Minireview

The Epidemiology of Second Primary Cancers

Lois B. Travis
Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Bethesda, Maryland

Abstract

Background: Due to improvements in early detection, supportive care, and treatment, the number of cancer survivors in the United States has tripled since 1971 and is growing by 2% each year. In 2001, there were ~10 million cancer survivors, representing 3.5% of the population. As survival after a diagnosis of cancer improves, quantification of the late effects of cancer and its therapy become critical. One of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. Second- or higher-order cancers now account for ~16% of incident cancers reported to the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. Subsequent neoplasms may not necessarily be attributable to prior cancer treatment but may also reflect the effect of shared etiologic factors, environmental exposures, host characteristics, and combinations of influences, including gene-environment and gene-gene interactions.

Methods/Results: This review will focus on selected highlights and recent findings in treatment-associated malignancies, with an emphasis on survivors of adult cancer. Current study methods will also be summarized.

Conclusions: Important opportunities for future research include the prospective identification of patient subgroups that might be at heightened susceptibility of developing therapy-associated second cancers to modify planned treatments or select alternative management strategies. For the burgeoning population of cancer survivors treated successfully with past regimens, including those therapies that have been subsequently refined, continued quantification of late effects, including second cancers, remains highly relevant in terms of raising clinician and patient awareness, for informed counseling, and for the development of risk-adapted long-term management strategies.

Introduction

Due to improvements in early detection, supportive care, and treatment, the number of cancer survivors in the United States has tripled since 1971 and is growing by 2% each year (1). In 2001, there were ~10 million cancer survivors, representing 3.5% of the U.S. population. The 5-year relative survival rate among all cancer patients is now 66% (2). As survival after a diagnosis of cancer improves, identification and quantification of the late effects of cancer and its therapy have become critical. One of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. The number of patients with multiple primary cancers is growing rapidly, with independent malignancies comprising ~16% (or 1 in 6) incident cancers reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program in 2003 (2). Moreover, second solid tumors are a leading cause of mortality among several populations of long-term survivors, including patients with Hodgkin lymphoma (3). Second cancers can reflect the late sequelae of treatment as well as the effect of lifestyle factors, environmental exposures, host factors, and combinations of influences, including gene-environment and gene-gene interactions (4). Travis et al. (5) recently grouped second primary cancers into three major categories according to predominant etiologic influences (i.e., treatment-related, syndromic, and those due to shared etiologic factors), emphasizing the nonexclusivity of these groups. Because multiple primary cancers were recently comprehensively reviewed (4, 6, 7), with directions for future research summarized earlier this year (5), the current minireview will focus on selected highlights and recent findings in treatment-associated malignancies, with an emphasis on survivors of adult cancer; methodologic issues involved in these studies will also be summarized. Second tumors among childhood cancer survivors were recently described by Bhatia (8). Syndromic cancers were described in detail earlier (5) and are now summarized in the accompanying minireview by Vogel (9) together with early detection strategies. Mayne and Cartmel (10) examine chemoprevention approaches for second primary cancers.

Methods to Evaluate Second Cancer Risk

Cohort Studies. Two classic epidemiologic study designs (cohort and case-control methods) have been used in most studies of therapy-related cancers (11). In a cohort study, a group of cancer patients is identified by means of clearly specified inclusion criteria [e.g., all 1-year survivors of testicular cancer reported to designated population-based cancer registries (12)]. These patients can then be either retrospectively or prospectively followed for the occurrence
of second cancers. Sources of cohort studies include population-based cancer registries, such as the NCI Surveillance, Epidemiology, and End Results Program. Strengths of these registries include the sizable numbers of subjects, which allows detection of even small second cancer risks and the opportunity to describe in detail the effect of latency, sex, and age at first and at second cancer diagnosis (12). In addition, the observed and expected numbers of second cancers are derived from the same population. The population-based nature of the registries averts the problem of selection or referral bias that may confound clinical series. A major drawback of these registries, however, is that cancer therapy data are quite limited, usually comprising only the initial course of therapy, and then in terms of broad categories, such as radiotherapy or chemotherapy. There are no data available either for radiotherapy fields or for the names and doses of cytotoxic drugs. Moreover, information on subsequent treatment is not collected. Although underascertainment of second cancers can result from migration of subjects from Surveillance, Epidemiology, and End Results Program areas, this is an almost negligible concern in nationwide registries, such as those in Scandinavia. Data derived from population-based registries permit a powerful evaluation of site-specific second cancer risk according to a variety of relevant variables and enable observation of trends in risk over time as cancer treatments evolve (13). Registries also serve as an ideal setting for nested case-control studies in which comprehensive evaluations of treatment effects, including delineation of dose-response relations with radiation and cytotoxic drugs, can be undertaken.

