Methods to Assess Adverse Health-Related Outcomes in Cancer Survivors

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Abstract

Designing a study focused on adverse health-related outcomes among cancer survivors is complex. Similarly, reading and interpreting the findings of a survivorship-focused study requires an appreciation of the complexities of study design, potential biases, confounding factors, and other limitations. The topic areas are broad—study design, comparison populations, measures of risk, key health outcomes of interest, potential modifying factors to consider. With brevity, this article includes basic information to consider within these areas as well as examples and concepts intended to advance the science of survivorship research and encourage further reading and exploration. *Cancer Epidemiol Biomarkers Prev; 20(10); 2022–34. ©2011 AACR.*

Introduction

The sophistication of survivorship-focused studies and the reporting of adverse health-related outcomes have advanced much in the last 2 decades. Our goal is to provide an overview of study design, potential biases, primary outcomes, key covariates, and measures of risk that should be considered when designing a new study or interpreting the findings of an existing study. The intended audience for this article includes both beginning and intermediate-level investigators and consumers of survivorship-focused literature, and, hopefully, seasoned researchers will add something new to their repertoire in the process. We have, collectively, integrated our research experiences and insights as a guide and have sought to highlight potential pitfalls to avoid. There is, however, no perfect study—each investigator must consider how to best accomplish the study aims, balancing potential strengths and limitations, often directly limited by one's available resources.

Study Designs to Measure Risk of Adverse Health-Related Outcomes in Cancer Survivors

When assessing adverse health outcomes in cancer survivors, typical epidemiologic study designs are the cohort study and the nested case–control study (1–4). In contrast with studies on treatment efficacy, the clinical trial design is not an absolute requirement to prove causality for studies on the risk of late adverse outcomes because in most situations, confounding by indication does not play a role. Especially in cancer patients without comorbidity, it is unlikely that treating physicians historically adapted optimal cancer therapy for individual patients based on considerations about the long-term risk of specific late adverse treatment effects (5).

Cohort studies

Because most cohort studies have been conducted retrospectively, follow-up of all patients in such studies should be completed up to some point in the recent past. Selection bias in these studies may arise if only part of all patients treated in the inclusion period is included in the study. For example, the Childhood Cancer Survivor Study (CCSS) cohort does not include 31% of the original cohort because of loss to follow-up or refusal to participate (6). When a complete retrospective cohort is studied, selection bias may still occur if follow-up is less complete for survivors who remain healthy (and are censored at date of last follow-up) than for patients with adverse events, who usually remain under surveillance or return to clinical follow-up (1). In a study on second malignancy risk in Hodgkin lymphoma survivors, in which only 50% of patients were contacted in the previous 6 years, sensitivity analyses showed that risk estimates substantially decreased (nearly halved) when patients with incomplete follow-up were censored at time of data collection instead of date of last medical follow-up (7). Unfortunately, completeness of follow-up up to a specific point in the recent past is often not reported in survivorship studies.

Cohorts of cancer survivors can be derived from several sources, including population-based cancer registries, hospital-based cancer registries, or cooperative group/clinical trial series. Each of these sources has specific advantages and disadvantages.

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Cohort studies using population-based cancer registries generally have large numbers of patients available, which allows the detection of even small excess risks (1–4, 8–10). As a result of including the entire population of individuals, the full spectrum of treatment exposures experienced are included. Thoughtful analysis of such cohort data in relation to specific types of cancer and calendar period of diagnosis has often uncovered heterogeneity in risks of specific adverse health outcomes which may be explored further within a nested case–control study to understand more precisely the contribution specific treatments. By including the entire population exposed, the risks are less subject to bias resulting from a more or less aggressively treated subset of the entire population being included. For outcomes such as second primary neoplasms and cause of death, there is the possibility of linking a population-based cohort of survivors to population-based registries. The methods of ascertainment and coding of observed and expected events are identical, avoiding some elements of bias resulting from different ascertainment or coding procedures for observed and expected numbers. Where population-based registries were established back to the 1940s, for example, the Nordic countries and the United Kingdom, there is the opportunity to investigate risks among very long-term survivors. Without at least 20 to 30 years of follow-up after cancer treatment, adverse outcomes associated with long latency periods may go undetected. The major disadvantage of population-based registries is the general lack of detailed information. If treatment data are available in population-based registries, radiation is typically categorized as yes/no without the field of therapy (and organs irradiated) or dose of radiation. Similarly, chemotherapy may be categorized as yes/no without information on specific agents or cumulative dosages of key agents (e.g., anthracyclines, alkylating agents). Furthermore, exposures may be misclassified if only the first treatment is registered. In addition, population-based registries generally do not have information about family history or lifestyle behaviors or the presence of premorbid or comorbid conditions. To increase available information with regard to therapeutic exposures, cancer registries have been linked to claims-based datasets; for example, the U. S. Surveillance, Epidemiology and End Results Program (SEER) can be linked with Medicare medical claims data (11). The major limitations of such studies are that they do not account for selection bias in who gets specific cancer treatments, and there is limited data on prognostic factors and comorbidities that must often be inferred from coded diagnoses and billing documents, rather than from clinical information in the medical record. Furthermore, doses of chemotherapy or radiation are typically not available (12), and this method may be restricted to certain age groups (e.g., the elderly population enrolled in U.S. Medicare). Lastly, the outcome of interest may be underreported if survivors migrate out of the catchment area under surveillance. For example, in the United States, underascertainment of second cancer risk can result from migration of subjects from SEER areas (4, 8). In nationwide population-based registries, such as exist in many European countries, this is relatively uncommon and migration is recorded.

