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Subsequent Primary Neoplasms

Risks, Risk Factors, Surveillance, and Future Research

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KEYWORDS

- Subsequent primary neoplasms • Second malignant neoplasms
- Second primary cancers • Secondary cancers • Radiotherapy • Chemotherapy
- Genetic variation • Genetic susceptibility • Surveillance • Screening
- Follow-up guidelines

KEY POINTS

- Risks of subsequent primary neoplasms after childhood, teenage, and young adult cancer are provided from large-scale cohorts which yield the most reliable estimates.
- Radiotherapy and chemotherapy for childhood cancer are each evaluated as a risk factor for subsequent primary neoplasms.
- New investigations are evaluating whether genomic variants modify treatment-related subsequent neoplasm risk among childhood cancer survivors.

Continued

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- Surveillance, screening, and clinical follow-up guidelines for subsequent primary neoplasms after childhood cancer are each considered.
- Priorities for future research concerning subsequent primary neoplasms after childhood cancer are briefly summarized.

RISKS OF SUBSEQUENT PRIMARY NEOPLASMS AFTER CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCER

Survivors of childhood cancer experience substantial premature mortality; in the British Childhood Cancer Survivor Study (BCCSS) cohort, by 50 years from diagnosis 30% of 5-year survivors had died when 6% were expected to have died from mortality rates in the general population.[1] Analysis of the same cohort revealed that among survivors at least 45 years from diagnosis 51% of excess number of deaths were caused by subsequent primary neoplasm (SPN).[1] However, efforts to reduce therapeutic exposures in more recent decades has contributed to a decline in late mortality in general and from SPN in particular, among 5-year survivors of childhood cancer.[2]

In this article the authors consider the risks of SPN after childhood cancer and compare these risks with those observed after adolescent and young adult (AYA) cancer; the carcinogenic impact of treatment of childhood cancer with radiotherapy and chemotherapy; the influence of inherited genetic susceptibility on the development of SPNs; and the role of surveillance, screening, and clinical follow-up guidelines.

Risks of Subsequent Primary Neoplasms After Childhood Cancer

The most reliable estimates of risk of SPN result from large-scale cohort studies with systematic long-term follow-up. Two large-scale population-based registry ascertained cohorts of childhood cancer survivors have been established: one in the United Kingdom, the BCCSS,[3–5] and another including all of the Nordic countries.[6] Three large-scale hospital-based cohorts of childhood cancer survivors have also been established: the North American Childhood Cancer Survivor Study (CCSS),[7–9] the Dutch Childhood Cancer Oncology Group—Long-Term Effects After Childhood Cancer (DCOG-LATER) cohort,[10,11] and the French Childhood Cancer Survivor Study (FCCSS).[12,13] A recent review of risk estimates resulting from the initial 4 of these cohorts concluded that beyond age 40 years the standardized incidence ratio (SIR) was consistently at least 2-fold that expected and the absolute excess risk (AER) increased with attained age.[14] Both SIRs and AERs were similar across cohorts younger than 40 years.[14]

Types of SPN observed in excess of that expected from the general population varies substantially by both attained age and interval from diagnosis. For example, within the BCCSS brain tumors and sarcomas, as an SPN accounted for 63% of the excess number of SPNs observed among survivors aged 5 to 19 years; in contrast 52% of the excess number of SPNs observed among survivors older than 40 years were carcinomas of digestive, genitourinary, respiratory, and breast sites.[3]

A pan-European collaboration has been initiated to exploit the advantages that Europe has relating to the establishment of population-based cancer registration in the Nordic countries and United Kingdom during the 1940s, 1950s, and 1960s, depending on the country. In the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) SPN cohort comprises the largest ever

assembled SPN cohort comprising 69,460 5-year survivors of cancer diagnosed before age 20 years in 12 European countries within which there was systematic ascertainment of all SPNs diagnosed.[15,16]

