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Secondary malignancies across the age spectrum

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Abstract

Development of a second malignancy is one of the most serious late effects in survivors of both childhood and adult-onset cancers. Patterns of second malignancy risk across the age spectrum can differ in terms of the types of second malignancies observed, magnitude of the risks, the latency period, associated risk factors, and modifying influences. Potential explanations for the varying risk patterns by age include differences in susceptibility of individual tissue/organ to carcinogenesis based on stage of development and level of tissue maturity, microenvironment, attained age, and lifestyle factors. A thorough understanding of these differences is essential when considering treatment modifications in newly diagnosed cancer patients that are aimed at reducing the risk of second malignancy and other late effects without compromising cure. Moreover, an understanding of the variations in second cancer risk according to age at treatment is important in customizing patient follow-up.

Introduction

Improvement in early cancer detection as well as advances in therapy and supportive care have resulted in an increasing number of cancer survivors [1]. Second malignancies have emerged as one of the most serious late effects of treatment for both survivors of childhood cancer and adult-onset cancer. A number of potential influences, in addition to radiation and chemotherapy, are known to either contribute to or modify the development of second primary cancers. These include genetic predisposition, environmental exposures, hormonal factors and immune function [2]. Moreover, in considering the site-specific risks of second malignancies, several factors may explain the observed varying patterns of second cancer development based on age at diagnosis and treatment. These include differences in follow-up time and attained age, stage of development of individual organs or tissues at risk, hormonal milieu, and prevalence and chance of cure for the same disease presenting in children versus adults.

In this article, the site-specific risk of second malignancies after selected childhood and adult-onset cancers will be reviewed. In particular, the risk of second malignancy after Hodgkin lymphoma (HL), a highly curable disease that affects both children and adults, will be examined for both age groups. Finally, age-related differences in the risks of second primary cancers of breast, thyroid, and lung will be discussed as specific examples illustrating the differences in patterns of second malignancy development after childhood and adult-onset cancer, respectively.

Overview of Second Malignancy Risks After Selected Childhood Tumors

Advances in the treatment of childhood cancer have resulted in excellent prognosis for cure, with a five-year survival rate at around 75% [1]. Despite such improvements, childhood cancer survivors remain at increased risk for life-threatening treatment-associated complications including major organ toxicity and secondary malignancies [3–8]. Several large cohort studies have shown that secondary malignancies are the leading cause of treatment-related premature mortality in five-year survivors of childhood cancer [6, 8, 9]. Although it is recognized that the majority of childhood cancer survivors will not be diagnosed with a second primary cancer, the 20-year cumulative incidence of secondary malignancies in five-year survivors of 3–4% is of concern. Furthermore, as childhood cancer survivors are followed to older adulthood, the cumulative incidence of secondary malignancies continues to increase [6].

Radiation-associated solid tumors are the most common type of secondary malignancies observed in childhood cancer survivors; however, survivors are also at increased risk for chemotherapy-associated hematologic malignancies [3, 4]. Along with treatment exposures, the etiologic factors that contribute to the development of secondary malignancies in childhood cancer survivors include primary cancer diagnosis, age and developmental stage at cancer diagnosis, gender, duration of follow-up, attained age, and hereditary cancer predisposition. Childhood acute lymphoblastic leukemia (ALL), retinoblastoma (RB), and Hodgkin lymphoma (HL) are representative pediatric cancer types that have an excellent prognosis for long-term survival, but also have well-characterized risks for secondary malignancies. The most prevalent secondary malignancies associated with these three pediatric cancers will be reviewed in this section, illustrating the interplay of various etiologic factors related to the development of subsequent cancers in childhood cancer survivors.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) represents approximately 25% of all childhood cancer diagnoses, with a peak age of incidence between 2 and 6 years. Currently, the overall 5-year relative survival is 80% [1]. Curative therapy includes multi-agent chemotherapy and prophylaxis against central nervous system (CNS) leukemia with intrathecal chemotherapy and/or cranial radiation. Stem cell transplant is reserved for poor prognostic features at diagnosis, or if conventional therapy fails. Although the majority of children with ALL become five-year survivors, secondary malignancies and other adverse events reduce longer-term survival.

