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Solid Tumor Second Primary Neoplasms: Who is at Risk, What Can We Do?

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Abstract

Eighteen percent of incident malignancies in the U.S. are a second (or subsequent) cancer. Second primary neoplasms (SPN), particularly solid tumors, are a major cause of mortality and serious morbidity among cancer survivors successfully cured of their first cancer. Multiple etiologies may lead to a cancer survivor subsequently being diagnosed with an SPN, including radiotherapy for the first cancer, unhealthy lifestyle behaviors, germline and somatic mutations, aging, or an interaction between any of these factors. In this article, we discuss these factors and synthesize this information for use in clinical practice, including preventive strategies and screening recommendations for SPNs.

Introduction

It has been estimated that 18% of incident malignancies in the U.S. are a second (or subsequent) cancer.¹ Second primary neoplasms (SPN), particularly solid tumors, are a major cause of mortality and serious morbidity among cancer survivors successfully cured of their first cancer. Multiple etiologies may lead to a cancer survivor subsequently being diagnosed with an SPN, including radiotherapy for the first cancer, unhealthy lifestyle behaviors, germline and somatic mutations, aging, or an interaction between any of these factors. In this article, we discuss these factors and synthesize this information for use in clinical practice, including preventive strategies and screening recommendations for SPNs.

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For more information, the reader is referred to a comprehensive chapter on second primary cancers by Travis et al.²

Radiotherapy-associated solid tumor SPNs

The relationship between therapeutic radiation and the risk of solid tumor SPNs has been long recognized. Indeed, this topic was discussed by Dr. George Hutchison³ at the first ‘late effects’ conference convened by the National Cancer Institute - the *Conference on the Delayed Consequences of Cancer Therapy: Proven and Potential* - held in 1975. Studies have shown an excess risk of the following types of neoplasms in patients treated with radiotherapy: central nervous system tumors; head and neck squamous cell carcinoma, digestive tract cancers (esophageal, stomach, colon, rectal, liver, pancreas), other common adult carcinomas (breast, thyroid, lung, kidney, prostate), bone and soft tissue sarcomas, and skin cancer (melanoma, nonmelanoma skin cancer).⁴⁻¹⁵ Indeed, the list of organs that have not been reported as sites of excess risk for neoplasia is much shorter. To date, there has not been a study that we are aware of that demonstrates an increase in risk of testicular cancer following radiation of the testis.^{4,16,17} While there appears to be a reduced risk of ovarian cancer in the first 10 years following pelvic radiation for cervical cancer, an excess risk of ovarian cancer develops beyond 30 years following radiation.^{11,18} These observations suggest that germ cells within the testes, and to a lesser degree the ovaries, are exquisitely sensitive to the cell-killing effects of radiation (and thus may not be prone to future tumorigenesis). This idea is supported by the low dose of radiation needed to render a male azoospermic or induce ovarian failure in a female.

While radiotherapy is commonly noted as a major causative factor in the development of a second neoplasm, it is important to realize that only 8% of SPNs are due to radiotherapy, with the remainder being due to genetic factors, lifestyle behaviors, and aging.¹⁶ Nevertheless, radiation oncologists and physicists continue to strive to improve the methods and techniques for delivering radiotherapy, evolving from the early days of using cobalt-60 isotopes to deliver radiotherapy to the use of linear accelerators, intensity modulated radiation therapy, 3D conformal radiation therapy, and the recent introduction of proton radiation therapy. Concurrently, investigators have studied the lowest effective dose of radiation, with or without adjuvant or neoadjuvant chemotherapy, to provide a lasting cure. Indeed, radiation remains, and will remain for the foreseeable future, a critically important modality in the successful treatment of many cancers. In the following paragraphs, we emphasize key points for the clinician and discuss four radiation-associated SPN sites: breast, colorectal/stomach, thyroid, and skin cancer. In separate sections below, we discuss the interaction between radiotherapy, lifestyle behaviors, and genetic factors and provide recommendations for screening for radiation-associated SPNs.

