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REVIEW ARTICLE

Risk, Risk Factors, and Surveillance of Subsequent Malignant Neoplasms in Survivors of Childhood Cancer: A Review

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ABSTRACT

Subsequent malignant neoplasms (SMNs) in childhood cancer survivors cause substantial morbidity and mortality. This review summarizes recent literature on SMN epidemiology, risk factors, surveillance, and interventions. Survivors of childhood cancer experience long-term increased SMN risk compared with the general population, with a greater than twofold increased solid tumor risk extending beyond age 40 years. There is a dose-dependent increased risk for solid tumors after radiotherapy, with the highest risks for tumors occurring in or near the treatment field (eg, greater than fivefold increased risk for breast, brain, thyroid, skin, bone, and soft tissue malignancies). Alkylating and anthracycline chemotherapies increase the risk for development of several solid malignancies in addition to acute leukemia/myelodysplasia, and these risks may be modified by other patient characteristics, such as age at exposure and, potentially, inherited genetic susceptibility. Strategies for identifying survivors at risk and initiating long-term surveillance have improved and interventions are underway to improve knowledge about late-treatment effects among survivors and caregivers. Better understanding of treatment-related risk factors and genetic susceptibility holds promise for refining surveillance strategies and, ultimately, upfront cancer therapies.

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INTRODUCTION

Survival after childhood cancer now exceeds 80% throughout the United States and much of Europe.[1,2] With this improvement in survival over the last five decades, there has been increased recognition of late health complications, including subsequent malignant neoplasms (SMNs), among survivors. SMNs, defined as new primary malignancies after an initial cancer diagnosis, are the most frequent cause of nonrelapse late mortality, accounting for nearly half of nonrelapse deaths among 5-year survivors.[3] This review highlights up-to-date evidence on SMN risk, risk factors, and surveillance efforts.

CUMULATIVE INCIDENCE AND RISK FOR SUBSEQUENT NEOPLASMS

Multi-institution and population-based cohort studies, based in Europe and North America, designed to follow long-term survivors of childhood cancer, have been instrumental in describing SMN epidemiology. These cohort consortia have led efforts to characterize late effects experienced by survivors and have provided important data that have helped guide current cancer therapies and guidelines for surveillance of survivors of childhood cancer.

The largest SMN series have been reported by the North American Childhood Cancer Survivor Study (CCSS), the British Childhood Cancer Survivor Study (BCCSS), a collaborative effort from the Nordic countries cancer registries, and the Dutch Childhood Cancer Oncology Group-Long-Term Effects After Childhood Cancer (DCOG-LATER) cohort. These groups have shown that an increased SMN risk persists with advancing attained age. All four studies reported that beyond age 40 years, the standardized incidence ratio (SIR) was at least twofold and that the absolute excess risk (AER) increased with attained age (Fig 1).[7,10-12] Despite consistent SIRs and AERs across cohorts before age 40 years, the CCSS and DCOG-LATER studies reported higher SIRs and AERs than the BCCSS or Nordic countries for older attained ages. A potential explanation is that the BCCSS and the Nordic country cohorts include patients who received their diagnosis between 1940 and 1969, an era of low overall survival rates for pediatric cancer. Most survivors from this era received treatments with minimal carcinogenic potential, such as

