval applications that provide access to cancer statistics stored in online databases. These systems do not perform calculations;, they display reports using databases of statistics generated by other software. Many of these statistics are provided in the SEER Cancer Statistics Review or other SEER Statistical Publications.

Statistical Research and Applications Branch (SRAB): — srab.cancer.gov/

SRAB conducts and supports statistical research, modeling, and collaboration related to the cancer surveillance and cancer control missions of the NCI.

Research within SRAB is targeted at improving and developing statistical methods and models for use in the analysis and presentation of population-based cancer statistics, as well as in the broader areas of cancer surveillance and cancer control research.

Areas of Research include:

- Cancer Control Practices and their Effect on the Cancer Burden
- Cancer Progress Measures
- Solutions for Quantitative Problems in Cancer Surveillance and Control
- Geographic Information Systems, Spatial Analysis, and Data Visualization
- Program Evaluation, Meta-Analysis and Outcomes Research
- Survey Methodology, Design & Analysis
- Population Risk Assessment Methodology
- General Statistical Methodology

Office of Cancer Survivorship — cancercontrol.cancer.gov/ocs/

The mission of NCI's Office of Cancer Survivorship (OCS) is to enhance the quality and length of survival of all persons diagnosed with cancer and to minimize or stabilize adverse effects experienced during cancer survivorship. The Office of Cancer

Survivorship conducts and supports research that both examines and addresses the long- and short-term physical, psychological, social, and economic effects of cancer and its treatment among pediatric and adult survivors of cancer and their families.

The Office of Cancer Survivorship

- Develops an agenda for the continuous acquisition of knowledge concerning the problems and challenges facing cancer survivors and their families.
- Supports studies to increase the length of survival for cancer patients and improve the quality of survival of all individuals diagnosed with cancer and their families, including those that involve prevention of subsequent disease and disability.
- Promotes the dissemination of information to professionals who treat cancer patients and to the public concerning the problems and needs of cancer survivors and their families.

Applied Research (ARP) appliedresearch.cancer.gov/

ARP's mission is to evaluate patterns and trends in cancer-associated health behaviors, practices, genetic susceptibilities, health services, and outcomes. ARP monitors and evaluates these factors among the general population and among specific populations in the United States, and determines their influence on patterns and trends in cancer incidence, morbidity, mortality, survival, cost, and health-related quality of life.

ARP Areas of Research

- Monitoring risk and health behaviors
- Improving methods for assessing cancer-relevant exposures
- Monitoring cancer screening behaviors in populations
- Examining the dissemination of cancer treatment in populations
- Advancing methods and systems for measuring and monitoring quality of cancer care
- Estimating cost and benefit of cancer interventions at the population level
- Describing and understanding cancer-related health disparities
- Improving methods for questionnaire design and testing

THE FOLLOWING NON-NCI/NIH WEB SITES MAY PROVIDE HELPFUL INFORMATION, BUT THE CONTENTS HAVE NOT BEEN REVIEWED AND ARE NOT UPDATED BY NCI STAFF.

Disclaimer: This list is a sample of information related to cancer only and in no way represents a comprehensive source of information on any topic. NCI does not endorse any of the organizations and holds no liability or responsibility as to their content, importance, accuracy, quality, relevance, completeness, availability or veracity. Further, NCI neither advocates reliance on nor endorses anything contained within the materials. Medical advice requires a medical examination and you should consult a doctor with your concerns.

American Cancer Society (ACS) www.cancer.org

The ACS is a nationwide, community-based, voluntary health organization. Headquartered in Atlanta, Georgia, the ACS has state divisions and more than 3,400 local offices. The ACS provides information about cancer, cancer treatment, support groups and services, and special health needs of patients and survivors. Also available from the ACS are many resources and publications, including information about cancer, cancer prevention, risks, early detection, symptoms, and statistics by year and state.

American Society of Clinical Oncology (ASCO) www.asco.org

ASCO is the world's leading professional organization representing physicians who treat people with cancer. ASCO's members set the standard for patient care worldwide and lead the way in carrying out clinical research aimed at improving the prevention, diagnosis, and treatment of cancer.

Cancer Hope www.cancerhopenetwork.org

Cancer Hope Network is a not-for-profit organization that provides free and confidential one-on-one support to cancer patients and their families. Cancer patients and/or family members are matched with trained volunteers who have themselves undergone and recovered from a similar cancer experience.

Cancer in Adolescents and Young Adults www.springerlink.com

This book will provide information about the types of cancer affecting adolescents and young adults, presenting symptoms and signs, diagnosis, treatment choices, outcome statistics, and how these differ from younger and older persons affected by cancer. To be published in 2006 by Springer Verlag Publishing; Heidelberg, Germany.

C-Change www.ndoc.org/default.asp

C-Change is an organization comprised of the nation's key cancer leaders from government, business, and nonprofit sectors. These leaders share the vision of a future where cancer is prevented, detected early, and cured, or managed successfully as a chronic illness. The mission of C-Change is to leverage the combined expertise and resources of its members to eliminate cancer as a (major) public health problem at the earliest possible time.