Radiation-associated breast cancer

Hancock, Tucker, and Hoppe first described an excess risk of breast cancer in women treated with chest radiation for Hodgkin lymphoma.¹⁹ Since that initial observation, numerous studies have contributed to our understanding of radiation-associated breast cancer.^{6,14,20-30} A recent systematic review by Henderson et al provided risk estimates for breast cancer in women treated with chest radiotherapy prior to age 30, described the clinical characteristics of these breast cancers and outcomes after therapy, and discussed the potential benefits and harms associated with breast cancer surveillance.³¹

Risk of breast cancer following radiotherapy is age related; women below age 30 are at highest risk for future breast cancer.^{4,30} The cumulative incidence of breast cancer by age 40 to 45 years ranges from 13% to 20% (Figure 1),^{6,26,31} similar to the risk of breast cancer in female carriers of a BRCA gene mutation.³² Women treated for Hodgkin lymphoma with

mantle or involved field (excluding the axillary nodes) radiotherapy are at highest risk; however, other radiation fields involving the chest, such as hemithorax, whole lung and total body irradiation, are associated with an elevated risk. Risk of breast cancer begins about 8 to 10 years following radiation, does not plateau with aging, and increases linearly with chest radiation dose (Figure 2, **Panel A**).^{4,6,23,30,31}

Decreasing the volume of breast tissue exposed to radiation is associated with a decreased breast cancer risk. For example, contemporary radiotherapy for Hodgkin lymphoma has evolved from radiating the mantle field (cervical, supraclavicular, infraclavicular, mediastinal, and axillary lymph nodes) to radiating only the involved field (or when possible, omitting the upfront use of radiation). Thus, if the axillary nodes are not involved, they are not irradiated. Omitting the axillary nodes and restricting the field to areas of involvement can reduce the volume of irradiated breast tissue by 64%,³³ resulting in a 2.0 to 2.5-fold reduction in risk.^{21,30} Interestingly, reducing lifetime exposure to endogenous estrogen (e.g., ovarian failure or premature menopause) is also associated with a reduction in chest radiation-associated breast cancer risk.^{23,30,31}

Due to the extensive fields of radiation, breast cancer following radiotherapy is frequently bilateral (synchronous and asynchronous).^{24,31,34} Histology, hormone receptor status of breast tumors, and human epidermal growth factor receptor 2 (HER2) status appear similar to that of women in the general population with breast cancer.^{31,34} Nevertheless, 5-year survival is lower for this high risk group than in the general population. This inferiority in outcomes appears to be due to the late stage in diagnosis of breast cancer in these young women and to limitations of breast cancer therapy due to prior therapeutic exposures.^{31,34,35} Thus, early detection is essential for improving outcomes.

Radiation-associated colorectal and stomach cancer

Several studies have demonstrated an elevated risk of colorectal and stomach cancer following radiotherapy, including rectal cancer following radiation for prostate cancer¹² and colorectal and stomach cancer following abdominopelvic radiation for cervical cancer,^{11,36} Hodgkin lymphoma,^{4,6,37,38} testicular cancer,³⁷ and childhood cancer.^{9,39} Risk of radiation-associated colorectal and stomach cancer does not appear to be modified by age at exposure or by gender. Reulen et al found that the cumulative risk of colorectal cancer in childhood cancer survivors treated with abdominopelvic radiation was similar to that of individuals in the general population with two or more first degree relatives with colorectal cancer.⁹ As observed with breast cancer, there appears to be a linear relationship between radiation dose and risk of colorectal or stomach cancer.^{36–39} Interestingly, procarbazine, particularly higher cumulative doses, appears to potentiate this radiation-associated risk.^{37–39} There is a modestly longer latency period from radiation to diagnosis of colorectal or stomach cancer than that observed with breast cancer; generally over 10 years. To date, there are no studies that have identified how other factors, such as family history of colorectal cancer, modify risk. Further, there is not data yet on whether the aggressiveness of tumors or the long-term outcomes of patients with a secondary colorectal or stomach cancer is different from those with gastrointestinal cancer in the general population.

