Chapter 2
Methods

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The maturation of large cancer registries in the U.S. and internationally has greatly enhanced our ability to identify large numbers of patients with multiple primary cancers (Boice et al, 1985; Curtis et al, 1985; Sankila et al, 1995; Travis et al, 1996, 2005; Neugut et al, 1999; Crocetti et al, 2001; Dong and Hemminki, 2001; van Leeuwen and Travis, 2005; Mellemkjaer et al, 2006; Schottenfeld and Beebe-Dimmer, 2006). The high-quality, population-based cancer registries from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program (Ries et al, 2006) provide a unique resource with which to evaluate the risk of subsequent cancers due to the extremely large number of survivors (more than 2 million), long follow-up period (since 1973), and standardized registry methods.

This current monograph utilizes the SEER database to provide a comprehensive evaluation of the risk of subsequent malignancies among patients initially diagnosed with 1 of more than 50 types of adult and 18 types of childhood primary cancer. The purpose of this chapter is to lay the foundation for subsequent chapters by describing the SEER study populations and analytic methodology used for the monograph. The presentation and interpretation of the statistical results are explained, along with the strengths and limitations of the study.

Study Population: SEER Cancer Registries

The SEER Program was established in 1973 to collect high-quality, population-based data on cancer incidence and survival in the U.S. (Hankey et al, 1999). Areas initially included in 1973 were the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, and the metropolitan areas of Detroit and San Francisco-Oakland (Ries et al, 2006; NCI, 2006a). The 13-county Seattle-Puget Sound area was added in 1974, and the metropolitan area of Atlanta was included in 1975. Persons in the SEER geographic areas resemble the U.S. population in the proportion of persons below the poverty level or with less than a high school diploma but differ in having higher percentages of urban and foreign-born residents. The study population for the current monograph includes the nearly 2 million cancer patients reported to the 9 SEER registries from 1973 to 2000, with follow-up for subsequent cancer occurrence extending up to 27 years, in order to ensure consistency of geographic areas over the longest time period possible. Additional SEER registries that contribute to cancer incidence reporting, but are not included in the current survey, are the more recently added areas of Los Angeles and San Jose-Monterey, Kentucky, New Jersey, the remaining geographic areas in California, Louisiana, and the smaller registries of rural Georgia and Alaska natives.

The SEER registries maintain a high level of ascertainment of incident cancer cases through searches of records of hospitals and radiotherapy units, as well as private diagnostic laboratories and treatment centers. All cancers occurring among residents of the defined geographic areas are reportable to SEER; however, second or later ("subsequent") cancers diagnosed among patients who migrate out of their SEER registry area are not reportable, and migration status is not recorded in the SEER database. Information routinely collected by the registries includes patient demographics (sex, race, age, place of residence), date of cancer diagnosis, primary cancer site and morphology, diagnosis confirmation by microscopic study or other methods, extent of disease (stage), first course of cancer-directed treatment, vital status, date last known to be alive or date of death, and cause of death for those who have died. A high rate of follow-up (≥97%) for vital status (alive/dead) is achieved by actively tracing all living patients (regardless of out-migration) and by linking with state and national death registries.

The SEER rules for classifying multiple primary cancers depend on the cancer site of origin, date of diagnosis, histology, tumor behavior (i.e., *in situ* versus invasive), and laterality of paired organs (NCI, 2006b). In general, all metachronous cancers (occurring 2 or more months after initial diagnosis) are considered as separate primaries unless the medical record states that the tumor is recurrent or metastatic. Notable exceptions to this rule are multiple adenocarcinomas of the prostate and multiple transitional cell carcinomas of the bladder (histology 8120-8130), which are reported as single primaries. Multiple tumors occurring on both sides of paired organs, such as the breast and testes, are generally considered to be independent cancers. Rules for determining multiple primaries of the lymphatic and hematopoietic system are

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

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more complex and depend on the specific histologic types involved. International coding rules for multiple cancers are more restrictive than those used in the U.S. Cancers that occur at the same site or different sides of a paired organ are usually considered to be 1 primary under international coding rules, unless the 2 tumors belong to separate histologic categories (IARC, 2004).