Other sources of patient cohorts in which second cancer risk can be determined include hospital-based tumor registries and clinical trials. Hospital-based tumor registries offer the advantage of detailed patient information, although inconsistent follow-up, administration of a variety of treatments, and underascertainment of second cancers can limit the usefulness of these sources. If follow-up is more complete for patients with second cancers than for those who remain well, exaggerated risks result. Strengths of clinical trial data include the availability of detailed information for protocol therapies and the potential for direct comparisons between treatment effects for second cancer risk in randomized groups of patients. Weaknesses include the lack of information on off-protocol therapy, limited follow-up, and frequently incomplete ascertainment of long-term adverse events, including second cancers. The relatively small number of patients in many trials also does not allow sufficient statistical power to accurately evaluate long-term treatment sequelae.

Several straightforward risk measures can be estimated from cohort studies. A commonly used comparison in relation to the general population is the observed to expected ratio (or standardized incidence ratio) of second cancers. Person-years of observation in the cohort, stratified by age, sex, calendar year, etc., are used to estimate the expected numbers of second cancers based on cancer incidence rates in the general population. The observed number of second cancers is then compared with the number expected. A second type of calculation is the absolute excess risk, which is estimated by subtracting the expected number of second cancers from the observed number, dividing by the person-years at risk, and then multiplying by 10,000. To allow for more careful adjustment of the effects of age at first and second cancer diagnosis, latency, and calendar year considerations, multi-variable statistical methods have been successfully used (12).

Even a large standardized incidence ratio can translate into small absolute risks if the second cancer is rare in the general population. For example, in an international registry-based study of Hodgkin lymphoma (14), the absolute excess risk of acute myelogenous leukemia (AML) was ~6 excess cases per 10,000 patients yearly, whereas the standardized incidence ratio was >20. Thus, the absolute excess risk is particularly useful in showing which second cancers account for the greatest disease burden in a population and permits a ready comparison with other late sequelae.

Another means to measure risk in cohort studies involve actuarial approaches in which censored data methods are used to evaluate in-cohort risk (e.g., the proportion of patients in whom a second cancer is diagnosed in a specified time period). A standard measure is the cumulative absolute risk, in which methods that allow for competing risks (15) should be incorporated, because a patient may die of another cause before a second cancer is diagnosed. Even with actuarial estimation procedures, second cancer risk can still be overestimated if follow-up is more complete for cancer patients with complications than for those who remain well.

Case-Control Studies. Nested case-control studies of cancer survivors offer an efficient approach to examine in detail the role of treatment in second cancer risk, including quantification of the dose-response relation with radiation or cumulative drug dose (16, 17). With this type of design, the occurrence of second cancers (cases) is ascertained in a well-defined cohort of cancer survivors. Controls are a stratified, random matched sample of subjects without a second cancer derived from the same cohort. Treatments between cases and matched controls are then compared. A weakness of case-control studies is that statistical methods require specification of a reference category. An optimal group would be nonexposed patients; however, this choice is typically unavailable. One approach is to select patients managed with surgery only or a low-dose exposure group, bearing in mind that, with the latter choice, the estimates may be diminished. An alternative, successful approach is to use continuous variables (e.g., radiation dose) to model second cancer risk (18). A potential disadvantage of nested case-control studies is overmatching. In general, the intent of matching is to ensure comparability of cases and controls on confounders. Overmatching occurs when a matching factor is not a confounder, such as cancer stage, because stage commonly determines therapy. The drawbacks of overmatching include lessened statistical power to detect associations and larger standard errors. A bias in the relative risk estimates should not occur.