Radiation-associated thyroid cancer

An elevated risk of thyroid cancer following non-therapeutic low doses of ionizing radiation has long been recognized. Thus, it is not surprising that there have been numerous studies of the increased risk of thyroid cancer following therapeutic radiation involving the head, neck, and chest regions.^{4,6,7,9,10,40} In contrast to the linear relationship between radiation dose and breast, colorectal, and stomach cancer, there is a linear-exponential relationship between radiation dose and thyroid cancer (Figure 2, **Panel B**).⁷ The peak risk occurs with thyroid

radiation doses of 15 to 20 Gy, with diminishing excess risk with doses of more than 30 Gy. This phenomenon is due to a cell-killing effect associated with high doses of radiation. There appears to be some modifying effect of age at radiation, with younger individuals having the highest risk.⁴ Women have a modestly higher risk of radiation-associated cancer compared to males.⁷ The histology of thyroid cancer is similar to that among individuals without a prior cancer history, with the vast majority of cases being papillary or follicular carcinoma. As in the general population, thyroid cancer following radiotherapy tends to be an indolent cancer with very high rates of 5-year survival.

Radiation-associated skin cancer

Nonmelanoma skin cancer is the most common radiation-associated solid tumor.^{9,10,41–44} As with breast, colorectal, and gastric cancer, there is a linear dose relationship between radiation and nonmelanoma skin cancer.⁴² Gender does not affect risk. While these tumors, generally basal cell carcinomas, are ubiquitous and indolent, the recurrent need for medical evaluations and biopsies adds to the emotional and financial cost among survivors.

Importantly, while much less frequent in occurrence, melanoma is associated with radiotherapy. An increased risk of melanoma has been reported in large population-based or multi-institutional cohort studies of Hodgkin lymphoma survivors^{4,44,45} and in childhood cancer survivors.^{9,10} Braam et al conducted a systematic review of studies reporting on melanoma following a childhood cancer and identified radiotherapy as a risk factor.⁴⁶ More recently, Pappo et al reported that the cumulative incidence of melanoma at age 35 years from a childhood cancer was 0.55%.⁴⁷ The number of cases was too small to determine the modifying effect of radiotherapy or interactions with other factors, such as family history or having fair skin.

Lifestyle-related solid tumor SPNs

Head and neck squamous cell carcinoma (HNSCC) represents a collection of cancers arising in the mucosal surfaces inside the head and neck (e.g., oral cavity, pharynx and larynx). Tobacco and alcohol remain the leading risk factors for HNSCC.^{48,49} Metachronous SPN develop in approximately 20–30% of all patients diagnosed with HNSCC at a rate of 3–5% annually and are responsible for about a third of deaths in patients diagnosed with HNSCC.^{50–55} The pathogenesis of an SPN in survivors of a head and neck cancer illustrates the concept of field cancerization where chronic exposure to carcinogens (i.e., tobacco or alcohol) induces dysplastic changes which predispose to the development of cancer throughout the aerodigestive tract.⁵⁶ As an example of the influence of risk of an SPN based on continuance of smoking, Khuri et al reported that the annual SPN rate was 4.2%, 3.2%, and 1.9% for current, former, and never smokers, respectively.⁵⁷

The most common sites of SPN are in the head and neck, lung and esophagus.^{50,51,58} Despite a shared etiology, the occurrence of SPN is not uniform across all patients. For example, patients with oral cavity cancer are more likely to be diagnosed with a subsequent HNSCC while patients diagnosed with larynx cancer are more likely to be diagnosed with a new primary lung cancer.⁵¹ Patients with a primary hypopharynx cancer have the greatest risk of a SPN.⁵¹

Inherited cancer syndromes and solid tumor SPNs

Among cancer survivors, prior therapeutic exposures and lifestyle factors play an additive role in determining individual second cancer risk. For patients with hereditary cancer predisposition syndromes, such as hereditary retinoblastoma and Li-Fraumeni and Lynch syndromes, consideration of the interplay of these interactions is particularly critical.

Retinoblastoma is a rare pediatric tumor of the eye with survival rates exceeding 95% in the United States.⁵⁹ In the genetic form of the disease, usually due to a germline mutation in the *Rb-1* tumor suppressor gene, patients develop ocular malignancies at a very young age and have an increased lifetime risk of SPNs^{60–62} including bone and soft-tissue sarcomas, melanoma, epithelial cancers, and brain tumors.^{61,63–65} Long-term follow-up of a cohort of 1601 retinoblastoma survivors demonstrated that survivors of hereditary retinoblastoma have a cumulative risk of SPN of 36% by 50 years after diagnosis compared to 6% in patients with the non-hereditary, or sporadic, form of the disease. Hereditary retinoblastoma is an excellent example of how a common treatment exposure potentiates risk. Radiotherapy (predominantly orbital radiotherapy) increases the risk of an SPN by 3-fold in an individual with hereditary retinoblastoma.^{60,61} The modifying effect of radiation is illustrated in Figure 3. This observation led investigators to seek non-irradiating approaches in the treatment of hereditary retinoblastoma.