The SEER Program collects data on the first course of cancer-directed therapy (surgery, radiation, chemotherapy, hormonal therapy, immunotherapy, and other therapy). Prior to 1988, the first course was defined to include all treatment administered to the patient within 4 months after the initiation of therapy (2 months for leukemias) or until disease progression, whichever was earlier. Beginning in 1988, all case reports included the entire first course of therapy, regardless of duration (NCI, 2006b). Because cancer patients commonly receive surgery and radiation therapy at hospitals or medical centers that routinely report to the central registries, these treatments are captured for the large majority of patients. Data on treatments commonly given outside the hospital setting—such as chemotherapy, hormonal therapy, and immunotherapy—are incomplete and therefore are not included in the public-use SEER database or in this monograph. The SEER Program also does not record palliative therapy or therapy given after the initial course of treatment.

Analytic Methods

The cohort study is the most frequent epidemiologic approach used to determine if an observed number of subsequent cancers occurs more or less frequently than would be expected by chance alone. With this study design, a defined population of persons with a specific first cancer is followed over time for a number of years to examine the risk of developing a subsequent primary cancer, with the person-years at risk (PYR) allocated by age, sex, and other factors (Monson, 1974; Schoenberg and Myers, 1977). The ratio of observed to expected subsequent cancers (O/E) is then calculated by dividing the observed number of new cancers by the number expected if patients in the cohort experienced the same cancer rates as persons in the general reference population (Boice et al, 1985; Begg, 1999; van Leeuwen and Travis, 2005). The O/E ratio (or standardized incidence ratio, SIR) is frequently referred to as the "relative risk" because it compares the incidence rate of the event of interest (e.g., subsequent breast cancer) to the baseline incidence rate of that cancer (e.g., all breast cancer) in a general population of persons of comparable age, sex, and time distribution. The relative risk is generally considered a measure of the strength of an association. Another useful statistic is the excess absolute risk (EAR), which is calculated as the difference between the subsequent cancer rate in the cohort being evaluated and the rate expected in the standard population. The EAR is frequently used to measure the overall burden due to subsequent cancers.

O/E and EAR Calculations

For the monograph, we evaluated all patients diagnosed with an invasive cancer as a first primary malignancy who were reported to 1 of 9 SEER registries between January 1, 1973, and December 31, 2000. Because heightened screening of cancer patients during the initial medical work-up tends to identify many simultaneous cancers, we excluded from the calculations the first 2 months of follow-up and the new malignancies occurring within this initial 2-month period. The PYR for each individual began at 2 months after the date of the initial cancer diagnosis and ended at the date of last known vital status, death, or the end of study (December 31, 2000), whichever occurred first. SEER cancer registry incidence files were searched for subsequent primary cancers that developed at least 2 months after the patient's first primary diagnosis and before the study cutoff date. All second and later (third, fourth, etc.) invasive cancers were included in the observed numbers of cases to be comparable with the expected number derived from baseline SEER incidence rates, which include all multiple tumors. Non-melanoma skin cancers, with the exception of Kaposi sarcoma, were excluded because most such tumors (i.e., basal cell and squamous cell skin cancers) are not reportable to the SEER Program. For each initial cancer site grouping, the PYR and observed cases of cancer were stratified according to age at initial diagnosis (5-year groups), race (whites/unknown, blacks, other races), sex, and 5-year calendar year intervals. Cancer incidence rates were computed for the 9 SEER areas combined for each type of invasive cancer, by race, sex, age, and calendar-year group, and were multiplied by the accumulated PYR to estimate the expected number of subsequent malignancies for each stratum. The total observed and expected numbers of subsequent cancers for each stratum were then summed. The O/E ratios for each subsequent cancer site were calculated as the observed number divided by the expected number of subsequent cancer cases.

Tests on the statistical significance of the O/E ratios were performed under the assumptions that the observed number of subsequent cancers followed a Poisson distribution, and that no variation was associated with the expected number of cases. Byar's accurate approximation to the exact Poisson distribution was used to calculate 95% confidence intervals (Breslow and Day, 1987). The O/E ratios for which the 95% confidence interval excluded 1.0 were designated as statistically significant ($P<0.05$) and are indicated in the monograph tables with an asterisk (*).