Treatment-Related Leukemias

Both chemotherapy and radiotherapy can induce AML, although risks after the administration of cytotoxic drugs are considerably higher. At least two syndromes of chemotherapy-related AML have been described (19). Following treatment with alkylating agents, leukemia risk begins to increase at 1 to 2 years, peaks at 5 to 10 years, and then decreases. Many times there is a preceding myelodysplastic syndrome. Typical chromosomal abnormalities frequently include unbalanced translocations or deletions involving portions of chromosome 5 and/or 7 consisting of loss of all or part of the long arm of the chromosome. Alkylating agents that induce human leukemia include busulfan, carbustine, chlorambucil, cyclophosphamide, dihydroxybusulfan, lonustine, melphalan, prednimustine, and semustine (reviewed in ref. 6). The risk of alkylating agent-related AML typically increases with increasing cumulative dose or duration of therapy. It is not clear whether procarbazine, which also has an underlying mechanism of action similar to alkylating agents, is associated with human leukemia (reviewed in ref. 6). Leukemias that follow alkylating agent therapy are generally refractory to
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treatment and associated with poor survival (20). Recently, Ng et al. (21) showed in a large series that the median survival after the development of acute leukemia among Hodgkin lymphoma patients was only 0.4 year, with a 5-year relative survival rate of 4.9% (0.0-14.2%).

In the past, the platinum compounds have generally not been considered human leukemogens despite their formation of intrastrand and interstrand DNA cross-links similar to bifunctional alkylating agents. In recent studies of patients treated with platinum-based regimens for ovarian cancer (22) or testis cancer (23), however, cumulative dose of cisplatin was associated with significantly increased risks of leukemia in multivariable analyses that took into account other treatment factors. In the largest study to date of secondary lymphoma patients was only 0.4 year, with a 5-year relative survival rate of 4.9% (0.0-14.2%).

Relative risks for cumulative platinum doses of <500, 500 to 749, 750 to 999, and ≥1,000 mg were 1.9, 2.1, 4.1, and 7.6, respectively (P trend < 0.001). A multivariate model that adjusted for cumulative amount of cyclophosphamide and doxorubicin did not provide a better fit to the data than a model that took into account only categories of cumulative platinum doses. Risk also increased with duration of platinum-based chemotherapy, with a relative risk of 7.0 among women who were treated for >12 months (P for trend = 0.001). Women who received radiotherapy and platinum-based chemotherapy had a significantly higher risk than women who received platinum alone (P = 0.006) in a multivariate model that adjusted for cumulative amount of drug. It was estimated that, among 10,000 women with ovarian cancer treated for 6 months with a cumulative dose of 500 to 1,000 mg cisplatin or >1,000 mg and followed for 10 years, an excess of 21 and 71 cases of leukemia, respectively, might be expected.

Topoisomerase II inhibitor-related AML develops after treatment with cytotoxic drugs that target DNA topoisomerase II, particularly the epipodophyllotoxins etoposide and teniposide. Evidence also suggests that the antirhynctines doxorubicin and epipodophyllotoxins may be associated with this type of leukemia (reviewed in ref. 19). These leukemias tend to have a shorter induction period, with a median latency of only 2 to 3 years after the last drug exposure, usually monoblastic or myelomonocytic, and balanced chromosomal translocations occur, frequently involving 11q23 (the MLL gene), typically t(9;11), t(11;19), and t(6;11) or 21q22. It seems that patients who develop topoisomerase II inhibitor-related AML usually respond to therapy comparably with patients who develop de novo leukemia of the same subtype (24), although additional follow-up is recommended to reliably evaluate long-term survival (19).

The spectrum of chemotherapy-related leukemias includes acute lymphoblastic leukemia, which has been reported after topoisomerase II inhibitors, and frequently shows a t(4;11)(q21;q23) chromosomal translocation (19). Although chronic myelogenous leukemia has been included in several analytic studies in which associations with prior chemotherapy have been evaluated (22, 25, 26), independent estimates of risk have not been calculated. Whether the administration of hematopoietic colony-stimulating factors in the setting of intensive chemotherapy may further increase the risk of secondary AML (27) deserves additional evaluation.