CureSearch curesearch.org/

Representing the combined efforts of the Children's Oncology Group (COG) and the National Childhood Cancer Foundation (NCCF), CureSearch was established with one goal: to find a cure for childhood cancer. The CureSearch Web site offers information, research, and resources to health professionals and parents of children and adolescents with cancer.

Fertile Hope www.fertilehope.org/

Fertile Hope is a national nonprofit organization dedicated to providing reproductive information, support, and hope to cancer patients whose medical treatments present the risk of infertility.

Leukemia & Lymphoma Society www.leukemia.org/

The Leukemia & Lymphoma Society is the world's largest voluntary health organization dedicated to funding blood cancer research, education, and patient services. The Society's mission: Cure leukemia, lymphoma, Hodgkin's disease, and myeloma, and improve the quality of life of patients and their families.

LIVESTRONG™ Young Adult Alliance www.livestrong.org/youngadult

The mission of the LIVESTRONG™ Young Adult Alliance is to improve survival rates and quality of life for young adults living with cancer by promoting relevant research and the delivery of patient care, generating awareness of the issue, being a voice for young adults with cancer, and advancing helpful community-based programs and services.

National Comprehensive Cancer Network www.nccn.org

The National Comprehensive Cancer Network (NCCN), an alliance of 19 of the world's leading cancer centers, is an authoritative source of information to help patients and health professionals make informed decisions about cancer care. Through the collective expertise of its member institutions, the NCCN develops, updates, and disseminates a complete library of clinical practice guidelines. These guidelines are the standard for clinical policy in oncology. NCCN is a not-for-profit, tax-exempt corporation.

People Living With Cancer www.peoplelivingwithcancer.org

People Living With Cancer, the patient information website of the American Society of Clinical Oncology (ASCO), is designed to help patients and families make informed health-care decisions. The site provides information on more than 85 types of cancer, clinical trials, coping, side effects, a "Find an Oncologist" database, message boards, patient support organizations, and more.

Planet Cancer www.planetcancer.org/

Planet Cancer is a non-profit organization that supports young adults with cancer. Planet Cancer's dynamic online community uses humor, current news, and interactive forums to help young adults create a network of peer support, as they communicate with other survivors worldwide about issues they face and how to cope with the disease. Planet Cancer also hosts several face-to-face retreats throughout the year, forming strong friendship bonds among young adult cancer patients and survivors.

The Pediatric Brain Tumor Foundation (PBTF) www.pbtfus.org:

The Pediatric Brain Tumor Foundation is a nonprofit organization that seeks to find the cause and cure of brain tumors in children by supporting medical research, increasing public awareness of the disease and aiding in early detection and treatment of childhood brain tumors.

Ulman Cancer Fund for Young Adults www.ulmanfund.org/index.asp

The Mission of The Ulman Cancer Fund for Young Adults is to provide support programs, education, and resources—free of charge—to benefit young adults, their families, and friends who are affected by cancer, and to promote awareness and prevention of cancer.

Young Survival Coalition www.youngsurvival.org/

The Young Survival Coalition (YSC) is the only international, non-profit network of breast cancer survivors and supporters dedicated to the concerns and issues that are unique to young women and breast cancer. Through action, advocacy, and awareness, the YSC seeks to educate the medical, research, and legislative communities and to persuade them to address breast cancer in women aged 40 and under. The YSC also serves as a point of contact for young women living with breast cancer.