A major advantage of clinical trial databases is that detailed treatment data on all patients are available. Comparison of adverse health outcomes between the treatment arms of the trial controls for any intrinsic risk that the event of interest is associated with the primary cancer or that treatment choice is determined by a clinician's concern about a specific adverse outcome in high-risk patients (confounding by indication). However, there are several limitations to conducting studies focused on late outcomes through the clinical trial infrastructure. The number of patients enrolled in a particular trial may be relatively small. Combining data from a number of trials poses other problems, such as the standardized collection of long-term follow-up data on adverse health outcomes. The main endpoints of interest in most clinical trials are treatment response and survival, and long-term follow-up data on other outcomes tend to be very incomplete (and potentially biased). Ganz described the challenges to long-term studies conducted through cooperative groups, including exclusion of patients with known comorbidities, lack of racial/ethnic diversity, and high loss-to-follow-up rates (12). However, as illustrated by Bhatia and colleagues from the Children's Oncology Group, the accurate ascertainment of early occurring second malignancies, such as treatment-related leukemia, can be successfully accomplished within the cooperative group setting (13). Ideally, routine reporting and assessment of major adverse health outcomes should become an integral part of clinical trials (12, 14). In fact, we strongly encourage regulatory agencies to request that late toxicity be listed among endpoints of new clinical trials, in particular those involving children and young adults with cancer (because the long-term survival is already achieved in most patients with contemporary therapy).

Many cancer treatment centers maintain hospital-based cancer registries, and institutional series are a common source of retrospective reviews of long-term treatment outcome. Many hospital-based registries have been in existence for decades and collect extensive data on treatment and follow-up. Compared with trial data, hospital registries provide a wider range of treatments and dose levels, which may yield important information on the spectrum of adverse events. Many studies of adverse health outcomes following childhood cancer or Hodgkin lymphoma have been based on single center (15, 16), regional consortiums (17–19), or large multi-institutional cohorts, such as the CCSS (20, 21). A disadvantage of hospital-based cancer survivor studies is that the overall risk of adverse events may not be generalizable to all cancer patients in the population, because patients in the large treatment centers maintaining registries may have received more intensive treatments. For example, older hospital-based studies have observed larger risks of

leukemia after chemotherapy for Hodgkin lymphoma than population-based studies (2, 22, 23). Another important consideration is the comparability of surveillance and reporting of adverse outcome between patients studied in large institutional reviews, and the general population, who are often used to report "expected" rates of disease (discussed below; ref. 24). Lastly, risk estimates from small, single-institution retrospective reviews should be viewed with caution, until replicated in other settings.

Nested case–control studies

The cohort study is a more costly study design for examining detailed treatment factors (e.g., cumulative dose of alkylating agents, radiation dosimetry) in relation to the risk of infrequently occurring adverse events, such as second malignancies. Most cohorts are fairly large (to yield precise estimates), rendering the collection of detailed treatment data expensive and time consuming. The nested case–control study within an existing cohort is a more efficient and cost-effective approach to answer specific research questions. Treatment factors are compared between all cases, with the event of interest and a random sample of all patients in the cohort who did not develop the event of interest. Several landmark case–control studies on adverse events in cancer survivors have shown the strengths of this approach (22, 25–36). Matching factors employed in most case–control studies include sex, year of birth, calendar year of diagnosis of the first primary cancer, site of first primary malignancy, and study center. The most important criterion for control selection is that each control must have survived for at least as long as the interval between the diagnoses of the first primary malignancy and the event of interest in the corresponding case, without developing the event of interest and with the organ at risk *in situ* (29, 37, 38). The purpose of matching should be to ensure comparability of cases and controls on confounding factors. Matching on factors which are not confounders (most commonly those not related to the outcome of interest) may lead to overmatching, which reduces statistical power (4, 39, 40). If there is misclassification of the exposure variable (treatment), matching on a nonconfounding factor which is related to the exposure variable can produce downward bias, resulting in attenuation of risk estimates (41, 42). For example, matching on cancer center may result in overmatching when there are substantial differences in the treatments employed by different cancer centers. When omitting cancer center as a matching factor, advantage can be taken of the wide spectrum of treatments and dose levels in the whole cohort, resulting in greater statistical power. The same applies to primary cancer site and calendar year of primary cancer diagnosis as matching factors, unless these variables are associated with the risk of the event of interest. Yet, many case–control studies have matched on these factors, mostly for practical reasons. Nested case–control studies within CCSS did not match on type of childhood malignancy. Rather, a supplemental control matched on type of initial cancer was selected for case–control sets, in which none of the selected controls had the same type of first cancer, to allow for analyses restricted to matched sets with the same primary malignancy (28, 29). A recent case–control study examining radiation dose and chemotherapy as risk factors for second stomach cancer was nested in a combined cohort of survivors of Hodgkin lymphoma and testicular cancer and did not match on primary cancer site (43). Future studies should carefully consider the pros and cons of including specific matching factors in the design phase.