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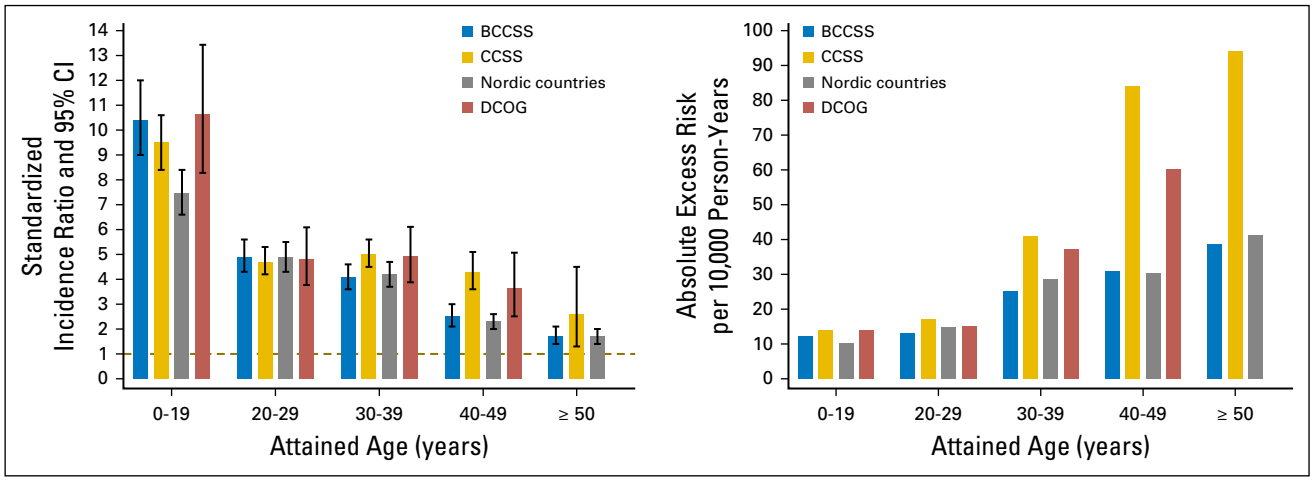

Fig 1. Standardized incidence ratios and absolute excess risk of subsequent malignant neoplasm by attained age in international cohorts of survivors of childhood cancer.

surgery alone, low-energy radiotherapy, or single-agent chemotherapy. Because survivors treated before 1970 make up the majority of patients with higher attained ages, it is not surprising that the treatment-related excess risks are lower.[4]

The first analysis of SMN risk from the CCSS reported a 20-year cumulative incidence of 3.2%, with a sixfold increased risk compared with the general population (SIR, 6.4; 95% CI, 5.7 to 7.1).[5] In a follow-up report, SMN cumulative incidence was reported at 30 years and had increased to 7.9%, whereas the risk for malignancy remained stable from the previous report (SIR, 6.0; 95% CI, 5.5 to 6.4), with the greatest SIRs observed for cancers of the bone, CNS, thyroid, head and neck, and breast.[6] Survivors experienced a fourfold increased risk of developing a malignancy after age 40 years compared with the general population (SIR, 4.4; 95% CI, 3.8 to 5.0), with the greatest risk observed for cancers of the breast, kidney, thyroid, and soft tissue sarcoma (STS).[7] The most recent comprehensive report of SMNs from the CCSS reported 15-year cumulative SMN incidence by decade of diagnosis and showed that those whose cancer was diagnosed in the 1990s had a significantly lower incidence of subsequent malignancy compared with those diagnosed in the 1970s (1.3% *v* 2.1%; $P < .001$).[8]

Within Great Britain, before the development of the BCCSS, SMN incidence and risk were reported from a retrospective cohort of 16,541 3-year survivors of childhood cancer who were identified through the National Register of Childhood Tumors.[9] Among survivors of nonretinoblastoma primary cancers, the 20-year cumulative SMN incidence was 2.8% and survivors experienced a nearly sixfold increased risk for malignancy compared with the general population (SIR, 5.8; 95% CI, 5.0 to 6.7). The greatest risk was observed for cancers of the bone, CNS, endocrine system, and STS.[9] Subsequently, the population-based BCCSS reported on long-term risks of SMNs in 17,981 5-year survivors whose cancer was diagnosed when they were between age 0 and 14 years between 1940 and 1991.[10] The study identified a fourfold increased risk for SMNs compared with the general population (SIR, 3.9; 95% CI, 3.6 to 4.2).[10] The BCCSS showed that survivors remain at increased risk for SMNs beyond age 40 years, with a 2.5-fold increased SIR for ages 40 to 49 years (95% CI, 2.1 to 3.0) and 1.7-fold increased SIR beyond 50 years (95% CI, 1.4 to 2.1). The greatest AER after age 40 years was for SMNs of the GI (AER, 5.9 per 10,000 person-years) and genitourinary (AER, 6.0 per 10,000 person-years) systems, with these two sites accounting for 36% of the total AER after age 40 years.[10]