There was particular focus on subsequent primary bone, soft tissue sarcoma, digestive and genitourinary cancers because these 4 cancer types account for a substantial proportion of the excess number of SPNs observed in the short and long term. Approximately 300 subsequent primary cancers of each of these 4 types have been included in 4 nested case-control studies (1200 cases in total) to investigate the extent to which cumulative dose of radiation from radiotherapy, cumulative dose of specific cytotoxics, and particular genomic factors extracted from saliva are related to risk of developing specific types of SPN. So far the authors have published the cohort studies relating to bone[17] and soft tissue sarcoma.[18]

Risks of Subsequent Primary Neoplasms After Adolescent and Young Adult Cancer

Large-scale studies of survivors of AYA cancer have tended to focus on risks of SPNs after specific common cancers such as lymphoma, testes, or breast cancer. Only 2 studies have investigated the risks of developing any SPN after each type of AYA cancer. One study was based on Surveillance, Epidemiology and End Results (SEER) registry data and the main finding from this study was that AYA cancer survivors had a higher absolute risk of developing an SPN compared with childhood or mature adult cancer survivors.[19] This study did not investigate the risks of specific SPNs after each AYA cancer.[19] Recently published is the largest ever study to investigate the risks of SPNs after each specific AYA cancer and the first to provide excess risks of specific types of SPN after each of 16 types of AYA cancer, the Teenage and Young Adult Cancer Survivor Study.[20] The Teenage and Young Adult Cancer Survivor Study is a population-based cohort of 200,945 5-year survivors of cancer diagnosed when aged 15 to 39 years in England and Wales from January 1971 to December 2006. During 2,631,326 person-years of follow-up 12,321 SPNs were diagnosed in 11,565 survivors.[20]

The recent publication relating to the Teenage and Young Adult Cancer Survivor Study illustrates 2 key new findings.[20] Firstly, in individuals who survived at least 30 years from diagnosis of cervical cancer, testicular cancer, Hodgkin lymphoma in women, breast cancer, and Hodgkin lymphoma in men, the authors identified a small number of specific SPNs that account for 82%, 61%, 58%, 45%, and 41% of the total excess number of neoplasms, respectively, and provides an evidence base to inform priorities for clinical long-term follow-up.[20] Secondly, lung cancer accounted for a substantial proportion of the excess number of neoplasms across all AYA groups investigated and indicates need for further work aimed at preventing and reducing the risk of this cancer among current and future survivors. This latter finding is in marked contrast to survivors of childhood cancer who do not experience such substantial excess risks of lung cancer, and this may relate to the evidence that survivors of AYA cancer smoke notably in excess of that expected from the general population, and in contrast survivors of childhood cancer smoke much less than that expected from the general population.[20]

SUBSEQUENT PRIMARY NEOPLASM RISK RELATED TO RADIOTHERAPY

Radiotherapy exposure has been recognized as a risk factor for SPNs among childhood cancer survivors for decades. One of the first comprehensive reports on SPNs among childhood cancer survivors demonstrated that most of the SPNs developed in previously irradiated sites.[21]

Breast Cancer

Radiotherapy exposure to the chest is an important risk factor for female breast cancer.[22–25] Recent studies suggest that even at lower absorbed doses to the breast (<20 Gy), breast cancer risk can be substantially elevated,[24,26] especially among survivors who were exposed to a large volume of the breast, such as whole lung irradiation for pulmonary metastases in Wilms tumor or Ewing sarcoma survivors.[24] A linear dose-response relation has been observed in several studies.[22,24,26] Hormonal exposure can modify the radiation-related risk of breast cancer. Survivors who also received radiation to the ovaries were reported to have lower radiation-related breast cancer risks.[22,26] Furthermore, the effect of radiation has been suggested to be stronger when administered near menarche.[8] In addition, there is some recent evidence for a stronger effect of radiation among those who also received anthracyclines.[26]