The Li-Fraumeni syndrome (LFS) is another rare, dominantly inherited disorder associated with germline mutations in the *TP53* tumor suppressor gene. Similar to patients with the genetic form of retinoblastoma, patients with LFS have markedly elevated rates of early onset cancers including soft tissue sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinoma, acute leukemia, and other malignancies.^{66–68} A study of 200 patients from 24 Li-Fraumeni kindreds found a cumulative probability of second cancer occurrence of 57% at 30 years after diagnosis of a first cancer with the highest risk observed for survivors of childhood cancers.⁶⁹ Others have shown that the lifetime risk of developing a cancer in *TP53* mutation carriers is as high as 73% for males and almost 100% for females.⁷⁰ Studies of Li-Fraumeni patients have also suggested a role for ionizing radiation sensitivity in the development of subsequent cancers.^{69,71}

Lynch syndrome, also referred to as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominantly inherited disorder of cancer susceptibility caused by germline mutations in DNA mismatch repair (MMR), including *MLH1*, *MSH2*, *PMS1*, and *MSH6*.^{72–74} Following a diagnosis of colorectal cancer, MMR carriers have an excess risk for extracolonic cancers including the following sites: kidney, bladder, small intestine, stomach, hepatobiliary, prostate, endometrial, breast, and ovary.^{75,76} By 20 years after a colorectal cancer, Win et al reported that 5.2% of the MMR carriers had been diagnosed with a urinary tract cancer.⁷⁵

Radiation, gene-environment, and solid tumor SPNs

While high-penetrance genes, such as *Rb-1*, may increase the risk of radiation-associated solid tumor SPNs, the prevalence of such genes is quite low and thus their contribution to the overall risk of solid tumor SPNs is modest. The most likely pathway for radiation-induced tumorigenesis is via DNA damage. It is well established that DNA damage and defective DNA damage repair is pivotal in the development of cancer (Figure 4).⁷⁷ Thus, investigators have begun to examine common polymorphisms in low-penetrance genes responsible for DNA repair which may be associated with radiation-induced solid tumor SPNs. Best and colleagues from the Childhood Cancer Survivor Study (CCSS) performed a genomewide association study (GWAS) on specimens from survivors of childhood Hodgkin lymphoma with an SPN in the radiation field (100 cases) compared to survivors also treated with radiation but without an SPN (89 controls).⁷⁸ They identified two variants at chromosome 6q21 associated with SPNs in the radiation field and replicated this association in another group of childhood Hodgkin lymphoma survivors. The variants comprise a risk locus associated with decreased basal *PRDM1* expression and impaired induction of *PRDM1* by radiation exposure, suggesting that this novel gene-exposure interaction may implicate *PRDM1* in the etiology of radiation-induced SPNs. Interestingly, there did not

appear to be an association between these two genetic variants among survivors of young adult Hodgkin lymphoma. To extend this line of inquiry, investigators from the NCI and the CCSS, led by Morton, Chanock, and Bhatia, are currently performing GWAS on a large sample of childhood cancer survivors. This effort should lead to new discovery and advance our understanding of the genetic underpinnings of radiation-associated SPN.

Using a different approach, Broeks and colleagues hypothesized that radiation may induce distinctive genomic aberrations and subsequent gene expression resulting in a specific breast tumor molecular profile following radiation exposure.⁷⁹ To test this hypothesis, they performed gene expression profiling on 22 breast tumors that occurred within a radiation field in women treated for Hodgkin lymphoma and compared these profiles to those of 20 controls who had breast tumors without a history of radiation. The radiation-associated tumors were often of the intrinsic basal breast tumor subtype, showed a chromosomal instability profile, and a higher expression of the proliferation marker Ki-67 (Figure 5).

Interactions between treatment exposures and lifestyle behaviors

Unhealthy lifestyle behaviors also potentiate the risk of a solid tumor SPN. Here, we provide two examples of this growing area of research.