The combined Nordic cohort, which consists of registry data from Denmark, Finland, Iceland, Norway, and Sweden, spans the diagnosis years between 1943 and 2005. This study[11] identified a threefold increased risk for a SMN compared with the general population (SIR, 3.3; 95% CI, 3.1 to 3.5) and showed the highest risk for developing SMNs of the bone, connective tissue, CNS, and endocrine glands. The risk for a SMN occurring between ages 40 and 70 years was 1.5- to 2.3-fold that of the general population. Individuals treated in the most recent era of study (1975 to 2005) experienced higher age-specific incidence rates compared with those treated earlier.[11]

The DCOG-LATER study reported a fivefold increase in SMN SIR compared with the general population (SIR, 5.2; 95% CI, 4.6 to 5.8) among 6,165 5-year survivors diagnosed between 1963 and 2001, and a 25-year cumulative SMN incidence of 3.9%.[12] The SIR was still significantly increased after ≥ 30 years (SIR, 3.8; 95% CI, 2.8 to 4.9) and the AER substantially increased with increasing follow-up time. There was no significant decrease in cumulative incidence of SMNs for survivors treated in the 1990s compared with those treated earlier, in contrast to what was reported by the CCSS.[8,12]

Collaborative work among multiple European countries is forthcoming under the umbrella of the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare). Pooled cohort and case-control studies on the risk of SMNs among 69,460 5-year survivors across 12 European countries are underway.[13] This large-scale study provides a means for consistent data collection and reporting across cohorts and overcomes the limitations in size and available data observed in previous studies.[14]

RISK FACTORS

Radiotherapy and SMN Development

Radiation dose–related SMN risk has been studied for many cancers, as summarized in Fig 2.[15] Dose-response studies rely on the radiotherapy target dose (ie, the dose delivered to the tumor

and its surroundings), which is valid for proximal tissues. For more distant tissues, exposures are estimated using dose-reconstruction methods, accounting for patient and treatment characteristics (eg, treatment dose, beam energy, field size and configuration).[16]

CNS tumors occur in excess after cranial radiotherapy, mainly among survivors of pediatric brain tumors and acute leukemia.[10] The CCSS and BCCSS reported dose-response trends for glioma (excess odds ratio [EOR] per Gy, 0.33 and 0.079, respectively) and nonmalignant and malignant meningioma (EOR per Gy, 1.06 and 5.1, respectively).[17,18] A 39-fold excess risk of salivary gland tumors was reported by the CCSS, with an estimated excess relative risk per Gy of 0.36, with most observed cases occurring after leukemia or lymphoma.[19] An international pooled analysis of thyroid cancer in survivors of childhood cancer showed a dose-response plateau between 10 and 30 Gy and decreasing risk at higher doses (Fig 3),[20] hypothesized to be due to cell killing, with stronger dose-responses for those who were youngest at the time of exposure.[20] Additional analysis of low-dose radiation exposure showed significant dose-response trends at < 0.2 and < 0.1 Gy ($P < .01$) persisting > 45 years after exposure.[21]

Data on lung cancer in cohorts of survivors of childhood cancer are limited. The Nordic cohort reported eight cases, for a 3.9-fold increased risk (95% CI, 1.7 to 7.6) in survivors with an attained age of 40 to 79 years.[11] In addition, large studies of survivors of Hodgkin lymphoma (HL) who were treated as children and young adults showed that lung cancer risk was elevated after chest radiation and that radiation incurred a multiplicative effect in smokers.[22,23]

Female breast cancer risk is increased, particularly after chest/absorbed doses > 10 Gy,[24] with an established linear dose-response relationship (Fig 4).[25] There is growing evidence for heightened radiation sensitivity surrounding menarche,[26] with risk persisting 40 to 45 years after radiotherapy,[7,22] and reduction of radiation-related risk among women with premature menopause (Fig 4).[25] Cumulative incidence of breast cancer by age 50 years in women treated with chest irradiation for HL has been estimated at 35%. The cumulative incidence by age 45 years for other survivors of childhood cancer treated with chest irradiation was 15%, presumably lower because of lower radiation treatment doses.[24] Excess risk for breast cancer was also shown after total-body irradiation at a young age.[12]