Sarcoma

Sarcoma risk is increased in childhood cancer survivors and both radiotherapy and chemotherapy have been implicated to contribute to this excess risk.[4,25,27–29] A nested case-control study within the CCSS cohort found a linear dose-response for any sarcoma.[27] Several reports evaluated the radiation dose-response for *bone* sarcoma or *soft tissue* sarcoma specifically. For *bone* sarcoma, an increased risk with increasing dose has been observed.[4,29–31] However, some of these reports suggested a decline in relative risk at doses above 40 Gy.[4,30] Among the studies on *soft tissue* sarcoma, results were consistent with a linear dose-response relationship between radiation dose and risk.[12,28,32] In general, the dose-related risk seemed somewhat higher for *bone* sarcoma than for *soft tissue* sarcoma.[33]

Thyroid Cancer

A pooled analysis, consisting of data from 2 cohort studies and 2 case-control studies among childhood cancer survivors, showed that the relative risk of thyroid cancer increased linearly with radiation dose up to 10 Gy, after which the risk plateaued.[34] At doses higher than 30 Gy, the risk seems to decline, possibly because of cell-killing effects. The dose-response relationship was stronger among those exposed to radiotherapy at a younger age.

Colorectal Cancer

Risk of colorectal cancer has been shown to be elevated among childhood cancer survivors, and abdominal radiotherapy has been implicated as a risk factor.[3,13,35,36] Researchers from the French Childhood Cancer Survivor Cohort and the St Jude Lifetime Cohort (SJL) found a radiation dose-dependent effect on colorectal cancer risk,[13,36] and the results of the SJL study also suggested an effect of radiation volume, as the risk increased with an increasing number of colonic segments irradiated.[36] Cumulative incidence of colorectal cancer was shown to be similar to that among individuals with 2 or more first-degree relatives with colorectal cancer in the British Childhood Cancer Survivor Study.[3]

Central Nervous System Tumors

Central nervous system (CNS) tumors occur in excess among childhood cancer survivors.[10,37,38] Nearly all meningiomas and most of the gliomas present in survivors treated with cranial or craniospinal irradiation for brain tumors or acute lymphoblastic leukemia.[10,37,38] For both gliomas and meningiomas, a linear dose-response relation has been observed, which seems to be stronger for meningioma (range of excess

relative risks (ERRs): 0.30–5.1 per Gy)[10,37,38] than for gliomas (range of ERRs: 0.079–0.33 per Gy).[37,38]

Nonmelanoma Skin Cancer

Nonmelanoma skin cancer, particularly basal cell carcinoma, is the most frequently observed SPN among childhood cancer survivors. Most of the basal cell carcinomas occur among previously irradiated patients.[11,39,40] A study in the Dutch LATER cohort observed that basal cell carcinoma risks increased with increasing skin surface area exposed.[11] A nested case-control study in the CCSS cohort demonstrated a linear radiation dose-response relation, with an ERR of 1.09 per Gy.[40]

Salivary Gland Tumors

Salivary gland tumor risks are elevated among childhood cancer survivors and a linear radiation dose-response relation was observed in a study in the CCSS cohort (ERR = 0.36 per Gy).[41]

Leukemia

In addition to the strong effects of chemotherapy on leukemia risk among childhood cancer survivors,[5,42–47] there is some evidence that radiotherapy exposure might add to the increased risk of subsequent leukemia.[5,44]

The results presented earlier mainly represent data from patients with childhood cancer treated decades ago, because those patients have sufficient follow-up time to evaluate risk of SPNs. In recent decades, radiotherapy practices have changed. Where possible, radiotherapy has been avoided or fields and doses have been reduced. For example, technological advances have led to the introduction of new techniques such as intensity-modulated radiotherapy (IMRT) and proton radiotherapy. These techniques aim to reduce the radiotherapy dose to the surrounding tissue, which might reduce the risk of SPNs.[48,49] However, with IMRT, the larger volume exposed to radiation (although at lower dose) can potentially increase SPN risk.[50,51] Proton therapy leads to an improvement in dose distribution by reducing the entrance dose and having virtually no exit dose.[52] However, there are some concerns regarding the secondary dose from neutron scatter with proton therapy, which might lead to an increased SPN risk compared with photon therapy.[53,54] It is important to carefully monitor patients with childhood cancer treated with those modern radiotherapy techniques and evaluate SPN risks in this population.

