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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