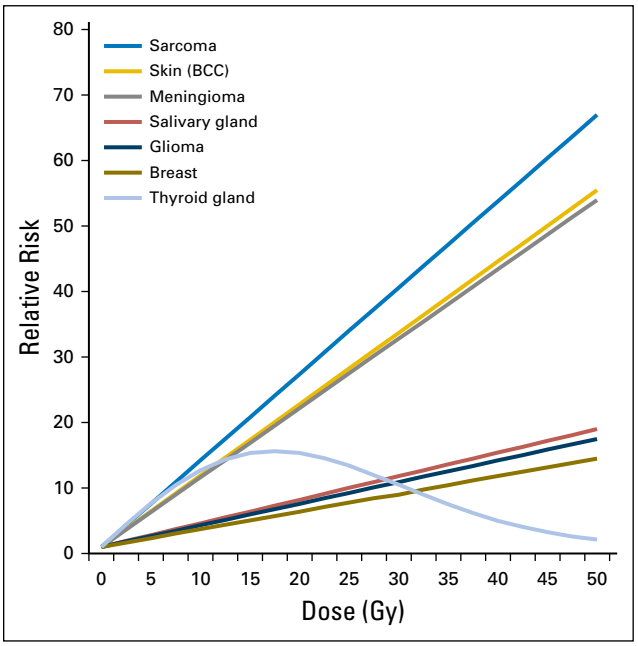

Fig 2. Fitted radiation dose response by type of second cancer, on the basis of previously published reports from the Childhood Cancer Survivor Study. Reprinted with permission.[15]

GI tract SMNs occur in excess many years after childhood cancer (SIRs range from 2.0 to 30.0).[10,27-29] The CCSS reported that survivors treated with abdominal radiation experienced an 11-fold increased risk for GI SMNs (SIR, 11.2; 95% CI, 7.6 to 16.4).[27] The St Jude Lifetime Cohort (SJLIFE) showed a radiation dose-response by 10-Gy increments of prescribed dose for colon cancer,[28] whereas a relative risk per dose (Gy) to digestive organs of 1.13 was reported in Europe.[29] The BCCSS investigators reported a nearly fivefold increased risk for GI cancers (SIR, 4.6; 95% CI, 3.8 to 5.6). Cumulative incidence of colorectal cancer by age 50 years was 1.4% (95% CI, 0.7% to 2.6%) for survivors treated with abdominopelvic irradiation, similar to rates observed in individuals with two or more first-degree relatives affected by colorectal cancer.[10]

A summary of six studies of subsequent sarcomas among survivors of childhood cancer[30] showed a linear dose-response > 10 Gy, with a possible decrease at doses > 40 Gy for bone sarcoma, and with higher relative risks for bone sarcoma compared with STS. Nonmelanoma skin cancer, most often basal cell carcinoma, represents the most common subtype of solid cancer after radiotherapy, of which $> 90\%$ occur in the radiation field (EOR per Gy, 1.09).[31]

Most studies examining radiotherapy-associated SMNs analyze radiotherapy from the era of two-dimensional imaging. However, dose distribution across healthy tissues is changed with modern radiotherapy techniques, such as intensity-modulated radiotherapy and proton therapy. Proton beam radiotherapy involves no dose deposition in tissues behind the tumor, which could reduce SMN risk, but because of small sample size and other methodologic challenges, the single study on SMN risk after proton therapy is inconclusive.[32] It will be critical to study how these changes in technique have effected SMN risk among survivors treated more recently.

Chemotherapy and SMN Development

The best-established association between chemotherapy and SMNs is for therapy-related acute myeloid leukemia (*t*-AML) and therapy-related myelodysplastic syndrome (*t*-MDS). Dose-dependent risks for *t*-AML and *t*-MDS are high ($>$ 10-fold increased) after almost all alkylating agents, as well as topoisomerase II inhibitors[33-36]; however, the leukemogenicity of different agents varies substantially and the AER is low because of the low background risk. *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 and 7 abnormalities.[33] In contrast, *t*-AML after topoisomerase II inhibitor exposure typically arises < 3 years after therapy, is rarely preceded by MDS, and is most frequently characterized by 11q23 rearrangements.[37]

Chemotherapy also increases risk for nonhematologic SMNs, which typically occur > 10 years after exposure.[33] Alkylating-agent