ICCC GROUP	MORPHOLOGY	TOPOGRAPHY
I LEUKEMIA		
(a) Lymphoid leukemia		
Excluding ALL	9820, 9822-9827, 9850	C00.0-C80.9
ALL	9821	C00.0-C80.9
(b) Acute non-lymphocytic leukemia		
Excluding AML	9840, 9841, 9864, 9866, 9867, 9891, 9894, 9910	C00.0-C80.9
AML	9861	C00.0-C80.9
(c) Chronic myeloid leukemia	9863, 9868	C00.0-C80.9
(d) Other specified leukemias	9830, 9842, 9860, 9862, 9870-9890, 9892, 9893, 9900, 9930-9941	C00.0-C80.9
(e) Unspecified leukemias	9800-9804	C00.0-C80.9
II LYMPHOMAS AND RETICULOENDOTHELIAL NEOPLASMS		
(a) Hodgkin lymphoma	9650-9667	C00.0-C80.9
(b) Non-Hodgkin lymphoma	9591-9595, 9670-9686, 9690-9717, 9723, 9688	C00.0-C80.9
(c) Burkitt lymphoma	9687	C00.0-C80.9
(d) Misc. lymphoreticular neoplasms.	9720, 9731-9764	C00.0-C80.9
(e) Unspecified lymphomas	9590	C00.0-C80.9
III CNS AND MISCELLANEOUS INTRACRANIAL AND INTRASPINAL NEOPLASMS		
(a) Ependymoma	9383, 9390-9394	C00.0-C80.9
(b) Astrocytoma	9380	C72.3
	9381, 9400-9441	C00.0-C80.9
(c) Primitive neuroectodermal tumors	9470, 9500 (CNS & endocine only), 9362 (all sites)	C00.0-C80.9*
(d) Other gliomas	9380	C70.0-C72.2, C72.4- C72.9
	9382, 9384, 9442-9460, 9481	C00.0-C80.9
(e) Miscellaneous intracranial and intraspinal neoplasms	8270-8281, 8300, 9350-9362, 9480, 9505, 9530-9539	C00.0-C80.9
(f) Unspecified intracranial and intraspinal neoplasms	8000-8004	C70.0-C72.9, C75.1- C75.3
IV-VI (NEUROBLASTOMA, RETINOBLASTOMA, RENAL TUMORS) ARE NOT INCLUDED IN THIS MONOGRAPH.		
VII HEPATIC TUMORS		
(a) Hepatoblastoma	8970	C00.0-C80.9
(b) Hepatic carcinoma	8010-8041, 8050-8075, 8082, 8120-2, 8140-8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244-8246, 8260-8263, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573	C22.0, C22.1
	8160-8180	C00.0-C80.9
(c) Unspecified malignant hepatic tumors	8000-8004	C22.0, C22.1
VIII MALIGNANT BONE TUMORS		
(a) Osteosarcoma	9180-9200	C00.0-C80.9
(b) Chrondosarcoma	9220-9230	C00.0-C80.9
	9231, 9240	C40.0-C41.9
(c) Ewing sarcoma	9260	C40.0-C41.9, C80.9
	9363, 9364, 9374	C40.0-C41.9

° Modified version of ICCC: see http://www.seer.cancer.gov/iccc/

* For this monograph, cases with site codes C00.0-C69.9, C73.9-C75.0, C75.4-C77.9 were removed

ICCC GROUP	MORPHOLOGY	TOPOGRAPHY
(d) Other specified malignant bone tumors	8812, 9250, 9261-9330, 9370	C00.0-C80.9
(e) Unspecified malignant bone tumors	8000-8004, 8800, 8801, 8803, 8804	C40.0-C41.9
IX SOFT TISSUE SARCOMAS		
(a) Rhabdomyosarcoma and embryonal sarcoma	8900-8920, 8991	C00.0-C80.9
(b) Fibrosarcoma, neurofibrosarcoma, other fibromatous neoplasms	8810, 8811, 8813-8833, 9540-9561	C00.0-C80.9
(c) Kaposi's sarcoma	9140	C00.0-C80.9
(d) Other specified soft tissue sarcomas	8840-8896, 8982, 8990, 9040-9044, 9120-9134, 9150, 9170, 9251, 9581	C00.0-C80.9
	8963	C00.0-C63.9, C65.9- C76.8
	9231, 9240, 9363, 9364	C00.0-C39.9, C44.0- C80.9
	9260	C00.0-C39.9, C47.0- C76.8
(e) Unspecified soft tissue sarcomas	8800-8804	C00.0-C39.9, C44.0- C80.9
X GERM-CELL, TROPHOBLASTIC AND OTHER GONADAL NEOPLASMS		
(c) Gonadal germ-cell tumors	9060-9102	C56.9, C62.0-C62.9
(d) Gonadal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573	C56.9, C62.0-C62.9
	8380, 8381, 8441-8473	C00.0-C80.9
(e) Other and unspecified malignant gonadal tumors	8590-8670, 9000	C00.0-C80.9
	8000-8004	C56.9, C62.0-C62.9
XI CARCINOMAS AND OTHER MALIGNANT EPITHELIAL NEOPLASMS		
(b) Thyroid carcinoma	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8573	C73.9
	8330-8350	C00.0-C80.9
(d) Malignant melanoma	8720-8780	C00.0-C80.9
(e) Skin carcinoma	8010-8041, 8050-8075, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940	C44.0-C44.9
(f) Other and unspecified carcinomas	8010-8082, 8120-8155, 8190-8263, 8290, 8310, 8314-8323, 8430-8440, 8480-8580, 8940, 8941	C00.0-C10.9, C12.9- C21.8, C23.9-C39.9, C48.0-C48.8, C50.0- C55.9, C57.0-C61.9, C63.0-C63.9, C65.9- C72.9, C75.0-C80.9
XII OTHER AND UNSPECIFIED MALIGNANT NEOPLASMS		
(a) Other specified malignant tumors	8930, 8933, 8950, 8951, 8971-8981, 9020, 9050-9053, 9110, 9580	C00.0-C80.9
(b) Other unspecified malignant tumors	8000-8004	C00.0-C21.8, C23.9- C39.9, C42.0-C55.9, C57.0-C61.9, C63.0- C63.9, C65.9-C69.9, C73.9-C75.0, C75.4- C80.9

° Modified version of ICCC: see http://www.seer.cancer.gov/iccc/

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