As in each case–control study, it is critical to the validity of the study results that the controls are truly representative of all patients who did not develop the event of interest. For example, biased results may be obtained when controls with untraceable records are replaced with controls with traceable records, because untraceability of records may be related to intensive treatment or a recent new diagnosis. Surprisingly, the proportions of traced records for selected cases and controls are rarely reported in cancer survivor studies and procedures to be followed in case of missing medical records are lacking.

Comparison populations

To evaluate whether the risk of adverse events in cancer survivors is increased, comparison with general population rates is an important first step. Standardized mortality ratios (SMR) can be estimated (as discussed below) by comparing with the mortality rates of the general population. Standardized incidence ratios (SIR) can only be estimated for adverse events for which age-, sex-, and calendar year–specific disease rates are available for the general population; in most jurisdictions, this is the case for second malignancy, but not most other events.

Differences in surveillance intensity and case definition between study patients and the control population should be considered. In many studies, the outcome of interest in study subjects is determined through active clinical follow-up, whereas the expected rate is estimated from a population-based registry (44, 45). The more active search for events in the study group and nonrandom loss to clinic follow-up may overestimate risk. For example, a recent CCSS study showed that risks of chronic diseases derived from only those survivors who were seen in a cancer center or follow-up clinic were overestimated by 9.3% (46).

Compared with the general population, cancer survivors may also have a different risk profile for the outcome of interest (e.g., due to differences in lifestyle). For example, several studies suggest that breast cancer patients have an overall decreased incidence of and mortality from cardiovascular disease compared with the general population (possibly due to differences in risk factors for breast cancer and cardiovascular disease and to a healthier lifestyle among breast cancer survivors), whereas direct comparison of irradiated and nonirradiated patients shows an increased risk from radiation (47–49).

When using general population rates for comparison, adjustment for lifestyle factors is not possible. Therefore,

other comparison groups are recommended. A sibling comparison group is more similar to the survivor population with respect to lifestyle, socioeconomic factors, and genetic factors (6, 50). Sibling controls have been used in studies focusing on outcomes such as fertility, subclinical outcomes, and quality of life (6, 21, 51, 52). Limitations of sibling controls include potential selection bias through nonresponse, which may result from unwillingness of the cancer survivor to involve a sibling or nonparticipation of the sibling. Bias may result if sibling nonresponse is related to the outcome of interest. For example, siblings with a childwish may be more likely to participate in a study of markers for premature menopause. To examine the effects of specific treatments on the risk of adverse health outcomes, comparisons between treatments are mandatory. Preferably, a reference group of patients unexposed to radiation and chemotherapy should be used. This is possible when examining late effects of treatment for testicular cancer or breast cancer but, unfortunately, not in studies of survivors of lymphoma or leukemia. In such cases, the lowest exposure category can be used as the reference (22, 31, 32), or the risk can be modeled using a continuous treatment variable such as radiation dose. When comparing risks across treatment groups, pitfalls are that the duration of follow-up or the calendar period of treatment may differ between treatments. This may cause bias if the treatment-related risk of the outcome of interest changes over time (as with a long induction period for most radiation-associated cancers), or the background incidence of the event of interest changes over time.

Primary Outcomes: Measurement and Ascertainment

Mortality

The most common method of ascertaining cause-specific mortality is by obtaining information from death certificates. Most countries use an international death certificate and a standardized approach with the International Classification of Diseases (ICD) for coding cause of death and associated conditions. This is an imperfect process, with multiple types of individuals from different backgrounds completing the death certificate (53–55). Standardization of this process has evolved as governmental agencies have sought to improve the reliability, validity, and reproducibility of the data and to provide the causal chain that led to death as well as contributing conditions. The U. S. National Center for Health Statistics recently published an informative review on this topic (56). As noted by the authors, despite the limitations of mortality data on the basis of death certificates, they remain the best available disease-specific information. Indeed, death certificate–derived cause-specific mortality continues to be the standard used in large cohort studies (57–61).

In the United States, cause-specific mortality data can be obtained by conducting a National Death Index search of the individuals within a cohort. A similar linkage approach is available in the United Kingdom and several other countries in Europe. In Canada, the death statistics are maintained in provincial registries; there is not a country-wide registry available.

Subsequent primary neoplasms

Because malignant cancers are rigorously ascertained by population-based cancer registries, including primary and subsequent primary malignancies (excluding nonmelanoma skin cancer), numerous studies have used such registries to determine risk estimates for subsequent primary neoplasms (SPN) following various primary cancers (11, 62–83).