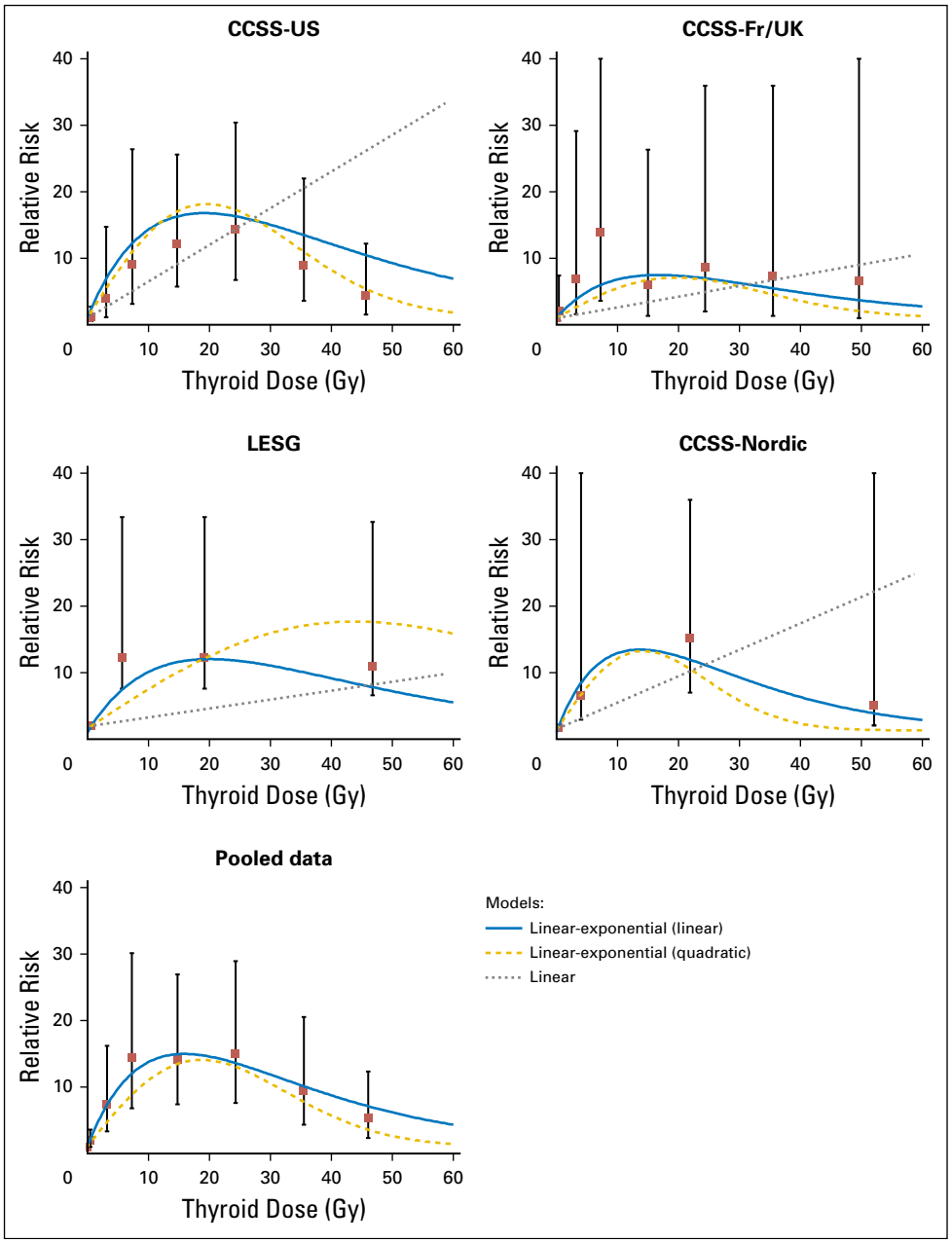

Fig 3. Relative risks and 95% CIs for categories of radiation dose and fitted dose-response models for four original studies and for all data combined (pooled analysis) for subsequent thyroid cancer. Category-specific relative risks for the LESG and CCSS-Nordic Studies were adjusted using the fitted linear-exponential (linear) model to reflect a referent of zero dose. CCSS, Childhood Cancer Survivor Study; Fr/UK, France and United Kingdom; LESG, Late Effects Study Group. Reprinted with permission.[20]