To compute the excess absolute risk or EAR, we subtracted the expected number of subsequent cancers from the observed number of cancer cases; the difference was then divided by the PYR, and the number of excess cancer cases was expressed per 10,000 PYR, $[(O-E)/PYR] \times 10{,}000$. O/E and EAR calculations were performed using the "MP-SIR" session of SEER*Stat, a publicly available, interactive, Windows-based program for analyzing cancer registry data (NCI, 2006c).

Understanding Relative Versus Absolute Risks

The relative risk (O/E) provides a useful tool to test etiologic hypotheses and to screen for significantly increased or decreased risks of developing new malignancies (Begg, 1999). A sharply elevated relative risk based on a large number of subsequent cancer cases provides strong evidence of a positive association with the first primary cancer. Significantly increased risks between 2 malignancies that are bidirectional in nature (elevated risks for cancer B after cancer A, and also for cancer A after cancer B), are suggestive of shared etiologic factors, particularly when the elevation in risk persists beyond the initial follow-up period (≥5 years) and the risk appears unrelated to initial therapy. High relative risks of subsequent cancer can sometimes be associated with low EARs, for example when the baseline cancer incidence rate in the referent population is low, as with therapy-related acute leukemia or when studying children and young adults. In contrast, modest or even small increases in the relative risk can result in high EARs of new malignancies at older ages, when the background cancer burden in the referent population is greatest. In general, the EAR is often the most useful measure of risk to assess the impact of the subsequent cancer burden in a specific population of cancer patients, or when interest centers on the potential effectiveness of screening or prevention programs.

Both relative risks and EARs of subsequent cancers can vary by age, sex, time since diagnosis, or other baseline factors. Thus, comparisons of risk for different types of second cancers or across cohorts can be misleading when patient groups being compared have different underlying distributions of one or more of these factors (Armstrong, 1995). In this case, it may be necessary to stratify the analysis to evaluate risk within homogeneous patient subgroups, for example, within similar age and time intervals. Alternatively, multivariate regression methods may be employed to adjust for differences in baseline characteristics of age and other factors and to account for confounding variables, as used in studies of treatment-related second cancers (Yasui et al, 2003; Zablotska and Neugut, 2003; Travis et al, 2005; van Leeuwen and Travis, 2005). In this monograph, we have stratified most results by sex, age, time since diagnosis, and radiation treatment, whenever possible.

Cumulative Incidence

We calculated the cumulative incidence as the percentage of patients developing a second malignancy by a specified time (10, 15, or 25 years) after the initial cancer diagnosis, while taking into account the competing risk of death among patients who did not develop a second malignancy (Gooley et al, 1999; see Appendix 1). It is important to recognize that when the risk from competing outcomes is large, the cumulative incidence function is the more appropriate statistic to use as compared with actuarial methods of cumulative risk (e.g., Kaplan Meier methods, Kaplan and Meier, 1958), which censor patients at the time of the competing event. The cumulative incidence is an absolute measure of second cancer incidence and, in general, tends to rise with increasing age of the cohort at risk. The measure, by itself, provides no indication of whether the second cancer incidence is higher or lower than the cancer incidence rate prevailing in the general population. Cumulative incidence calculations were performed for the monograph using a program by Gooley et al. (1999), and 95% confidence intervals by a program developed by Choudhury (2002). (See also the software program "stcompet" from StataCorp, described in Coviello and Boggess, 2004.)

Presentation of Results

Results are presented in 16 chapters, organized by grouping of initial cancer sites. Cancer diagnoses were categorized according to the International Classification of Diseases for Oncology, second edition (ICD-O-2) (Percy et al, 1990). Definitions of the first and subsequent cancer sites, and groupings by histologic type, are given in Appendices 2.A-2.D. Each chapter provides background information for the first cancer(s) (survival statistics, usual therapy, etc.), major risk factors, and a Results and Discussion section that describes the patterns of subsequent cancer risks and discusses the findings in relation to potential risk factors and previous studies of multiple primary cancers.