SUBSEQUENT PRIMARY NEOPLASM RISK RELATED TO CHEMOTHERAPY

Recent work has continued to highlight the independent influence of chemotherapy on the risk of SPNs in childhood cancer survivors. In the CCSS, among survivors exposed to only chemotherapy there was a 2.8-fold increased SPN risk compared with the general population (95% confidence interval [CI]: 2.5–3.2).[55] Chemotherapy increases the risk of both hematologic and solid SPN, depending on type and cumulative dose.

Chemotherapy and Subsequent Hematologic Malignancy

The most well-established association between chemotherapy and SPN relates to therapy-related acute myeloid leukemia (t-AML) and myelodysplastic syndrome (t-MDS).[5] Dose-dependent risks for t-AML/t-MDS are high (>10-fold increased) after almost all alkylating agents and topoisomerase II inhibitors.[5,45,56] Notably, the

leukemogenicity of different agents in these chemotherapy families varies substantially, and the absolute excess risk is low due to the low background risk in the age-matched general population. Development of t-AML after alkylating agent exposure typically arises after a latency of 5 to 8 years, is frequently preceded by MDS, and often has a complex karyotype with chromosome 5/7 abnormalities.[5] In contrast, t-AML after topoisomerase II inhibitor exposure typically arises less than 3 years following therapy, is rarely preceded by MDS, and is most frequently characterized by 11q23 rearrangements.[57]

Chemotherapy and Subsequent Solid Tumors

Chemotherapy increases risk for solid SPN, which often occur at least 10 years after exposure.[14] Several classes of chemotherapy directly or indirectly affect the risk of development of these SPNs.

Alkylating agents

Alkylating agent exposures increase risk for gastrointestinal, thyroid, lung, breast, and bladder cancers; melanomas; and sarcomas.[4,29,35,36,55,58–62] Specifically, cyclophosphamide increases sarcoma risk in a dose-dependent manner.[4,25,27,29] Likewise, cyclophosphamide equivalent doses of greater than 18,000 mg/m^2 increase breast cancer risk by 3-fold (SIR, 3.0; 95% CI, 1.2–7.7).[60] Procarbazine and platinum have been associated with 3.2 (95% CI, 1.1–9.4) and 7.6-fold (95% CI, 2.3–25.5) increased risks, respectively, of gastrointestinal SPNs.[35] Procarbazine-related risks for the gastrointestinal tract may be related to direct exposure of the mucosa,[27,36,58] whereas the mechanisms of carcinogenesis for agents administered intravenously are unknown.

Anthracyclines

Risk for breast cancer and other solid malignancies, including sarcoma, are increased after anthracycline exposure.[25,27,60,63] In the CCSS cohort, risk for breast cancer in survivors treated with greater than 250 mg/m^2 of anthracycline and without chest radiotherapy exposure was increased by nearly 4-fold compared with the general population (SIR, 3.8; 95% CI 1.7–8.3).[60] Both the DCOG-LATER cohort and the SJL cohorts reported similar findings. The DCOG-LATER cohort reported a dose-dependent relationship between breast cancer risk and doxorubicin (P_{trend} <0.001).[25] The SJL cohort reported an increasing breast cancer risk in both those exposed to 1 to 249 mg/m^2 (hazard ratio [HR] = 2.6, 95% CI 1.1–6.2, P = .034) and those exposed to greater than 250 mg/m^2 (HR = 13.4, 95% CI 5.5–32.5, P<.001) of anthracyclines.[25,63] In both the CCSS and DCOG-LATER reports, breast cancer risk was highest after Li Fraumeni syndrome–associated cancers, suggesting a possible interaction between chemotherapy and genetic predisposition.[25,60] However, with whole-exome sequencing available in the SJL cohort, the risk of breast cancer remained elevated in survivors exposed to greater than 250 mg/m^2 excluding those survivors with an identified cancer predisposition gene.[63]