Leukemia following chemotherapy for Hodgkin lymphoma is perhaps the most comprehensively studied treatment-associated malignancy. The largest analytic investigations to date (28-32) collectively show that combination chemotherapy that includes mechlorethamine and procarbazine, frequently given with vincristine and prednisone in the MOPP regimen (33), is associated with the largest risks of leukemia. Estimates of the overall relative risk, the most common measure presented, range from 3.5 to ~24 and are typically estimated compared with patients given radiotherapy only. The relative risk of leukemia increases both with increasing cumulative dose and with increasing number of cycles of MOPP. The cumulative risk of leukemia 15 years following treatment with MOPP ranges from 3.4% to 9.5%, whereas the cumulative risk after treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is much smaller, ranging from 0.7% to 1.3%. The risk of leukemia following MOPP/ABVD combination regimens seems intermediate, with a 10-year cumulative risk of 2.1%.

The risk of leukemia following radiation is considerably smaller than after chemotherapy, frequently on the order of 1-2-fold. Leukemia risk is usually greatest about 5 to 9 years after radiotherapy exposure and then slowly declines. Radiation-related leukemia risk is a function of dose to the active bone marrow, dose rate, and percentage of exposed marrow (reviewed in ref. 6). The excess risk of leukemia per unit of radiation dose is considerably larger at low doses than at high doses due to cell killing at higher doses (34). Thus, many studies in cancer patients have confirmed that high radiation doses to limited fields are associated with little or no increased risk of leukemia (34). In contrast, exposure of larger volumes of bone marrow to radiotherapy may result in considerably higher risks as shown in breast cancer patients treated with past radiation treatments to chest, abdominal, and pelvic fields, with resultant 11-fold risks of leukemia (23). Low-dose total body irradiation [e.g., as previously used for non–Hodgkin lymphoma (reviewed in ref. 35)] has also been associated with high risks of leukemia. Radiation has been associated with increased risks of AML, chronic myelogenous leukemia, and acute lymphoblastic leukemia. Only chronic lymphocytic leukemia has not been linked with either prior radiotherapy or chemotherapy.

Therapy-Associated Solid Tumors

Radiotherapy induces solid tumors, with increased risks reported at numerous sites (34). A ranking of various tissues with respect to the carcinogenic influence of radiation was provided by Boice (Table 1; ref. 36). Organs that are particularly sensitive to the carcinogenic effects of radiation include breast and thyroid. In contrast to secondary leukemias, the latency period of therapy-associated solid tumors is usually much longer, typically ≥10 years. Despite the lower relative risks usually observed for treatment-related solid tumors, they typically account for the largest absolute burden of second cancers. In fact, breast cancer has emerged as the most common solid tumor among female survivors of Hodgkin lymphoma (14). Excess breast cancers, which are largely due to high-dose, large-field chest irradiation for Hodgkin lymphoma, are inversely correlated with age at treatment. The highest risks are observed among women treated for Hodgkin lymphoma at age <30 years (reviewed in ref. 37), a finding that parallels the known sensitivity of the breast to ionizing radiation in the young (38). To date, there has been one large analytic, international investigation of Hodgkin lymphoma patients that estimated long-term risk according to radiation dose to the area in the breast where cancer was later diagnosed and that took into account chemotherapy- or radiotherapy-related ovarian damage. This multicenter study (16) was conducted by the NCI and population-based cancer registries in Iowa, Ontario, Denmark, Finland, the Netherlands (17), and Sweden. Within a cohort of 3,817 1-year female survivors of Hodgkin lymphoma diagnosed at age <30 (1965-1994), 105 cases of breast cancer were
Table 1. Ranking of various tissues regarding carcinogenic influence of low-linear energy transfer radiation