In countries without nationwide cancer registries, complete ascertainment of SPNs through linkage is not possible. In the CCSS, SPNs are ascertained through self- or proxy report in the periodic surveys and/or death certificate. Subsequent primary neoplasms are then confirmed by pathology report or, when not available, confirmed by other medical records reviewed by study investigators (84). The British CCSS ascertains SPNs through flagging survivors at the National Health Service Central Registers (9). Flagging informs the investigators when a survivor develops an SPN or dies and provides linkage between the population-based cohort and the national population-based death and cancer registration systems. Confirmation of all SPNs is undertaken by writing to the relevant clinician(s) to obtain all diagnostic reports to confirm site, type, and date of diagnosis, with particular reference to the pathology reports. In a Dutch study of subsequent malignancy risk following Hodgkin lymphoma, the slides were reviewed for all cases of non-Hodgkin lymphoma (NHL), leukemia, and the myelodysplastic syndrome; for NHL cases, they additionally reviewed the original slides of Hodgkin lymphoma to exclude the possibility that it was a misdiagnosed NHL. For all other subsequent malignancies, they obtained pathology reports without reviewing the slides (85).

Nonmalignant neoplasms, such as meningiomas, and nonmelanoma skin cancers are also ascertained in several cohort studies through the mechanisms described above (9, 84, 86). However, because these SPNs are not included in the population-based cancer registries, the SIR and the absolute excess risk (AER) for these outcomes cannot be determined. In addition, analyses made on ICDO-2 classification may not be fully comparable with recent analyses based on ICDO-3. For example, pilocytic astrocytoma was changed from "malignant" (ICDO-2) to "uncertain" (ICDO-3). This change in category may lead to artificial changes in risk estimates when historical series are compared.

Adverse health outcomes and burden of morbidity

Following cancer therapy, survivors often develop new health problems of varying degrees of severity; some related to the therapy, others not. Numerous studies have investigated the occurrence of specific (a)symptomatic late outcomes, such as cardiomyopathy. Discussion of the

Table 1. Common terminology criteria for adverse events (CTCAE: versions 3 and 4)

- Grade 1–mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
  Example: diet controlled hypertension
- Grade 2–moderate: minimal, local or noninvasive intervention indicated; limiting age appropriate age-appropriate instrumental ADL[a]
  Example: hypertension requiring pharmacologic therapy
- Grade 3–severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; limiting self care ADL[b]
  Examples: congestive heart failure, ovarian failure
- Grade 4–life-threatening or disabling[c]
  Examples: myocardial infarction, organ transplant, second primary cancer (excluding nonmelanoma skin cancer), blindness
- Grade 5–death

Activities of Daily Living (ADL)
[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b]Self care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
NOTES: [c]In CTCAEv3 (87), disabling was included with life-threatening as a grade 4 condition. In CTCAEv4 (143), disabling conditions were described as being grade 3 (page 2); however, in the organ-based schema (pages 4–195), the disabling conditions are still scored as grade 4 (as they were in version 3). As an example, blindness was scored as a grade 3 in CTCAEv3 (pages 52–54). Blindness is a disabling but not a life-threatening condition but is scored as a grade 4 condition in the manual.

potential methods to ascertain and study specific late outcomes, including use of cross-sectional versus longitudinal assessments or measurement of surrogate markers, is beyond the scope of this article. Furthermore, the ascertainment and measurement of psychosocial outcomes is discussed in another paper in this series.

That being said, it is important to understand how to group different outcomes into summary scores. To standardize the reporting of morbidity during and after cancer therapy, a multidisciplinary group sponsored by the U.S. National Cancer Institute developed the Common Terminology Criteria for Adverse Events (CTCAE version 3; ref. 87). With this instrument, the incidence (or prevalence) and severity of both acute toxicities and chronic conditions can be captured (88). As illustrated in Table 1, there are 5 grades: mild, moderate, severe, life-threatening or disabling, or death.

Investigators in the CCSS used CTCAEv3 to score 137 different patient-reported outcomes (chronic physical health conditions) among 10,397 adult survivors of childhood cancer with a mean age of 26 years and compared results to 3,034 siblings (21). The use of CTCAEv3 as a scoring template allowed the investigators to estimate the 30-year cumulative incidence of having at least 1 chronic physical condition develop after the cancer diagnosis (grade 1–5; 73.4%; Fig. 1). Furthermore, the adjusted relative risk of a serious condition was more than 8-fold higher for survivors compared with noncancer siblings. This approach was also used for a cohort from a single-institution cancer registry in the Netherlands in the evaluation of 1,362 adult survivors of childhood cancer (median age, 24.4 years). In contrast to the CCSS, 94% of the Dutch cohort was evaluated by a physician (19). Notably, the findings were remarkably similar between the 2 populations, one using primarily patient-reported outcomes and the other clinician-measured outcomes (89). Both CCSS and the Dutch investigators have since used this approach to characterize the magnitude of risk for different cancer types, treatment exposures, and affected organ systems and identified high risk groups (20, 90–102).