Indirect associations of chemotherapy and subsequent primary neoplasm risk

Chemotherapy can indirectly affect SPN risk. In Hodgkin lymphoma survivors,[59,64,65] higher cumulative procarbazine exposure was associated with a greater reduction of breast cancer risk, with 30% and 67% risk reductions for regimens with less than 8.4 g/m^2 and greater than 8.4 g/m^2 procarbazine, respectively.[64,65] This risk reduction seems to reflect the higher frequency of premature menopause in more intensively chemotherapy-treated patients, and their resultant reduced exposure to ovarian hormones.[65–67] Similarly, high cumulative alkylator exposure significantly reduced breast

cancer risk in the CCSS cohort,[8] in contrast to earlier CCSS results that did not show a reduced breast cancer risk after alkylator therapy.[23] Breast cancer risk also increases in women with more than 10 years of ovarian function after chest radiotherapy compared with those with less.[8,65,67]

RISK OF SUBSEQUENT PRIMARY NEOPLASM AND GENOMICS

Inherited genetic susceptibility has long been known to play a role in SPN risk based on familial syndromes that predispose individuals to developing multiple primary neoplasms. Indeed, the occurrence of multiple primary tumors in an individual, particularly at a young age, was one of the earliest clues to inherited cancer predisposition syndromes.[68] Key examples of these syndromes include Li Fraumeni syndrome and hereditary retinoblastoma, which are caused by rare, highly penetrant germline mutations in the tumor suppressor genes *TP53* and *RB1*, respectively. In Li Fraumeni syndrome, overall, half of the women develop a first cancer by age 31 years and more than half of the men by age 46 years; of these individuals, approximately half will develop an SPN after a median of 10 years.[69] In contrast, in hereditary retinoblastoma nearly all individuals who inherit a germline mutation develop retinoblastoma in early childhood, typically within the first year of life. More than one-third of individuals are estimated to develop an SPN by age 40 years, although this estimate has been shown to vary by treatment exposure, specific *RB1* mutation, and family history of retinoblastoma.[70–73]

The field of cancer genomics has expanded rapidly in the last decade. Advances in technology and reductions in laboratory costs have now made it possible to broadly interrogate the entire genome using high-throughput microarray genotyping or next-generation sequencing in increasingly larger study populations. These advances are essential for enabling sufficient sample size to identify new disease-associated genes. In the general population, large-scale, international collaborative efforts to study breast cancer exemplify the discoveries that are possible with these new approaches. Genome-wide association studies (GWAS) using microarray genotyping for common single nucleotide polymorphisms have identified greater than 170 loci associated with breast cancer risk.[74] Although each of these individual loci has a very weak effect on risk (relative risks typically <1.2), combining the loci into a polygenic score provides dramatic risk stratification.[75] Large-scale sequencing studies also are demonstrating substantial heterogeneity in breast cancer risk associated with specific, rare mutations in *BRCA1* and *BRCA2*.[76]

Although these advances are only now beginning to be applied to assess genetic susceptibility to SPNs, as reviewed recently,[68,77,78] the future holds tremendous promise for advancing this research area to provide biological insights into SPN development and potentially changing clinical practice through front-line therapy decision-making and risk stratification for long-term patient follow-up. Paralleling research in the general population, most of the earliest studies focused on single nucleotide polymorphisms in candidate genes. However, unlike the general population, where specific exposure-disease relationships rarely have been taken into account in genetic association studies, initial studies in cancer survivors focused on genes in pathways such as DNA repair that mediate response to treatment exposures, which are the primary drivers of SPN risk. Although some of these reports have been promising, few have been replicated in independent study populations, thus further research is needed to clarify the role of common variation in DNA repair genes in SPN risk.

More recently, several GWAS or large-scale genotyping studies have been conducted to identify loci involved in SPN risk after childhood cancer, including SPN overall,

therapy-related acute myeloid leukemia, breast cancer, and basal cell carcinoma.[79–83] Those studies each have identified novel putative loci associated with SPN risk, with one study also suggesting that the genetic risk factors for breast cancer as an SPN overlap at least somewhat with those in the general population.[81] Although further replication of these findings will be essential before clinical translation because of the substantial risk of false-positive findings when broadly interrogating the genome, the common frequency of the risk allele for many of the identified variants (2% to >30% of the population) demonstrates the substantial potential for applying these results in clinical practice.