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Range of estimates</th>
<th>Comment</th>
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<tbody>
<tr>
<td></td>
<td>Relative risk at 1 Gy</td>
<td>Excess risk $\times 10^4$ person-Gy</td>
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<tr>
<td>Cancers frequently associated with radiation with authoritative risk estimates</td>
<td></td>
<td></td>
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<tr>
<td>Leukemia</td>
<td>1.2-5.4</td>
<td>0.5-2.7</td>
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<tr>
<td>Thyroid</td>
<td>1.3-3.5</td>
<td>0.4-9.1</td>
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<tr>
<td>Female breast</td>
<td>1.1-3.4</td>
<td>0.1-9.1</td>
</tr>
<tr>
<td>Cancers occasionally associated with robust risk estimates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1.0-2.0</td>
<td>0.0-0.6</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.0-1.5</td>
<td>0.0-0.7</td>
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<tr>
<td>Colon</td>
<td>1.0-1.7</td>
<td>0.0-3.2</td>
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<tr>
<td>Esophagus</td>
<td>1.2-1.8</td>
<td>0.2-0.6</td>
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<tr>
<td>Bladder</td>
<td>1.1-1.8</td>
<td>0.1-1.0</td>
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<tr>
<td>Ovary</td>
<td>1.0-2.3</td>
<td>0.1-0.7</td>
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<tr>
<td>Brain and nervous system</td>
<td>1.0-5.1</td>
<td>0.0-2.1</td>
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<tr>
<td>Liver</td>
<td>1.0-1.5</td>
<td>0.0-0.1-1.6</td>
</tr>
<tr>
<td>Cancers rarely associated with radiation with uncertain risk estimates*</td>
<td></td>
<td></td>
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<tr>
<td>Kidney</td>
<td>1.0-1.7</td>
<td>0.0-0.1</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>1.1-1.7</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.0-5.2</td>
<td>0.0-0.9</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1.0-2.0</td>
<td>0.1-2.5</td>
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<tr>
<td>Skin</td>
<td>1.0-2.0</td>
<td>0.1-2.5</td>
</tr>
<tr>
<td>Rectum</td>
<td>1.0-1.2</td>
<td>0.0-0.1</td>
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<tr>
<td>Uterus</td>
<td>1.0-1.01</td>
<td>0.0-0.5</td>
</tr>
<tr>
<td>Bone</td>
<td>1.0-1.1</td>
<td>0.0-0.2</td>
</tr>
<tr>
<td>Connective tissues</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Cancers never or sporadically associated with radiation with no risk estimates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>†</td>
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<tr>
<td>Pancreas</td>
<td>†</td>
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<tr>
<td>Hodgkin lymphoma</td>
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<tr>
<td>Prostate</td>
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<td>Testis</td>
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<tr>
<td>Cervix</td>
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<tr>
<td>Certain childhood cancers‡</td>
<td>†</td>
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</tr>
<tr>
<td>Supporting tissues of skeleton¹</td>
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</tbody>
</table>

NOTE: Modified with permission from Boice (36).

*Association is inconsistently found and/or available estimates of risk are highly uncertain.

†No reliable estimates available.

‡Sites for which radiation-induced cancers have not yet been reported or confirmed: retinoblastoma, Wilms’ tumor, neuroblastoma, and others of embryonic origin.

¹Muscles, tendons, and synovial membranes of joints.

identified and matched to a stratified, random sample of women with Hodgkin lymphoma who did not develop breast cancer. Statistical analyses were conducted to estimate the relative risk of breast cancer in terms of radiation dose to site of breast cancer and to the ovaries, cumulative dose of alkylating agent chemotherapy, and other risk factors. A radiation dose to the breast $\geq 4$ Gy was followed by a significantly increased 3.2-fold risk of breast cancer compared with women who received lower doses to the breast without alkylating agents. Risk of breast cancer increased with increasing radiation dose to reach 8-fold at $>40$ Gy ($P$ trend for dose $<0.001$). Excess radiotherapy-related breast cancers occurred for $>25$ years after exposure, with a statistically significant trend ($P = 0.03$) with radiation dose still evident. Radiotherapy combined with alkylating agents conferred a nonsignificant 1.4-fold risk of breast cancer, whereas treatment with alkylating agent chemotherapy alone was associated with a 40% reduction in risk. The risk of breast cancer decreased sharply with an increasing number of cycles of alkylating agent chemotherapy. A 50% decrease in breast cancer risk was also apparent following a dose of $\geq 5$ Gy to the ovaries. Reductions in risk were in accord with the proportion of women who experienced treatment-related menopause. The occurrence of menopause before age 40 years was associated with a significant decrease in breast cancer risk compared with women who remained premenopausal. The importance of hormonal stimulation on breast cancer risk following Hodgkin lymphoma chest radiotherapy was shown even more strongly in a separate report of the Dutch patients (17), for whom detailed information on number of years of menstruation after Hodgkin lymphoma treatment had been gathered.