exposure increases risk for GI, thyroid, lung, breast, and bladder cancers, as well as sarcoma.[22,23,28,38-43] Specifically, cyclophosphamide increases sarcoma risk in a dose-dependent manner.[12,38,42,44] Furthermore, cyclophosphamide equivalent doses of $>$ 18,000 mg/m^2 increase breast cancer risk by threefold (SIR, 3.0; 95% CI, 1.2 to 7.7),[41] and procarbazine and platinum have been associated with 3.2-fold (95% CI, 1.1 to 9.4) and 7.6-fold (95% CI, 2.3 to 25.5) increased risks, respectively, for GI SMNs.[40] Procarbazine-related risks for the GI tract may be related to direct exposure with the mucosa,[28,39,44] whereas the mechanisms of carcinogenesis for agents administered intravenously and for other malignancies are unknown.

Risk for breast cancer and other solid malignancies, including sarcoma, are increased after anthracycline exposure.[12,41,44] In the CCSS cohort, risk for breast cancer in survivors treated with $>$ 250 mg/m^2 anthracycline and without a history of chest radiotherapy is increased by nearly fourfold compared with risk in the general population (SIR, 3.8; 95% CI, 1.7 to 8.3).[41] The DCOG-LATER cohort reported similar findings, with a dose-dependent relationship between breast cancer risk and doxorubicin ($P_{trend} < .001$).[12] In 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.[12,41]

Chemotherapy can also indirectly affect SMN risk. In studies of adolescent and young adult survivors of HL,[22,45,46] higher cumulative procarbazine exposure was associated with a greater reduction of breast cancer risk, with 30% and 67% risk reductions for regimens of $<$ 8.4 g/m^2 and $>$ 8.4 g/m^2 procarbazine,

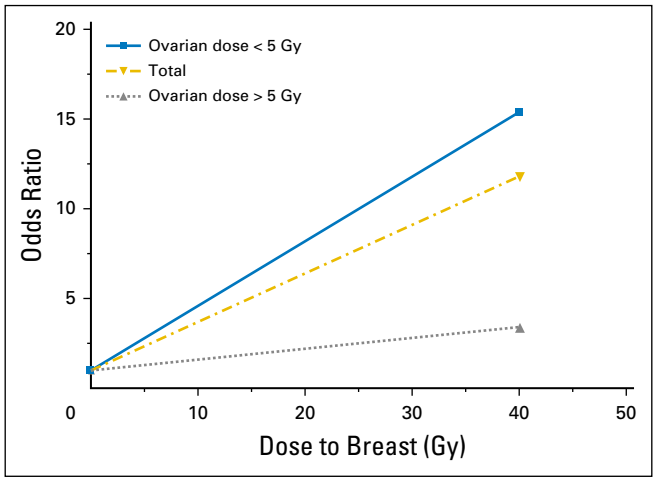

Fig 4. Breast cancer risk by radiation dose to the breast and ovary. Reprinted with permission.[25]

respectively.[45,46] This risk reduction seems to be due to the higher frequency of premature menopause in patients treated more intensively with chemotherapy and their resultant reduced exposure to ovarian hormones.[46-48] Similarly, high cumulative alkylator exposure significantly reduced breast cancer risk in the CCSS cohort,[26] in contrast to earlier CCSS results that did not show a reduced breast cancer risk after alkylator therapy.[49] Breast cancer risk also increases in women with > 10 years of ovarian function after chest radiotherapy compared with those with less.[26,46,48]

Genetics and SMN Development

Genomic advances in the last decade have expanded our understanding of cancer predisposition. Broadly, genetic contributions to cancer range from rare, highly penetrant variants that are often associated with familial cancer susceptibility syndromes to more common genetic variants associated with weakly or modestly elevated risk for cancer in the general population.