Broader understanding of the role of rare variants in SPN risk also is warranted because they may be associated with high risks, even if they account for a relatively small fraction of SPN. The first large-scale sequencing study of SPN after childhood cancer demonstrated that fewer than 10% of childhood cancer survivors harbor rare, damaging mutations in a known cancer predisposition gene.[84] Ongoing analyses of additional large-scale sequencing studies are expected in the coming years and promise to shed light on the role of rare variants in SPN risk.

ROLE OF SURVEILLANCE, SCREENING, AND CLINICAL FOLLOW-UP GUIDELINES

Rationale for Surveillance

As a consequence of past treatments, behavioral factors such as smoking and alcohol, and host factors such as genetics, specific groups of childhood cancer survivors have a 10-fold increased risk of developing an SPN.[85,86] Given the significant morbidity and risk for premature mortality resulting from SPNs, risk-adapted surveillance protocols have been developed with the goal of detecting SPNs at an earlier and more treatable stage. In other patient groups at high risk of malignancy, such as individuals with cancer predisposition syndromes, adherence to risk-adapted surveillance protocols have been shown to reduce mortality from SPNs.[85–87] The same is assumed to be true for childhood cancer survivors, but this has never been established in a clinical trial.[88] For survivors at elevated SPN risk, surveillance for a given neoplasm is warranted if surveillance modalities exist that do not cause significant morbidity, allow for earlier identification and intervention that might reduce the SPN's impact, and do not cause an excess of false-positive results that lead to unnecessary further testing or intervention.[89,90]

Surveillance Guidelines

Numerous organizations have developed recommendations for SPN surveillance in childhood cancer survivors.[91] Substantial variation exists between guidelines, but as a general principle, periodic follow-up by a physician that includes a history and physical examination focused on evaluation of irradiated structures is warranted for all survivors. There is also a general consensus that breast cancer surveillance is appropriate for female survivors who have received chest irradiation, but the specifics of the required surveillance vary. North American organizations (The Children's Oncology Group and The National Comprehensive Cancer Network) uniquely recommend colorectal cancer surveillance for survivors who have received abdominal and/or pelvic radiation.[92,93] In an attempt to create a common strategy for SPN surveillance, the International Guideline Harmonization Group (IGHG)[94] was formed. The IGHG has published recommendations for breast[95] and thyroid cancer[96] surveillance (available at http://www.ighg.org/) and is currently developing guidelines for CNS and colorectal cancer surveillance as well.

Current Guideline Adherence

Unfortunately, most adult survivors of childhood cancer are not adherent to the recommended SPN surveillance, potentially resulting in preventable morbidity and mortality. In one study of North American survivors enrolled in the CCSS, adherence to SPN surveillance was 12.6%, 37.0%, and 22.3% for breast, colorectal, and skin cancer surveillance, respectively (Yan A and Nathan P, unpublished data, 2019). Survivor reported barriers to surveillance include lack of time, forgetting, a perception that surveillance is not important, concerns about insurance coverage and cost, and lack of physician recommendation for surveillance.[97,98] Psychosocial barriers include poor mental health, lower socioeconomic status, and lower educational level.[99–101] In 2012, only 12% of US general internists[102] and 9% of US and Canadian family doctors[103] felt at least "somewhat familiar" with care guidelines for childhood cancer survivors. A lack of primary care provider comfort with care guidelines likely contributes to poor adherence as well. Regular engagement with the health care system, receipt of a treatment summary, and patient-provider communication discussing the need for surveillance have been associated with better adherence to surveillance guidelines.[104–108]