Standard data tables are typically included at the end of each chapter. Initial tables provide patient characteristics by sex, race, age, first course of cancer-directed therapy (surgery and/or radiation), and PYR. The number of patients with exactly 1, 2, 3, or 4 or more cancers is tabulated. The percentage of patients developing multiple primary tumors who have their cancers confirmed by histologic or other methods are described in overlapping categories: the percentage of cases with at least the first and second primary cancers (but not necessarily later cancers) histologically confirmed; the percentage with first, second, and all later primary cancers confirmed; and the percentage with only the first primary cancer confirmed, but not second, third, or later primary cancers. Tables that follow present the risk of developing a subsequent primary cancer (O/E and EAR) by years after diagnosis of the first cancer (time since diagnosis intervals: 2 months to 1 yr; 1-4 yrs; 5-9 yrs; ≥10 yrs; and total ≥2 months) for both sexes combined, by sex, and, when numbers are sufficient, by age at initial diagnosis. For selected sites of initial cancers, results are tabulated for long-term survivors (time since diagnosis intervals: 2 months to 9 yrs; 10-14 yrs; 15-19 yrs; ≥20 yrs; and total ≥2 months), by initial treatment (any radiotherapy, no radiotherapy), and, when informative, by histologic type. The number of patients at risk at the beginning of the follow-up interval ("number starting interval") is given, as well as the total PYR accumulated during the follow-up interval ("person-years in interval"). Note that the number of patients starting the interval decreases with each succeeding observation period (except for the total),

as patients are withdrawn from analysis due to death, loss to follow-up, or study end, whereas the sum of the PYR for each follow-up interval equals the total PYR.

The cumulative incidence (%) of developing a second cancer is provided for each initial cancer site grouping in the respective chapters, and for selected sites in line graphs within the text. Monograph Appendix 1 includes line graphs for 48 first primary cancer sites, giving the cumulative incidence of any second cancer and the cumulative probability of death from competing causes at 25 years after initial diagnosis. When the patterns of risk by age are of interest, bar graphs are included in the chapter text, displaying the O/E and EAR of subsequent cancers by age at initial cancer diagnosis.

Methodologic Limitations

The monograph results should be viewed in light of the potential sources of ascertainment bias, as well as diagnostic and other biases inherent in studies of multiple primary cancers, and these limitations should be taken into account in evaluating the results.

Assessment of Cancer Independence—A key assumption in the analysis of multiple primary cancers is that the individual malignancies are biologically independent. SEER registries rely on the pathology report as to whether a new malignancy is a separate primary cancer as opposed to a metastatic lesion or local recurrence of the original cancer. Histopathologic confirmation of the new malignancy increases the confidence in the diagnosis of a subsequent primary cancer, but it may not provide definitive evidence of independence. Correct classification as a multiple primary cancer may also be problematic when new malignancies arise at the same anatomic site and with the same histology as the first tumor, particularly in paired or contiguous organs. To address this issue, the monograph tables provide separate estimates of the risk of developing a subsequent cancer of an organ different from the first. (See Appendix 2.C for cancer site definitions.) Further difficulties occur when multiple tumors arise in the same tissue in what is known as the "field cancerization" process, for example, tobacco- and/or alcohol-related tumors of the oral cavity and pharynx. While SEER registries generally consider these field-related cancers to be separate malignancies, this research area is still evolving, and recent molecular studies report that multifocal tumors in some organs, such as the lower urinary tract, are likely to originate from a single transformed molecular clone (Habuchi, 2005).

Medical Surveillance Bias—Cancer patients are often under closer medical surveillance than persons in the general population. This increased scrutiny may lead to an ascertainment bias in the early detection of asymptomatic cancers that otherwise might not have been clinically evident for several years (known as lead-time bias). In addition, increased cancer screening and autopsy investigations frequently uncover indolent tumors that otherwise might not have been clinically detected during the patient's lifetime. Malignancies that are especially susceptible to detection by medical screening include cancers of the thyroid, kidney, and prostate. Conversely, underreporting of second and later cancers may occur among cancer survivors who have metastases or other serious comorbid conditions, or among those diagnosed at older ages whose life expectancy is short. New contralateral tumors of the lung, for example, are often underreported, as they are assumed to represent spread of the original cancer (Johnson, 1998). Artifactually reduced risks of subsequent cancers can also occur when surgery for the initial tumor removes one or more organs from risk, for example, when the uterus and ovaries are surgically removed during treatment for gynecologic cancers.