Although the findings from these 2 groups suggest that when measuring the overall burden of morbidity from large cohorts, patient-reported outcomes correspond reasonably well with physician-reported outcomes, we know that there are some subclinical/asymptomatic conditions that patients may be unaware of without testing (i.e., osteoporosis), some historical conditions that physicians may not record, and medical records that are incomplete. The cost, time, and resources to medically evaluate a large cohort may not be feasible. Bhatia and colleagues assessed the concordance of patient-reported and medical record abstracted outcomes in 100 cancer survivors. Specificities ranged from 75.4% for ocular complications to 100% for osteonecrosis (103). There was intermediate to excellent agreement (kappa = 0.4–1.0) for all complications evaluated.

In addition to ascertainment of chronic health conditions by patient report, medical examination, or medical record abstraction, investigators can also access this information through linkage with hospital discharge registries. The primary limitation of this approach is that these registries only capture conditions requiring hospitalization and that they may be less accurate when set up for billing reasons (104). The primary limitation of the former is that it only includes conditions requiring hospitalization.

Collecting, Measuring, Ascertaining, and Categorizing Key Covariates

Treatment exposures

Accurate ascertainment of therapeutic exposures is critical to the evaluation of associations with of the risk

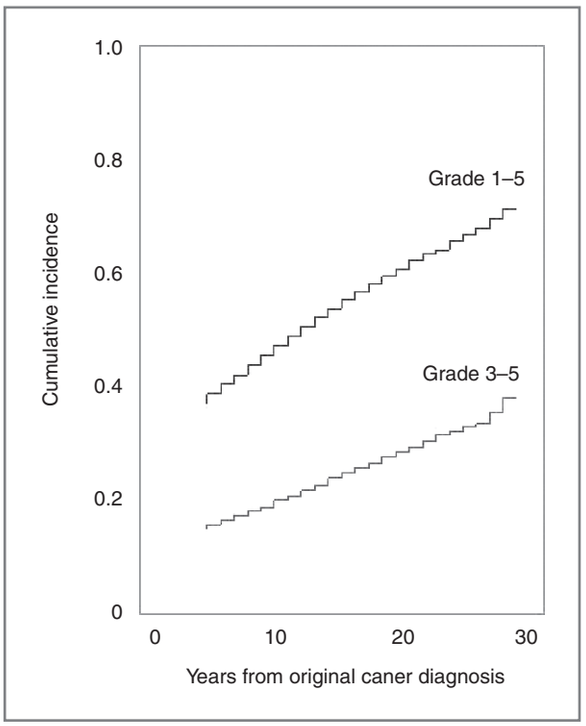


Figure 1. Cumulative incidence of chronic health conditions among 10,397 adult survivors of pediatric cancer with death treated as a competing risk. The severity of subsequent health conditions was scored according to the common terminology criteria for adverse events (version 3) as either mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4) or fatal (grade 5). Reprinted from Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572–8; used with permission.

of late outcomes (19, 105). The heterogeneity of therapeutic exposures for many cancers, regardless of age at therapy, can confound the analysis if only cancer diagnosis is known. For example, it is well understood that cranial radiotherapy substantially increases the risk of obesity in adult survivors of childhood acute lymphoblastic leukemia, particularly among women (106). There does not seem to be a risk of obesity in adult survivors of childhood ALL treated with chemotherapy only (without cranial radiotherapy; ref. 106). If the data is analyzed only by cancer diagnosis, and not by treatment exposure, the risk of obesity in this subgroup (cranial radiotherapy) may be missed. Similarly, lack of information about the field or dose of supradiaphragmatic radiation or the cumulative dose of doxorubicin limits findings studying cardiovascular outcomes of Hodgkin lymphoma survivors.

Patient-reported treatment information is generally not useful, as most patients are unaware of the details of their therapy or are inaccurate in their recall (107). Reliance solely on protocol planned therapy, without details of dose reductions or changes in treatment plans, is also not recommended. The gold standard for ascertainment of treatment exposure is a medical record abstraction of the delivered therapy by a trained individual. One of the cornerstones of the CCSS success has been accurate and detailed treatment exposures (50, 105). Briefly, for the original CCSS cohort enrollment, exposure information (yes/no) was abstracted from the medical record for 42 chemotherapeutic agents; cumulative doses were abstracted for 22 of these agents. Data were also obtained on cancer therapeutic surgical procedures done at any time from the date of diagnosis onward and on tumor site. For patients who received radiation therapy, the full therapy records were copied and sent to the Radiation Dosimetry Center to allow for detailed dosimetry in nested case control. Indeed, many adverse outcomes are associated with radiation therapy. Thus, it is imperative that high quality standards, such as those established by Stovall and colleagues, are used to estimate tissue and organ doses of radiation based upon the radiation charts and simulation fields (28, 29, 31, 32, 36, 108).