Smoking, chest radiotherapy, alkylating agent chemotherapy, and lung cancer

Perhaps the best example to illustrate the negative modifying effect of a lifestyle behavior on second cancer risk was an elegantly designed international population-based case-control study by Travis et al.⁸⁰ The cumulative amount of cytotoxic drugs, the radiation dose to the specific location in the lung where cancer developed, and tobacco use were compared for 222 Hodgkin lymphoma survivors who developed lung cancer and for 444 matched control Hodgkin lymphoma survivors. Chest radiation and alkylating agent chemotherapy, individually or combined, were associated with a modest increase in risk of lung cancer in the non-smokers and light smokers. However, when these two treatment exposures were assessed in moderate to heavy smokers (one to two packs a day), the risk increased by 20-fold. Thus, risk from smoking multiplied the risk of lung cancer due to the treatment exposures.

Cranial radiotherapy, obesity, physical inactivity, and breast cancer

From the 1960s through the 1990s, cranial radiotherapy was commonly used in the treatment of childhood acute lymphoblastic leukemia (ALL) to prevent central nervous system (CNS) relapse as well as to treat CNS disease. Cranial radiotherapy has long been established as a cause of obesity, body fatness, and physical inactivity, particularly in females treated at a young age.^{81–84} Some female ALL survivors, depending upon therapy, are also at risk for acute ovarian failure and premature menopause.^{85,86}

In the general population, it is well established that obesity is associated with postmenopausal breast cancer.^{87–90} It also appears that body fatness may be associated with estrogen receptor negative (ER-) breast cancer in pre-menopausal women.⁹¹ Physical inactivity, independent of obesity, increases risk of breast cancer, again with a stronger association for post-menopausal than pre-menopausal breast cancer.^{92,93}

So, it is reasonable to ask if female ALL survivors who are obese and physically inactive following their cranial radiotherapy will have an increased risk of post-menopausal breast cancer or ER- pre-menopausal breast cancer. While still at a young age (median age 25 to 35 years), there appears to be a modest increased risk of breast cancer in female ALL survivors followed in the CCSS.^{10,94} We are currently assessing the contribution of genetic factors, family history, obesity and physical activity to ER+ and ER- breast cancer in these CCSS

participants. This avenue of research - assessing potential interactions between therapeutic exposures, lifestyle behaviors, and genetic factors - will allow us to refine our prediction of risk while testing risk-reducing interventions.

Putting it all together - treatment exposures, lifestyle behaviors, genetic factors, aging, and solid tumor SPNs

The natural conclusion to the above sections is that while overall risk and individual factors of associated risk for an SPN have been well established, there is a need to better understand how each of these factors interacts. The aforementioned ongoing GWAS being performed at NCI in collaboration with CCSS will offer the opportunity for such study. Because the CCSS has highly detailed cancer therapeutic exposures and longitudinal data on lifestyle behaviors and comorbidities of a large cohort of childhood cancer survivors, the addition of genomic data will provide a platform to study multiple interactions. Interested investigators are encouraged to contact the CCSS for further information regarding this endeavor (<https://ccss.stjude.org>). This direction of research is also being followed in several settings abroad.

Predicting risk of solid tumor SPNs

The population-level findings discussed above can be used to predict the risk of an SPN in an individual. Models that predict the absolute risk of SPNs may enhance our ability to provide risk-based care to cancer survivors. Absolute risk, sometimes referred to as the individualized risk or the projected individualized probability, is the chance that a subject with a given set of characteristics will develop the disease over a specified time interval. Absolute risk models have become an integral part of providing health care and conducting research in a variety of different areas both within the oncology community and in other medical fields. For example, using data from the Framingham Heart Study cohort, a risk prediction model was developed in the 1970s to estimate the risk of coronary heart disease.⁹⁵⁻⁹⁷ Today, modified versions of the Framingham risk model are widely used by clinicians to make decisions on prevention and treatment strategies⁹⁸ and to educate patients,⁹⁹ as well as by researchers in the conduct of prevention trials.^{100,101}

A second well-known example is the Gail model, a breast cancer prediction model that was developed with the intent that it would facilitate conversations with women about their risk of developing breast cancer, help target screening and preventive strategies towards high-risk subsets of women, and aid in designing prevention studies.¹⁰² With the projections from this risk model easily available to both patients and physicians alike in the form of a Web-based calculator provided by the National Institutes of Health, the Gail model has become one of the most widely used cancer risk prediction models (<http://www.cancer.gov/bcrisktool>).