Multiple primary cancers within an individual can occur in several cancer susceptibility syndromes[50]; diagnoses often include rare histologies or occurrence at younger than expected ages. Most variants confer risk through an autosomal dominant inheritance pattern, although a few exhibit autosomal recessive, X-linked, or Y-linked patterns. Examples of inherited cancer predisposition syndromes are listed in Table 1. Understanding of the penetrance of and risks associated with these mutations, particularly in the absence of established family history, is evolving rapidly with the expansion of gene panel testing in recent years.

Research is increasingly focused on whether germline genetic variation modifies risk for treatment-related SMNs. Sensitivity to damage from ionizing radiation exposure has been reported among individuals with several cancer predisposition syndromes, such as ataxia telangiectasia, and in experimental studies demonstrating cellular radiosensitivity.[52,53] In the general population, most studies have focused on genetic variation in DNA damage detection and repair mechanisms as potential modifiers of treatment-related SMN risks, as reviewed recently.[54] However, these studies are limited by small sample sizes, insufficient treatment exposure data, or lack of replication of the reported findings. More recently, studies have agnostically interrogated common genetic variation across the genome to identify variants associated with SMN risk, including studies of *t*-MDS and *t*-AML,[55] SMNs after HL,[56] and breast cancer after childhood cancer.[57] Expansion of these studies through large-scale genomics efforts in survivors of cancer, such as the CCSS and the SJLIFE Cohort, should provide important insights into the role of genetic susceptibility in multiple primary cancers.

SURVEILLANCE AND INTERVENTION

In 2003, the Institute of Medicine called for lifelong risk-based health care for survivors of childhood cancer.[58] Given the high risk for morbidity and mortality resulting from SMNs, the Children's Oncology Group (COG) and others developed consensus-based surveillance guidelines for SMNs,[59,60] with the goal of detecting SMNs at earlier, more treatable stages. Guideline groups worldwide have formed the International Guideline Harmonization Group (IGHG) to provide harmonized evidence-based guidelines.[61]

Examination of other populations at increased cancer risk have shown that, for some solid cancers, early initiation of surveillance may improve outcomes. Breast cancer surveillance guidelines[60,62-64] have been prioritized, given the increased risk among survivors exposed to chest irradiation. Mammogram screening in high-risk survivors is associated with earlier breast cancer detection,[65] and combination breast magnetic resonance imaging and mammogram screening in survivors exposed to chest radiotherapy before age 30 years increases the specificity and detection of invasive breast cancer and ductal carcinoma in situ, a finding that is now reflected in screening guidelines.[60,62-64,66] The COG, DCOG-LATER, and the IGHG guidelines recommend that screening begin at age 25 years or 8 years after treatment, whichever occurs later. Recently, the COG has decreased the radiation exposure threshold to 10 Gy for initiating screening, consistent with the 2010 Dutch recommendations.[60,62] The COG, unlike other guidelines, recommends annual colonoscopy in survivors exposed to abdominal or pelvic radiation therapy, beginning at age 35 or 10 years after radiation exposure, whichever occurs last.[60] IGHG recommendations for colorectal cancer surveillance are expected in 2018. For skin cancer screening, the COG recommends yearly dermatologic examinations of the radiation field.[62]

Routine screening for thyroid cancer and CNS neoplasms remains controversial. Studies examining annual thyroid ultrasound surveillance suggest that a yearly physical examination is sufficient and may minimize the harm associated with overdiagnosis and overtreatment.[67] For survivors exposed to neck radiation, the COG recommends ultrasound and fine needle aspiration for palpable nodules. Similarly, routine radiographic screening for meningiomas is currently not recommended.[62]

Screening programs are recommended for survivors with known germline cancer predisposition syndromes, such as Li-Fraumeni syndrome, Lynch syndrome, and familial retinoblastoma. According to one study, nearly 10% of survivors of childhood cancer may harbor an actionable germline genetic mutation[68]; thus, it is imperative that risk-based care include yearly review of family history and referral for genetic counseling for survivors with a history suggestive of a cancer predisposition syndrome.