Mechanisms to Improve Adherence

To address barriers to receiving risk-adapted surveillance, the United States Institute of Medicine and the European collaboration PanCare have recommended that all childhood cancer survivors receive a treatment summary and survivorship care plan (SCP) that documents their cancer treatment–related health risks and the recommended surveillance.[109–111] The impact of SCPs on surveillance outcomes in childhood cancer survivors is unclear.[112] In fact, little is known about how best to increase the completion of recommended surveillance testing. A recent systematic review that evaluated interventions to improve surveillance adherence only identified one randomized trial where the intervention significantly increased SPN surveillance.[98,113] In this trial, mailed information coupled with motivational telephone interviewing increased adherence to mammography in women at risk for subsequent breast cancer.[98] Other interventions that have been tried with less success include motivational telephone counseling, SCP provision, web-based virtual information, and mailing of health risk information.[98,114–116]

Cancer Predisposition Syndromes

In addition to the risk of SPNs as a consequence of cancer therapy, a subset of survivors is at high risk of SPNs secondary to an underlying cancer predisposition syndrome. Nearly 10% of childhood cancer survivors have an actionable germline genetic mutation, making yearly review of family cancer history and subsequent referral to genetics when necessary imperative.[117] Specific guidelines have been created for the more common pediatric cancer predisposition syndromes, such as Li-Fraumeni syndrome[118] and Beckwith Wiedemann syndrome.[119] When no specific recommendations exist for a given syndrome, the American Association of Cancer Research recommends screening for malignancy if effective screening modalities exist and the overall risk exceeds 5% in the first 20 years of life. In addition, they recommend that when the overall risk is between 1% and 5%, screening can be considered on an individual basis.[120]

Summary

Despite the availability of numerous guidelines that guide health care providers in providing surveillance for SPNs in childhood cancer survivors, very few survivors

are currently adherent to recommendations, and few interventions have been successful in increasing surveillance. Further studies that develop and test interventions to improve adherence are needed.

PRIORITIES FOR FUTURE RESEARCH

Observational Studies to Address Specific Gaps in Knowledge

Subsequent primary neoplasms in survivors of adolescent and young adult cancer

A large population-based study described the risk of SPN in survivors of AYA cancer, reporting that a small number of specific SPNs account for a large proportion of the overall excess, with a prominence of lung cancer.[20] However, the association between therapeutic exposures and the risk of SPNs after AYA cancer remains unstudied, as does the role of lifestyle factors, which could have greater impact among AYA survivors than among childhood cancer survivors.[20]

Subsequent primary neoplasm risk in patients treated with immunotherapy

Targeted immunotherapy has emerged as an effective treatment option especially in pediatric malignancies.[121,122] Although the early toxicities are clearly described, there remains a significant gap in knowledge regarding the development of delayed complications, especially SPNs. Systematic, long-term follow-up of patients treated with targeted immunotherapy is needed to address this gap.

Solid subsequent primary neoplasm risk in patients treated with chemotherapy

Although the association between radiation and solid SPNs (thyroid, breast, brain, colorectal) is well established,[22,37,123] as is the risk between specific chemotherapeutic agents and therapy-related leukemia, there is emerging evidence regarding the role of adjuvant chemotherapy.[55] For example, treatment with anthracyclines may be a risk factor for thyroid cancer[55,61] and breast cancer.[55] These findings are based on small numbers of SPNs developing after exposure to a specific chemotherapy class. This gap could be addressed by pooling large well-characterized cohorts and case-control studies of survivors.

Subsequent primary neoplasm risk: interaction of behavioral factors or infections with genotoxic exposures

The risk of lung cancer is significantly increased in patients treated for Hodgkin lymphoma. Both chemotherapy and radiation contribute to the risk. Cigarette smoking multiplies the risk associated with both chemotherapy and radiation.[124,125] However, interaction between smoking and therapeutic exposures has not been examined for other types of SPN, such as esophageal, oropharyngeal, and gastric carcinoma. Furthermore, behavioral factors such as excessive alcohol consumption or a diet rich in processed meats has not been examined in this population. Finally, the interaction between chronic viral infections (hepatitis B virus, hepatitis C virus, human papillomavirus, Epstein-Barr virus) and prolonged immune suppression due to genotoxic exposures in increasing the risk of SPNs remains unstudied.