In contrast to these high profile models which have been studied, refined, and validated, and to models that predict the absolute risk of primary cancers in general, there is a dearth of models that predict the absolute risk of second cancers in cancer survivors, and even fewer which have been validated and are now routinely used in practice. While relevant for patients of all ages diagnosed with any primary cancer, risk prediction models that accurately identify people at high risk of second cancers are particularly important for long-term survivors of a primary cancer that is diagnosed at a young age. This is a growing group of individuals for whom advances in treatment have led to increased life expectancy, but who consequently may have a very high risk of developing second cancers over a long time span. Decisions over appropriate surveillance recommendations and prevention strategies for these cancer survivors are limited by the lack of accurate prediction models that incorporate all key pieces of information. In many cases, a useful model may require

combining known clinical risk factors in the general population together with factors related to the treatment for the primary cancer.

In the first cancer risk prediction model applicable to survivors of a primary cancer diagnosed at a young age, Travis, Gail, and colleagues analyzed data on women who had been treated for Hodgkin lymphoma by the age of 30 and had survived at least one year.¹⁰³ Of the 371 women in their analysis, 105 had developed breast cancer and the remaining 266 were matched controls. Taking into account age, year of lymphoma diagnosis, population incidence rates of breast cancer, and competing causes of death, Travis et al. estimated the cumulative absolute risk of breast cancer as a function of the radiation dose and chemotherapy used to treat the lymphoma. Their model did not incorporate traditional breast cancer risk factors such as family and reproductive histories due to the lack of available information nor has it been validated. Moskowitz, Oeffinger and colleagues from the CCSS, along with van Leeuwen and colleagues from the Dutch LATER cohort, are currently developing and validating a web-based calculator to predict absolute risk of breast cancer that integrates the many factors that may influence risk, including treatment-related factors and traditional risk factors.

Kovalchik and investigators from the CCSS recently developed and validated three models to predict absolute risk of thyroid cancer among 5-year survivors of childhood cancer. The model with the best discriminatory performance included sex, birth after 1970, age younger than 15 years when diagnosed with a childhood cancer, prior diagnosis of a thyroid nodule, history of radiation therapy, radiation therapy including the neck, and history of treatment with an alkylating agent.¹⁰⁴ The software for this model can be downloaded (<http://dceg.cancer.gov/tools/risk-assessment/tcrat>).

In addition to developing risk prediction models for solid tumor SPNs, it is essential to study and test their utility in facilitating shared or informed decision making among cancer survivors. This will necessitate the development of decision aid tools to simplify this information and to convey complex concepts such as risk in an understandable fashion. Similarly, modes of communicating this information, including in-person or via electronic communication (e.g., webbased, smart phone technology) will need to be evaluated.

Screening for solid tumor SPNs

While the American public largely believes that most cancers can be screened for, there remains few primary cancers for which evidence supports the benefits of screening while considering the harms such as false positive tests. In the U.S., various government-sponsored groups, such as the U. S. Preventive Service Task Force (USPSTF), and society-based national groups (e.g., American Cancer Society [ACS] and the National Comprehensive Cancer Network [NCCN]) periodically disseminate recommendations for cancer screening. In addition, there are similar ongoing efforts in Canada, Europe, and Asia. Notably, the USPSTF focuses solely on screening of a primary cancer and does not address screening for SPNs. In contrast, the ACS and NCCN have recently begun to include reviews and recommendations for SPN screening.

However, the longest-standing effort in the U.S. devoted to developing and disseminating recommendations for SPN screening is from the Children's Oncology Group (COG).¹⁰⁵ The COG is an NCI-supported clinical trials group and the world's largest organization devoted exclusively to childhood and adolescent cancer research. The COG consists of 200 children's hospitals, universities, and cancer centers across North America, Australia, New Zealand, and Europe. The COG *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*, which can be accessed on the internet

((<http://www.survivorshipguidelines.org>) is maintained and updated by the COG Long-Term Follow-Up Guidelines Core Committee. There are similar ongoing efforts in Europe.

In the following paragraphs, we provide organization-specific recommendations, report on adherence to screening practices where available, and highlight current NCI-supported studies testing methods to enhance screening for solid tumor SPNs.