In a thoughtful editorial, Yahalom (39) concluded that the results of the international study (16) implied that the smaller radiotherapy fields and lower doses now used to treat Hodgkin lymphoma should eventually result in lower risks of breast cancer. Before the publication of these studies (16, 17), there had been no convincing evidence to suggest that recent treatment modifications for Hodgkin lymphoma might translate into decreased long-term risks of solid tumors. In particular, the shape of the radiation dose-response relation for breast cancer was not clear, especially at large doses, where it had been postulated that cell-killing effects might produce smaller risks (38). Although these investigations (16, 17) imply that radiotherapy dose reduction in Hodgkin lymphoma may result in smaller breast cancer risks, long-term follow-up will be required to determine the degree to which risks can be reduced and the influence of modifying factors.

In the interim, increasing awareness of the large risk of breast cancer following therapy for Hodgkin lymphoma at a young age has created a need for informed counseling. However, estimates of the cumulative absolute risk of breast cancer among young women treated for Hodgkin lymphoma at age $\leq 30$ years have been sparse and inconsistent, spanning 4.2% to 34% at 20 to 25 years after therapy (40-43). Most
estimates have not taken into account the influence of alkylating agent therapy, which can lower breast cancer risk (16, 17), or the effect of competing causes of mortality (15). Accurate projections of breast cancer risk, as available for women in the general population (44), are important to evaluate the disease burden among the growing population of Hodgkin lymphoma survivors treated with regimens of the past and to facilitate the development of risk-adapted long-term follow-up recommendations. Estimates of the cumulative absolute risk of breast cancer among women treated for Hodgkin lymphoma at age ≥30 years were recently provided in terms of measures of radiation dose and chemotherapy, which are available from medical records (37). The estimates also took into account age and calendar year of Hodgkin lymphoma diagnosis, age at counseling, baseline breast cancer incidence rates, and competing causes of mortality. For example, for a Hodgkin lymphoma survivor who was treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, estimated cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4%, 11.1%, and 29.0%, respectively. Cumulative absolute risks were lower in women also treated with alkylating agents. In comparison, in the general population, the absolute risks of breast cancer in white women from age 20 years to ages 30, 40, 50, and 60 years are 0.04%, 0.5%, 2.0%, and 4.3%, respectively. The researchers (37) cautioned that the risk estimates are most relevant for Hodgkin lymphoma survivors treated with past regimens and should be used with considerable caution in patients treated with more recent approaches, including limited-field radiotherapy and/or ovary-sparing chemotherapy. As the number of cancer survivors grows, there will be a critical need for the provision of these types of estimates for various types of second cancers, according to treatment for the first cancer, even if standard therapy has since been refined. Thus, quantification of late effects, including second cancers, for successful therapies of the past remains highly relevant for long-term cancer survivors and health care providers.

Few data describe survival after diagnosis of a secondary solid tumor. The majority of information to date derives from patients with Hodgkin lymphoma. Survival according to type of secondary solid tumor (n = 131) was recently described among 1,319 Hodgkin lymphoma patients by Ng et al. (21). Median survival was 4.3 years, with a 5-year overall survival rate of 42.1% (95% confidence interval, 31.6-52.5). The poorest prognosis was observed for patients who developed lung cancer (n = 22 cases), who had a median survival of 1 year. The 5-year survival rate after development of a secondary gastrointestinal cancer (n = 24) was 12.4% (median survival, 1.9 years). For women who developed breast cancer (n = 39), the 5-year overall survival estimate was more favorable (76.1%), and the median survival time had not yet been reached. It is clear that additional studies are needed to describe survival after a second cancer diagnosis compared with de novo cancer in the general population and to describe covariates (e.g., patient age, stage, and antecedent treatment) that might account for any differences as well as genetic features (7).