The 15-year cumulative incidence of secondary malignancies for ALL survivors is between 2.5–4% [10–12]; however, data from a single institution cohort of over 2000 ALL survivors diagnosed from 1983–1995 show an increasing incidence of secondary malignancies with increasing duration of follow-up, with a cumulative incidence of 6% at 30 years [13]. The most commonly observed secondary malignancies include CNS tumors, leukemias/lymphomas, and skin cancers. Risk factors associated with secondary malignancies in ALL survivors are younger age at diagnosis (age <5), female gender, cranial/cranial spinal

radiation, and relapse [10, 11, 13]. Of note, a lower 10-year cumulative incidence of secondary malignancies, 1.2% (95% CI, 0.8%–1.5%), was reported in a cohort of ALL survivors treated after 1983, when fewer children received cranial radiation as CNS prophylaxis. [12]

Benign and malignant CNS tumors are reported in ALL survivors treated with cranial radiation. Additional risk factors for secondary CNS tumors are treatment at <5 years of age and presence of CNS leukemia at diagnosis [14, 15]. The most common types of secondary CNS malignancies are meningiomas and gliomas; however, primitive neuroectodermal tumors and CNS lymphomas have also been observed [14, 15]. Studies report a 10–20 fold increased relative risk of secondary brain tumors compared to age-matched general populations [11, 14]. The minimal latency period for secondary CNS malignancies varies by tumor type, from 9 years for secondary gliomas to 20 years for meningiomas [14, 15]. In a St. Jude's cohort study of 1,251 ALL survivors treated with cranial irradiation, the 20-year and 30-year cumulative incidence of CNS tumors was 1.4% and 3.0%, respectively [15]. In addition, there is a well-established dose response relationship between cranial radiation dose and incidence of secondary CNS tumors. Further analysis of the same St. Jude cohort showed that the 20-year cumulative incidence of CNS tumors increased in conjunction with radiation dose: 1% at 10–21Gy; 1.7% at >21–30 Gy; and 3.2% at >30Gy [15]. The contribution of chemotherapy to the risk of CNS malignancies is controversial. Clinical and laboratory studies have suggested an association between radiation-induced brain tumors and an intensive schedule of thiopurine-based chemotherapy [16]; however, epidemiologic data from the Childhood Cancer Survivor Study (CCSS) cohort found that chemotherapy did not alter brain tumor risk after adjusting for radiation dose [14].

Secondary hematologic malignancies are also observed in childhood ALL survivors [10, 17]. Acute leukemia and myelodysplasia are associated with exposure to high cumulative doses of alkylating agents and with topoisomerase II inhibitors including epipodophyllotoxins and anthracyclines [18]. Secondary leukemias associated with high dose alkylating agent exposure usually occur in older children, have a latency of 4–10 years, and are associated with myelodysplasia and deletions in chromosomes 5 and 7 [19]. In contrast, topoisomerase II-induced secondary leukemias are typically diagnosed in younger children, have a short latency period (median 1–3 years), and are associated with balanced chromosomal translocation 11q23, or less frequently 21q22 [16, 17, 19, 20]. The cumulative incidence of secondary leukemias is as high as 3.8% at 6 years in ALL survivors treated with topoisomerase II inhibitors [18]. A dose response relationship has been demonstrated for both alkylating agent and topoisomerase II associated leukemias [21]. In addition, the administration schedule of epipodophyllotoxins appears to contribute to the risk of secondary leukemias, as prolonged infusions were found to be an independent risk factor [18, 22]. The contribution of therapeutic radiation to the development of secondary leukemia is controversial with some studies finding no association between leukemia and exposure to radiation therapy [4, 18, 23] and others documenting subsequent leukemia in survivors after exposure to radiation in the absence of chemotherapy [17, 19, 23]. Thus, therapeutic radiation likely has a role in secondary leukemogenesis.