Breast cancer surveillance following chest radiotherapy for a childhood or young adult cancer

Several studies have examined the accuracy of breast screening modalities, particularly mammography and breast MRI, among childhood and young adult cancer survivors treated with chest radiation.³¹ In a recent study, Ng and colleagues prospectively studied the sensitivity and specificity of mammography and breast MRI in women treated with chest radiation for Hodgkin lymphoma. They found that the combination of both modalities was superior to either individual test.¹⁰⁶ For women treated with chest radiotherapy of 20 Gy or more, the COG,^{31,107} the NCCN,¹⁰⁸ and the International Late Effects of Childhood Cancer Guideline Harmonization Group¹⁰⁹ recommend annual mammography and breast MRI, starting at age 25 or 8 years after the radiation, whichever occurs last.

To characterize the breast cancer surveillance practices among female childhood cancer survivors treated with chest radiation, Oeffinger et al surveyed 1976 participants in the CCSS from the U.S and Canada.¹¹⁰ They reported that almost half of women between ages 25 and 39 had never had any breast imaging study and only 53% of women aged 40 to 50 were having regular mammography (less than 3% reported a breast MRI). The primary barrier was a lack of a physician recommendation for screening. A randomized intervention trial supported by the NCI is currently in progress in the CCSS to test the effectiveness of an intervention aimed at increasing breast cancer screening rates among this high risk population.

Colorectal cancer screening following abdominal or pelvic radiation

The COG¹⁰⁷ and the NCCN¹⁰⁸ recommend screening colonoscopy every five years in childhood, adolescent and young adult cancer survivors treated with more than 30 Gy of radiation to the abdomen or pelvis, starting at age 35 or 10 years after radiation, whichever occurs last. Nathan et al reported that only 17% of long-term childhood cancer survivors at risk for colorectal cancer reported ever having a colonoscopy.¹¹¹

The NCCN does not have a specific recommendation for colorectal cancer screening following radiation for cervical, prostate, or testicular cancer or Hodgkin lymphoma in individuals treated after the age of 30.

Thyroid cancer screening following radiation to the chest, neck, head

Thyroid nodules are extremely common among long-term survivors treated with radiotherapy to the neck area. Based on the indolent nature of thyroid cancer following radiotherapy and the marked frequency of thyroid nodules that can be imaged by ultrasound,¹¹² the COG¹⁰⁷ and the NCCN¹⁰⁸ recommend only an annual clinical examination (palpation) of the thyroid and do not recommend screening with ultrasound or other special modalities. If a nodule is palpated on exam, further evaluation should be similar to the standard of care of individuals with a thyroid nodule in the general population.

Skin cancer screening following radiation

The COG recommends an annual skin exam of the irradiated fields.¹⁰⁷ Nathan et al reported that only 26% of long-term survivors of childhood cancer reported ever having a complete

skin examination of all irradiated areas.¹¹¹ Geller and colleagues from the CCSS are currently conducting an NCI-sponsored study testing the effectiveness of different interventions aimed at enhancing skin cancer early detection practices.

Screening HNSCC survivors for a new HNSCC or lung cancer

Screening for a solid tumor SPN in an HNSCC survivor would seem reasonable, but the evidence is still sparse on how to optimally follow this group. Routine physical exams of the head and neck area are currently recommended for the early detection of metachronous HNSCC.¹¹³ However, the data guiding frequency, method or effectiveness of screening for second HNSCC is limited.^{114–117} The National Lung Screening Trial reported that low-dose thoracic computed tomography can reduce lung cancer mortality in patients with at least a 30 pack-year smoking history, but the implementation of these findings in a cohort of high-risk cancer survivors requires further study.^{118,119} Screening for esophageal cancer, even in high-risk adults, remains more controversial.¹²⁰ Although current surveillance guidelines are applied generically to all survivors, emerging data on the epidemiology of SPN in patients with HNSCC will hopefully inform a more individualized approach in the future.