Important issues for future research include delineation of the association between radiation dose and solid tumor excesses in the high-dose range, description of the long-term site-specific temporal patterns of radiation-associated cancer, and a better understanding of the interaction of radiotherapy with other factors, such as lifestyle influences (e.g., tobacco use) and genetic susceptibility (reviewed in refs. 4, 5, 7). Patients treated with newer radiation modalities, including radiation-induced monoclonal antibodies, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and stereotactic radiosurgery, should also be followed for possible late effects (reviewed in ref. 4).

A major unresolved issue in second cancer research is the extent to which chemotherapy can induce solid tumors, given the established carcinogenicity of cytotoxic drugs in laboratory animals (45). A small elevation in the relative risk of a frequently diagnosed human solid tumor translates into a substantially greater effect in the population than a similar elevation in leukemia, an infrequent cancer. Recently reported findings include dose-response relations between mechlorethamine and procarbazine to treat Hodgkin lymphoma and lung cancer risk, controlling for both tobacco use and radiotherapy dose (46). Other solid cancers that show a dose-dependent relation with cytotoxic drugs include bladder cancer (47) and bone sarcomas (48). A highly significant relationship (P trend for dose = 0.004) between increasing cumulative amount of cyclophosphamide and increasing bladder cancer risk was shown in a study of survivors of non–Hodgkin lymphoma, in whom risks reached 15-fold at total doses of ≥50 g (47). Hawkins et al. (48) showed that the risk of bone sarcomas increased linearly with increasing cumulative dose of alkylating agents given to treat childhood cancer. Important questions for future research include identification of susceptible organs, the magnitude and time-dependent nature of excess risk, the roles of age at exposure and attained age (12), gender, initial cancer type, and underlying host susceptibility.

The interaction of chemotherapy with radiation or other risk factors in the development of solid tumors should also be investigated further. For example, smoking multiplies the risk of either alkylating agent-associated (18, 46) or radiotherapy-associated (18, 46, 49) lung cancer. In contrast, the effect of chemotherapy and radiation on lung cancer risk after Hodgkin lymphoma seems additive (18, 46) as does the effect of cyclophosphamide and radiation on excess bladder cancers after non–Hodgkin lymphoma (47). Other relevant questions include the effect of the sequence and timing of exposures and interactions with other risk factors. Further, it will be important to understand whether relations between cytotoxic drugs, radiation, and solid tumor risk represent either an independent carcinogenic effect or radiosensitization by the chemotherapeutic agent, possible drug interference with the repair of radiation-induced DNA damage (50), or a combination of these and other possible mechanisms (reviewed in ref. 4).

Comment

There has been substantial progress in the description of treatment-related second cancers, but less so with regard to the quantification of dose-response relations with radiation and chemotherapy. Moreover, few data exist with regard to underlyling molecular mechanisms (7). It would seem logical to be able to prospectively identify patient subgroups that might be at heightened susceptibility of developing therapy-associated second cancers (or other adverse effects) to modify planned treatment approaches or select alternative management strategies. The meticulous measurement and recording of potentially carcinogenic exposures (chemotherapy and radiotherapy) provide an ideal research setting for the investigation of gene-environment and gene-gene interactions. Until recently, however, there was little consensus on either the infrastructure or design approaches needed to comprehensively investigate the molecular mechanisms of second cancers. Earlier this year, Travis et al. (5) provided recommendations on the research agenda, study design
conclusions, and infrastructural requirements needed to further our knowledge of the underlying genetic mechanisms of second primary cancers and thus to also provide the foundation for evidence-based strategies for patient management and possible intervention measures. The recommendations (Table 2) were based on the proceedings of a NCI-sponsored workshop, which included a transdisciplinary group of experts in the fields of epidemiology, statistics, molecular genetics, clinical genetics, pharmacogenomics, informatics, radiation biology, medical oncology, pediatric oncology, and radiation oncology and the advocacy community. The identified research priorities included (a) development of a national research infrastructure for studies of cancer survivorship; (b) creation of a coordinated system for biospecimen collection; (c) development of new technology, bioinformatics, and biomarkers; (d) design of new epidemiologic methods; and (e) development of evidence-based clinical practice guidelines. It was emphasized by workshop participants that many of the infrastructure resources and design strategies that would support second cancer research also provide an appropriate foundation for the investigation of other nonneoplastic adverse sequelae of cancer and its treatment. Given the burgeoning number of cancer survivors, research studies on behalf of these subjects assume significant public health importance and were highlighted as a major objective in the NCI Strategic Plan for FY2007 (51).