Radiobiological models that utilize 3-dimensional (3D) radiation dosimetry data to estimate the risk of late radiation toxicity could have significant utility for planning radiotherapy. However, a major challenge arises from having only 2-dimensional (2D) treatment planning information for patients with long-term follow-up. Various techniques have been used to reconstruct 3D heart, brain, and liver volumes from 2D imaging data for the planning of radiotherapy and surgery. In particular, imaging software that employs finite element deformable image registration can be used to facilitate 3D reconstruction of organ volumes using limited 2D radiotherapy imaging data (109). These methods can potentially be used to correlate normal tissue dosimetry, with late toxicity in a way that could be utilized in contemporary 3D radiotherapy treatment planning systems (104, 110).

Sociodemographics and lifestyle behaviors

Inclusion of key sociodemographics and lifestyle behaviors can enrich a survivorship-focused study (111). Table 2 lists some elements to consider in the study design, along with potential sources for question formatting.

Biological material

The study of adverse health outcomes in cancer survivors has largely advanced beyond descriptive reports. State-of-the-science studies are now assessing gene—environment treatment exposure interactions to identify subpopulations at highest risk for a particular outcome and to understand the causative trail leading to the outcome (14, 112, 113). Obtaining, storing, and analyzing genomic DNA is no longer cost prohibitive and should be considered (50). Material can be collected with a 2-mL whole-saliva sample that provides sufficient DNA quantity with high quality DNA for cohort studies (114). Saliva samples can be augmented with blood from those with key adverse outcomes, such as subsequent neoplasms or cardiac events.

Table 2. Additional factors (covariates) to consider

Category	Variable
Time related	Age at time of study or last contact
	Age at time of diagnosis of event of interest
	Age at time of primary cancer diagnosis
	Interval from cancer diagnosis to study
Sociodemographics	Gender
	Race and ethnicity
	Highest level of educational attainment
	Employment status
	Health insurance status
	Household and/or personal income
	Marital status
	Parity and age at first live birth
Lifestyle behaviors	Tobacco use
	Physical activity
	Alcohol use
Psychosocial/quality-of-life	SF-36 quality of life
	Depression and/or anxiety screen
	Fear of cancer
Miscellaneous	Functional status
	Limitations of activity
	Self efficacy

Useful sources of question items:
U. S. National Health Interview Survey (NHIS).
U. S. Behavioral Risk Factor Surveillance System (BRFSS).

Comorbidity scales and precancer comorbidities

Precancer comorbidities, such as ischemic coronary artery disease, can affect cancer outcomes. To account for these factors when comparing different cancer therapies, investigators have used comorbidity scales such as the Charlson Comorbidity Index (115, 116) and the Adult Comorbidity Evaluation-27 (117–119). However, a comorbidity summary score is less useful when studying late adverse outcomes. It is preferable to evaluate the association of specific comorbidities (rather than using a summary score) with different outcomes. For example, preexisting hypertension or diabetes increases the risk of developing radiation-induced cardiovascular disease (120). A recent study comparing irradiated breast cancer survivors with left-sided disease (with exposure of the heart to radiation) and right-sided disease showed that cardiovascular disease risks were especially high among women with left-sided disease and ischemic heart disease before breast cancer (104).

Measures of Risk

Commonly used measures of long-term health outcomes include SIR, AER, SMR, and the cumulative incidence (Table 3). The measure of risk which is appropriate is determined by the research question. In general, the AER is generally thought to be a better indicator of the clinical burden caused by the outcome being studied, because for rare diseases, SIRs can be very high with few excess events. With AER, it is important to consider attained age, because even a moderate excess risk relating to a disease occurring commonly in the underlying general population may give rise to a substantial number of excess cases (e.g., radiation-induced cardiovascular disease as cohorts attain ages beyond 50 years). Cause-specific mortality is another informative, but underutilized, long-term outcome (Fig. 2). Assessing cause-specific mortality can reveal important contributing factors to mortality, such as cardiac or pulmonary disease or second primary cancers, which may be directly or indirectly related to the therapy used for the first cancer (10, 48, 121–124). As discussed above, the major challenge to reporting cause-specific mortality is the accuracy of data attributing the cause of death.

Cumulative incidence is an expression of risk that is relatively easy to interpret clinically (Fig. 1). When calculating cumulative incidence, it is necessary to consider the risk of competing causes of death (i.e., death occurring before the outcome of interest; refs. 125, 126). Statistical methods that censor patients who die as equivalent to those lost to follow-up (e.g., Kaplan–Meier) will overestimate the cumulative incidence of nonfatal health outcomes if the study patients have a high risk of death from competing causes or have prolonged follow-up (18, 127). Similarly, in the calculation of SIR and AER, study patients who die before developing the outcome under study are removed from the risk set. Consequently, long-term SIR and AER estimates apply only to survivors, not to all patients entering the start of the follow-up period. This has implications when counseling newly diagnosed cancer patients about the risks of treatment: because survival outcomes are not known at the time treatment decisions are being made, risk estimates that only apply to survivors are not directly applicable. Such estimates may be more suitable for counseling and managing long-term survivors.