Screening survivors with a genetic cancer syndrome

Due to increased early onset and lifetime risks of SPN in patients with hereditary cancer syndromes, practitioners have recommended close monitoring of affected patients for early signs and symptoms of new cancers. While clinical surveillance protocols have been established for some hereditary cancer syndromes,¹²¹ similar procedures have not been universally recommended for children or young adults with hereditary retinoblastoma or Li-Fraumeni. A recent study, however, demonstrated the feasibility of a combined biochemical and imaging surveillance protocol in thirty-three *TP53* mutation carriers with Li-Fraumeni syndrome.¹²²

Prevention of solid tumor SPNs

Recognizing the potentiation of risk of a solid tumor SPN among smokers and sedentary and obese individuals, it is imperative that the clinician discuss the lifestyle behavioral changes. As we discuss with our patients, one cannot ‘undo’ the treatment exposures (which cured the primary cancer) nor change our underlying genetics. However, the opportunity to substantially reduce one’s risk by smoking cessation / avoidance, eating a healthy diet, and being physically active provides a survivor much control over his or her health and long-term outcomes.

An understudied area is chemoprevention for SPNs. In an NCI-supported multi-center study, Palomares and colleagues are evaluating the chemopreventive effect of low-dose tamoxifen on mammographic breast density and histologic and circulating biomarkers in women treated with chest radiotherapy prior to the age 40. Studies of other chemoprevention approaches, such as aspirin to prevent colorectal cancer following radiation, are warranted. Importantly, though, the sample size needed for many of these studies, particularly where reliable biomarkers of tumorigenesis are not available, can be prohibitively large.

Future Directions

In summary, much has been learned about the risk of solid tumor SPNs and some of the factors that modify risk have been identified. Certainly enough is known to provide guidance in caring for cancer survivors at high risk of a solid tumor SPN including screening and prevention strategies. However, to deliver personalized care, a more sophisticated understanding of the gene-lifestyle-treatment exposure environment will be needed. Encouragingly, the research capacity for study in this area has increased tremendously in the

last decade - both in the U.S. and internationally. We have highlighted some of the ongoing NCI-supported studies, recognizing that there are many other similar efforts in progress that will inform our care of cancer survivors and hopefully reduce the risk for or death from a solid tumor SPN.

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Figure 1. Cumulative incidence (middle line) of breast cancer as a function of age of the cohort of female survivors of Hodgkin's disease, with 95% CIs (upper and lower curves)
 From Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's Disease. *J Clin Oncol* 21:4386–4394, with permission.

Figure 2.

Panel A demonstrates a linear dose response relationship between radiation dose to the breast and risk of breast cancer. In contrast to the linear relationship between radiation dose and breast, colorectal, and stomach cancer, Panel B demonstrates the linear-exponential relationship between radiation dose and thyroid cancer. The peak risk occurs with thyroid radiation doses of 15 to 20 Gy, with diminishing excess risk with doses of more than 30 Gy. From Sigurdson AJ, Ronckers CM, Mertens AC, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet* 2005;365:2014-23 and Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the Childhood Cancer Survivor Study. *J Clin Oncol* 2009;27:3901-7, with permission.

Figure 3.

Cumulative incidence and 95% CIs of new cancers by time since diagnosis of hereditary retinoblastoma by radiotherapy.

From Kleinerman RA, Smith SA, Holowaty E, et al. Radiation Dose and Subsequent Risk for Stomach Cancer in Long-term Survivors of Cervical Cancer. *Int J Radiat Oncol Biol Phys.* 2013;86:922-9, with permission.

Figure 4. Sources and Consequences of DNA Damage

DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism, such as reactive oxygen species (ROS), or by spontaneous chemical reactions, such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (purple sphere), abasic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepair or replication of the damaged template, surviving cells may be subject to permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital

process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G denotes guanine, and T thymidine.

From Hoeijmakers JH. DNA damage, aging, and cancer. *N Engl J Med* 2009;361:1475-85, with permission.

Figure 5.

Dendrogram showing unsupervised hierarchical clustering of the gene expression data with BRB array tools using 4,040 significant oligos (centered correlation and complete linkage) IHC; ER status, PR, HER2 in red = positive, green = negative. Grade I = yellow, II = orange, III = red. Tumor subtype: normal = gray, lum A = light blue, lum B = dark blue, HER2 = orange, basal = red. CIN profile: no correlation = yellow, correlation = red. Radiation dose in white (0 Gy), light (1–4 Gy), middle (~20 Gy), dark (~40 Gy) blue. From Brooks A, Braaf LM, Wessels LF, et al: Radiation-associated breast tumors display a distinct gene expression profile. *Int J Radiat Oncol Biol Phys* 76:540-7, 2010, with permission.