In the interim, research progress over the last few decades has made it possible to identify those treatment regimens that are associated with high risks of second cancers. Although individual susceptibility factors remain largely unknown, groups of exposed patients can still be selected for close monitoring. Whenever effective screening methods (e.g., mammographic examination) are available, these should be included in patient follow-up. It is clear, however, that, in the absence of evidence-based recommendations for many second primary cancers (5), screening methods need to be tested among survivor populations to determine when screening should be initiated, frequency of screening, and corresponding attributes of the test modality (i.e., sensitivity, specificity, and predictive value; ref. 9). Preventive strategies (e.g., smoking cessation and avoidance of UV light) may also diminish the risk of selected second cancers, and cancer survivors should be encouraged to adopt practices consistent with a healthy lifestyle. Although cancer treatment represents a double-edged sword (52), it should be kept in mind that many new treatments have been accompanied by sizable improvements in patient survival. Thus, the benefits associated with many cancer treatments greatly exceed the risk of developing a second primary cancer. Further, as noted above, it should always be kept in mind that subsequent neoplasms may not necessarily be attributable solely to prior cancer treatment but may also reflect the effect of shared etiologic factors, environmental exposures, host characteristics, and combinations of influences, including gene-environment and gene-gene interactions.

Acknowledgments

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References


Table 2. Workshop recommendations for future research: genetic susceptibility and second primary cancers

1. Develop research infrastructure for studies of cancer survivorship
   Institute a systematic, national approach to develop research infrastructure for studies of genetic modifiers of late effects of cancer treatment, including second malignancies.
   Provide for rigorous ascertainment of multiple primary cancers with clinical annotation, detailed treatment data, and biospecimen collection.
   Establish multicenter cohorts of cancer survivors, with recruitment of transdisciplinary research teams dedicated to research the late effects of therapy.
   Expand the capacity of NCI cooperative groups to ascertain and study long-term outcomes in clinical trial populations, in support of survivorship research.

2. Create a coordinated system for biospecimen collection
   Standardize biospecimen collection, laboratory procedures, and documentation for blood and other DNA sources, normal tissue from target organs, and tumor tissue.
   Develop a centralized biospecimen repository or a tracking system ("virtual repository") to permit sample retrieval from multiple storage centers. Institute mechanisms for scientific review of specimen use and administrative procedures for specimen control.
   Support methodologic research to enhance the quality and lower the cost of biospecimen collection, processing, storage, and distribution.

3. Promote the development of new technology, bioinformatics, and biomarkers
   Identify new technologies for the analysis of germ-line and somatic genetic alterations to determine their contributions to second cancer risk.
   Reduce the amount of tissue and DNA needed for various assays, with standardization of protocols for whole genome amplification.
   Develop molecular profiles of tumors that incorporate analyses of etiologic pathways and therapeutic targets related to second cancers and other late outcomes.

4. Support the development of new epidemiologic methods
   Develop efficient epidemiologic study designs to investigate the role of genetic susceptibility to multiple primary cancers, including genetic modifiers of risk associated with treatment effects or other etiologic factors.
   Develop optimal approaches for selection of controls for case-control studies in which both treatment and genetic susceptibility play important roles.
   Include a biospecimen component in all study designs.

5. Develop evidence-based clinical practice guidelines
   Implement pilot studies of interventions to prevent second cancers within genetically defined, high-risk groups of patients.
   Integrate smoking cessation programs into research designs.
   Support research to provide evidence-based follow-up care for cancer survivors.

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Lois B. Travis


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