Several studies in cancer survivors used prevalence as an outcome measure because (part of) the cohort was not followed for a substantial portion of the follow-up time, and/or the outcome of interest could not be (accurately) assessed retrospectively, such as in the case of heart failure or pulmonary damage (especially if subclinical damage is considered as well), fatigue, or health-related quality of life (19, 128, 129).

Clinical interpretation of late toxicity risk

Measures of risk are frequently used to describe the late toxicity associated with specific treatments, for example, the risk of second cancers following radiation therapy or

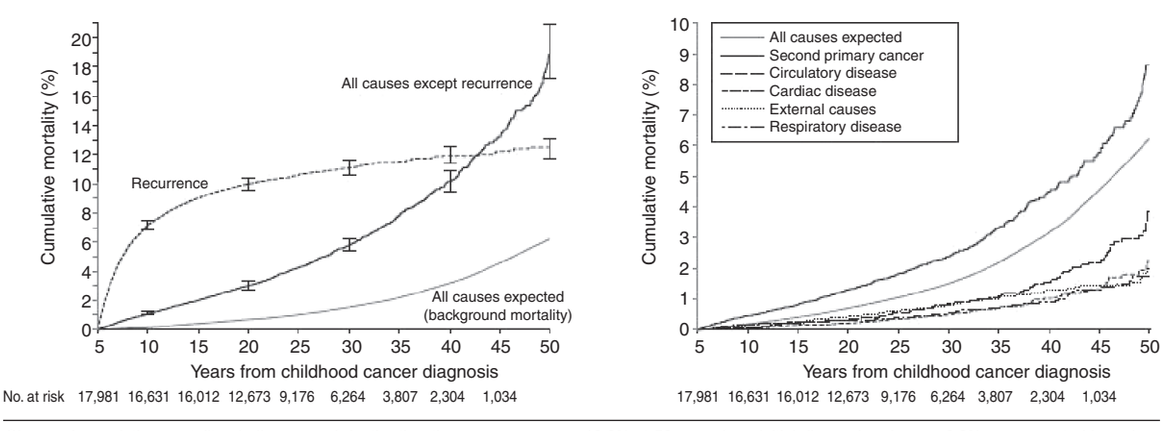
Table 3. Common measures of risk

- SIR: the ratio of the observed number of cases of the outcome of interest to the expected number in an age-, calendar period- and sex-matched general population under observation for a specified interval.
- SMR: the ratio of the observed number of deaths from the outcome of interest to the expected number of deaths based on age-, calendar period-, and sex-specific mortality rates for the country.
- AER: the absolute number of excess cases (i.e., the observed number–expected number divided by person-years at risk times 10,000) or deaths for a given quantity of person-years of follow-up.
- Cumulative incidence: the percent or proportion of the population of interest with a specific outcome by a set point in time (i.e., 20% cumulative incidence of breast cancer by 50 years of age). When calculating the cumulative incidence of a given outcome, it is necessary to consider the risk of competing causes of death (i.e., death occurring before the outcome of interest). Statistical methods designed to evaluate overall survival that censor patients who die as equivalent to those lost to follow-up (e.g., the Kaplan–Meier method) will overestimate the cumulative incidence of nonfatal health outcomes, particularly if the study patients have a high risk of death from competing causes, or have prolonged follow-up.

cardiac disease following anthracycline chemotherapy. Importantly, treatments are nonrandomly assigned with respect both to competing causes of death and other host factors. For example, patients with poor prognosis are generally provided more aggressive treatments and may be more likely to die of the primary disease without experiencing late toxicity; those who do survive after aggressive treatment may experience more late toxicity than their less aggressively-treated counterparts. Consequently, examining the toxicity among 5-year survivors may create the erroneous impression that reduction in treatment intensity will improve the overall outcome. Similarly, clinicians may modify treatments according to host factors known to be associated with the late effect of interest (e.g., age or sex). So, although studies describing the risk of late treatment toxicity are valuable to establish associations between exposure and outcome, and to quantify the risk of adverse events in historically treated patients, quantitative inferences about the impact that treatment modifications may have on long-term outcomes must be taken cautiously.

Innovative analysis of late toxicity data

Innovative analytic methods can help elucidate the biological mechanisms of late toxicity and facilitate better understanding of how treatment modifications may affect the incidence of late toxicity. Regression models that use time-dependent covariates can potentially elucidate the risk associated with exposures that accumulate over time (130–132). De Bruin and colleagues evaluated the duration of intact ovarian function on the risk of second breast cancer among female Hodgkin lymphoma survivors, adjusting for treatment and age (Fig. 3; ref. 18). Longer duration of intact ovarian function increased the risk of



Observed cumulative mortality of all causes of death other than recurrence was 19.0% at 50 years from initial diagnosis, whereas 6.3% was expected based on rates from the general population. Cumulative mortality of death due to recurrence increased rapidly with time from diagnosis to 8.9% by 15 years but then leveled off to 12.4% by 50 years. Cumulative mortality for each cause of death takes into account other causes of death as a competing risk. For second primary cancer, cumulative mortality increased gradually with time to 2.4% by 30 years but then increased rapidly to 8.6% by 50 years. For circulatory disease, the cumulative mortality was low by 30 years (0.8%) but increased to 3.9% by 50 years. Segment of y-axis shown in blue indicates cumulative mortality range of 0% to 10%. Error bars indicate 95% CIs.