Temporal Changes in Subsequent Primary Neoplasm Risk with Changes in Treatment Strategies

With the decrease in the proportion of patients receiving radiation as well as a progressive reduction in the dose and field of radiation, the relative rates of meningioma and nonmelanoma skin cancers have declined over the past several decades.[9] Additional follow-up using pooled data from other well-characterized cohorts is needed to understand whether the decline in SPNs is limited to just these 2 specific types of SPNs, or

whether smaller samples precluded the ability to detect trends for other SPNs, such as breast cancer. Further, these trends need to be placed within the context of increasing use of chemotherapy and changes in surveillance practice. Most importantly, as the cancer survivor population ages, it is important to understand the lifelong risk of SPN and particularly the types of SPNs that account for most of the excess observed later in life.

Identification of Survivors at Highest Risk of Subsequent Primary Neoplasm and Potential for Targeted Interventions

Although the magnitude of association between radiation exposure and SPN risk is moderate-to-large (3.1-fold to 15.9-fold)[126] with clear evidence for a dose-response relationship,[22,37,123] there is wide variation in individual susceptibility, suggesting the role of genetic susceptibility in modifying this association.[32,127–136] Genetic variants may modify the association between radiation and SPN risk or increase the risk of SPNs even in the absence of radiation.[60] Indeed, cancer survivors who carry a deleterious, high-penetrance mutation are at increased risk for SPNs.[132–134,137,138] However, the low frequency of these mutations in the general population[139] suggests that the attributable risk is likely small. The interindividual variability in risk of SPNs is more likely related to common polymorphisms in low-penetrance genes that regulate drug metabolism or those responsible for DNA repair.[140,141] Although there is significant effort currently expended on identifying genetic variants and their association with SPNs, an equally important aspect of this discovery currently lagging involves understanding the functional relevance of the identified genetic variants. Although we can speculate about the relevance of a specific genetic variant, it is critical to delve into the functional aspects of the identified variant in order to understand the mechanistic basis of SPNs; this is critical in order to develop risk-reducing interventions. An equally important, yet underutilized opportunity is the use of demographic, clinical (therapeutic exposures), behavioral, and genetic information to determine the individual risk of SPN. An example is the risk prediction model developed for survivors at risk for radiation-related brain tumors,[142] where the sensitivity and specificity of predicting survivors of childhood cancer at highest or lowest risk of subsequent CNS tumors was 87.5% and 83.5%, respectively.

Radiation continues to serve as a critical backbone of treatment of childhood cancer, and although there may be options to use alternative treatments on a case-by-case basis (for patients at highest risk of SPN), the pediatric oncology community is reluctant to replace radiation with alternative treatments for *all patients*. In addition, among childhood cancer survivors already exposed to radiation, offering screening or behavioral/pharmacologic interventions based on personal risk could be cost-effective and better accepted by the survivor population. Finally, a deeper understanding of the mechanistic basis of radiation-related SPNs would lead us closer to developing targeted interventions.

Screening recommendations for early detection of subsequent primary neoplasms in childhood cancer survivors

The primary goal of risk-based surveillance is to facilitate early detection of treatment-related complications (including SPNs) in childhood cancer survivors.[89,94] However, there is an opportunity to examine the cost-effectiveness of screening recommendations[95,96] that tailor the intensity of screening based on personal SPN risk. Simulation, using Markov health states is currently being used to address cost-effectiveness of breast cancer screening recommendations.[143]

Interventions to reduce subsequent primary neoplasm risk in childhood cancer survivors

Breast cancer, brain tumors, sarcoma, thyroid cancer, and gastrointestinal malignancies constitute most of the non-skin cancer SPNs. All these SPNs are radiation related, with a clear dose-response relationship. Understanding the pathogenesis of each of these tumors could inform specific interventions, which when applied in those at highest risk would significantly improve the efficacy of such an intervention. As an example, Bhatia and colleagues[144] recently completed a pharmacologic intervention for reducing the risk of radiation-related breast SPN in childhood cancer survivors, using a randomized, double-blinded, placebo-controlled trial design. The biological premise is based on the fact that endogenous estrogens play a role in radiation-related breast carcinogenesis.

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