Underascertainment of Subsequent Cancers Due to Out-migration—Subsequent cancers are not recorded in the SEER database for patients who migrate from their original SEER geographic area, regardless of whether they move into another SEER area. This underascertainment of subsequent cancer cases results in conservative (negatively biased) estimates of subsequent cancer risk, as the expected number of new malignancies is based on the assumption that patients remain at risk until their date of last known vital status or death. Although the impact of out-migration on subsequent cancer risk has not been assessed, this factor is likely to be important for highly mobile metropolitan areas, for the longest follow-up observation periods (10 and 20 years after initial diagnosis), and for children and young adults.

Radiation-related Cancers—O/E comparisons of irradiated with nonirradiated patients may underestimate the risk of radiation-related cancers when patients classified as "without initial radiotherapy" actually received radiotherapy that was not reported to registry databases (Du et al, 1999). Moreover, subsequent cancer risks for patients treated with radiotherapy may be difficult to interpret without accounting for the carcinogenic effects of chemotherapy, particularly in the case of therapy-related leukemia.

Interpretation of Small Numbers—In contrast to most other SEER reports of incidence and survival, the monograph tables include results for individual cancers that are based on small numbers of observed cases (less than 5 cases) over a large number of PYR. This comprehensive approach to data reporting for all subgroups enables the monograph user to combine observed and expected numbers over several cancer sites to detect broad etiologic patterns and permits comparison of findings for uncommon cancers with those of other studies.

Multiple Comparisons—The monograph aimed for the presentation of subsequent cancer risks by sex, age, time since diagnosis, and other factors, resulting in a large number of multiple comparisons for each initial cancer site. Multiple testing of stratified data tends to identify a number of statistically significant risks of subsequent cancer that may have occurred by chance alone (Savitz and Olshan, 1995; Goodman, 1998). To distinguish real from chance findings, the results should be viewed in light of the biologic plausibility of the association, consistency with previous second cancer studies, and epidemiologic characteristics of the tumors involved.

Methodologic Strengths

Notwithstanding the potential biases and caveats noted above, the SEER registry database represents a powerful analytic resource for assessing the incidence of new malignancies among cancer survivors. The SEER Program is generally considered to be the standard for quality among cancer registries around the world, with nearly complete reporting of incident cancer cases within the covered geographic areas. Because the SEER registries are population-based and are broadly representative of the U.S. population, these analyses avoid potential biases that can be introduced in hospital-based studies as a result of area referral patterns and incomplete follow-up. High rates of microscopic confirmation for new cancer cases, and the use of precise rules to ascertain and code first and later primary cancers, are key features of the SEER Program that help ensure the validity of the patterns observed.

This monograph provides the largest assessment to date of the risk of new cancers among cancer survivors. The study covers more than 2 million cancer survivors; nearly 390,000 patients were at risk for 10 or more years after the initial cancer developed, and almost 76,000 patients were at risk for 20 or more years. There were more than 11 million person-years at risk in the analysis, yielding 186,000 subsequent primary cancers. Because of these large numbers, the monograph is able to provide a wealth of new data on the risk of developing a subsequent cancer for most initial forms of cancer, including some uncommon sites. The detailed presentation in the monograph of subsequent cancer risks by time since initial diagnosis, sex, age, treatment, and histologic type provides a comprehensive resource from which causal hypotheses can be generated and tested in more focused analytic studies in the SEER Program or in other populations where second primary cancers can be evaluated (Curtis et al, 1992; Travis et al, 2000, 2002, 2003). Finally, the results presented in this monograph should be useful to clinicians in advising their cancer patients on long-term outcomes and the importance of medical supervision for prevention and early detection of new malignancies.

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