Table 1. Examples of Surveillance for Potential SMN in Patients with Identified Cancer Predisposition Syndromes

Cancer Predisposition Syndrome (associated gene)	Potential SMN	Surveillance/Prevention Guidelines
Li-Fraumeni syndrome (*TP53*)	CNS tumors	Annual brain*
	Sarcomas	Total body MRI*
	Leukemia	Annual mammogram and breast MRI surveillance starting at age 20-25 years, or individualized on the basis of earliest age of onset in family*
	Breast cancer	Consider bilateral prophylactic mastectomy*
	Colorectal cancer	Biennial colonoscopies beginning at age 40 years, or 10 years before the earliest known colon cancer in the family*
	Upper gastrointestinal tumors (eg, stomach and esophagus)	Annual dermatology examination*
	Lung cancer	Annual abdominal ultrasound*
	Melanoma	
	Pancreatic cancer	
	Adrenocortical cancer	
	Kidney cancer	
	Gonadal germ cell tumors	
Hereditary breast or ovarian cancer (*BRCA 1/2*)	Breast cancer (in men and women)	Annual screening mammogram to begin 10 years before the age of diagnosis of the youngest family member but not < 30 years old
	Ovarian cancer	Annual screening breast MRI to begin 10 years before the youngest family member but not < 25 years old†
	Fallopian tube cancer	Consider risk reduction strategies (eg, prophylactic mastectomy and/or oophorectomy, tamoxifen)†
	Pancreatic cancer	
	Prostate cancer	
Colorectal cancer/polyposis syndromes	FAP	FAP: Annual flexible sigmoidoscopy or colonoscopy between ages 10 and 15 years until surgery is warranted.† After colectomy, upper endoscopy is recommended starting at ages 20 to 25 years.
	Colorectal cancer	Lynch syndrome: Colonoscopy every 2 years beginning at age 20 to 25 years until age 40 years, then annually thereafter‡
	Stomach cancer	
	Small bowel malignancy	
	Pancreatic cancer	
	Biliary tree	
	Papillary thyroid cancer	
	Medulloblastoma (if not primary childhood cancer)	
	Hepatoblastoma (if not primary childhood cancer)	
	Lynch syndrome	
	Colorectal cancer	
	Pancreatic cancer	
	Endometrial cancer	
	Breast cancer	
	Ovarian cancer	
	Stomach cancer	
	Small bowel malignancy	
	Prostate cancer	
	Liver cancer	
	Urinary tract cancer	
	Kidney cancer	
	Bile duct cancers	
Familial retinoblastoma (*RB1*)	Osteosarcoma	Consider annual MRI in previous radiation field
	Soft tissue sarcoma	Annual physical examination
	Melanoma	Annual dermatology examination (with particular attention to the previous radiation field)§
	Lung cancer	
	Lymphoma	
	Bladder cancer	
	Endometrial cancer	
	Breast cancer	
	Brain tumors	
	Cancers of the nasopharynx	

Abbreviations: FAP, familial adenomatous polyposis; MRI, magnetic resonance imaging; SMN, subsequent malignant neoplasm.
*Modified Toronto Protocol.[51]
†National Comprehensive Cancer Network guidelines.
‡American College of Gastroenterology guidelines.
§Children's Oncology Group long-term follow-up guidelines.

Despite surveillance recommendations, many primary care providers are unaware of,[69] and many survivors are often nonadherent with,[70,71] recommended screenings. Interventions have been developed to improve awareness and adherence to screening guidelines for breast and skin cancer.[72,73] Additional study is necessary to inform SMN surveillance recommendations and to improve adherence as well as survivor and provider knowledge of these recommendations.

Few primary prevention strategies are available for SMN reduction. A phase II, multicenter, randomized, placebo-controlled trial is currently evaluating the use of low-dose tamoxifen for 2 years in female patients who received ≥ 12 Gy of chest irradiation before age 40 years. Prophylactic mastectomy is also offered to women exposed to chest radiotherapy at a young age.

In conclusion, we have learned a great deal about SMN risk, risk factors, genetic predisposition, and surveillance. New therapies in clinical practice necessitate ongoing research on SMN risk; prioritization of surveillance efforts and survivor and provider education are also necessary. Improved survival and recognition of late effects, including SMNs, reinforce the need for ongoing upfront therapy modifications to moderate late health risks and to improve long-term survivor health.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk, Risk Factors, and Surveillance of Subsequent Malignant Neoplasms in Survivors of Childhood Cancer: A Review

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