Figure 2. Cumulative mortality of causes of death among survivors of childhood cancer (reprinted from Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. JAMA. 2010;304:172–9; used with permission).

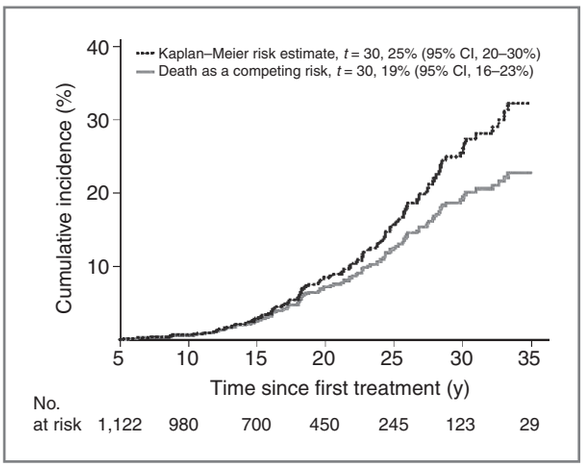


Figure 3. The cumulative incidence of breast cancer after Hodgkin lymphoma (reprinted from De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol. 2009;27:4239–46; used with permission).

breast cancer, suggesting a potential role for endogenous estrogens in the promotion of second breast cancer risk. The use of time-dependent covariates in multivariate models is appropriate in the evaluation of many health outcomes with risk factors that have cumulative effects over time (130–132). In practice, however, the collection of adequate exposure data is often not possible as medical records or administrative health data frequently do not include duration of relevant exposures.

As mentioned above, comparing the late toxicity associated with different treatments may be complicated by potential selection bias caused by the nonrandom assignment of treatment. Propensity score analyses may be useful to balance comparison groups with respect to known factors associated with treatment assignment (133). Propensity score analyses create logistic regression models with treatment exposure as the dependent variable, and known factors associated with the use of that treatment as the independent variables. Each patient can then be assigned a score that describes the probability of receiving that treatment, known as the propensity score. This score can then be used for stratification, matching or regression to facilitate comparison of outcome among exposed versus nonexposed patients who are balanced with respect to factors related to treatment (133). This approach can be superior to regression models by excluding patients who are never treated or always treated and focusing analyses on patients for whom there is true variability in the assignment of treatment. Notably, propensity score analyses are not a substitute for true randomization, which balances both known and unknown prognostic variables. These methods have been used recently to evaluate second cancer risk following treatment for nonseminomatous germ cell tumors (134).

One major limitation of epidemiologic studies of late adverse health outcomes is the necessity of waiting for a long interval before evaluating the late effect of interest. As a result, the risks described may apply to outdated treatments and be of limited relevance to newly diagnosed patients. However, as the relationship between normal tissue radiation exposure and second cancer risk is better understood, radiobiological models based on normal tissue radiation dosimetry are emerging as a means of predicting the second cancer risk associated with different contemporary radiotherapy treatments. Historically, these models have been based on extrapolations of the organ-specific dose-risk curves seen among atomic bomb survivors. More recently, models have incorporated data with regard to the risk associated with normal tissue exposures in the 5 to 40 Gy range to predict second cancer risks associated with different field sizes and doses (135), and different radiotherapy modalities (e.g., protons and photon intensity-modulated radiotherapy; refs. 136–139) for Hodgkin lymphoma treatment. The major limitation of these models is the relative absence of clinical validation. In addition, the CIs around second cancer risk estimates that are based primarily on radiation exposure are wide due, in part, to the significant variation in second cancer outcome among patients receiving comparable radiation therapy, presumably caused by unmeasured biological factors (140). Moreover, many studies that employ models report only differences in predicted excess relative risk between treatments and do not account for competing causes of death, limiting clinical utility.

Guidelines for the reporting of observational studies

Recognizing that observational studies provide critical insights into the effectiveness and toxicity of medical interventions, guidelines on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) have been published. The STROBE Statement provides recommendations about the reporting of observational studies (study design, inclusion criteria, statistical methods, etc; ref. 141). These guidelines, endorsed by the International Committee of Medical Journal Editors, are intended to facilitate the accurate and clear communication and interpretation of study results, but are not meant to prescribe appropriate study methods or rate the quality of research (141, 142).

Summary

In summary, we have attempted to cover, with brevity, a complex and evolving area of research and to offer our collective research experience to assist the reader in considering study design, approaches to ascertain primary outcomes and key covariates, and understanding the nuances of risk estimates.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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