Retinoblastoma

Retinoblastoma (RB) accounts for only 2% of childhood malignancies, with 80% of children diagnosed at <4 years of age. Treatment options for RB include enucleation, external beam radiation therapy, brachytherapy, cryotherapy, photocoagulation, thermotherapy, and chemotherapy. Although the five-year relative survival rate for RB is 95%, survivors are at risk for multiple secondary malignancies. Approximately 40% of cases of RB are hereditary, with an identifiable germline deletion in the Rb-1 tumor suppressor gene which confers a genetic predisposition to subsequent neoplasms [24]. The specific secondary malignancies

for which survivors with hereditary RB are at the highest risk include soft tissue sarcomas, bone sarcomas, and malignant melanoma. Risk for nasal cavity malignancies and brain tumors are also increased [25]. In addition, elevated risks of late-onset secondary epithelial cancers such as lung, female breast, bladder, colon, and corpus uteri are also observed as extended follow-up of large cohorts of RB survivors becomes available [25–27].

Genetic predisposition and treatment exposures are both etiologic factors in the development of secondary malignancies. Extended follow-up of a cohort of over 1,500 RB survivors shows that survivors with hereditary retinoblastoma treated with radiation therapy have a cumulative risk of secondary malignancy as high as 38.2% (95% CI, 32.6%–43.8%) at 50 years of follow-up, and, in comparison, the 50-year cumulative incidence of secondary malignancies for non-irradiated hereditary survivors was 21.0% (95% CI, 9.42%–35.6%) [25]. Further, the majority of secondary sarcomas observed in hereditary RB survivors are diagnosed in prior radiation fields (60–70%), and the remaining are diagnosed in anatomic locations beyond the radiation field, such as the lower extremities, where scatter dose would not be an etiologic consideration [25, 27]. In contrast, secondary melanomas are more likely to be diagnosed outside the radiation field, and risks for secondary melanoma are similar in both irradiated and nonirradiated survivors, thus supporting the hereditary predisposition for this specific secondary cancer.

In general, survivors of nonhereditary RB are not considered to be at increased risk of secondary malignancies except for soft tissue sarcomas (SIR 21.9, 95% CI 4.5–63.7) [27], and female breast cancer (SIR 2.8, 95% CI 1.1–5.9) [25]. It has been suggested that the increased risk of secondary malignancies in survivors with the non-hereditary form of RB is attributable to radiation exposure, or possibly incorrect classification of survivors as having the non-hereditary forms of RB when they actually are carriers of an RB-1 mutation [25, 27].

The most frequently observed secondary malignancies in hereditary RB survivors are bone and soft tissue sarcomas. The most common histiologic subtypes of sarcomas in order of frequency are leiomyosarcomas, fibrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, and liposarcoma [25]. For survivors of hereditary RB who received radiation, the relative risk for soft tissue sarcomas is over 100-fold (SIR=140, 95% CI, 96–196) compared to the age-matched general population, and the risk of subsequent bone sarcomas is close to 400-fold (SIR= 406, 95% CI 318–511) [25, 28, 29]. Similar to other radiation-associated secondary malignancies, there is an established dose-response relationship for secondary bone and soft tissue sarcomas [28, 29]. In addition, data supports that alkylating agent chemotherapy potentiates the risk of both radiation-associated bone sarcoma and soft tissue sarcomas [25, 30].

Attained age is another factor that alters risk for secondary malignancies. Survivors of hereditary RB <5 years old are at risk for “trilateral retinoblastoma” which is an intracranial neuroblastic tumor most often of the pineal gland. This secondary malignancy is rarely diagnosed in survivors >5 years old [31]. Similarly, the majority of second malignancies diagnosed in RB survivors <30 years are sarcomas, and >30 years of age the increased risk for epithelial cancers including breast, lung, colon, and bladder emerges [27]. In a Dutch registry based study of over 600 RB survivors, with over 40 years of follow-up, after age 40 years secondary epithelial cancers were more common than sarcomas in hereditary RB survivors [27]. Other studies have also identified an age difference in incidence of secondary sarcomas, with nonirradiated hereditary RB survivors >25 years old having a much lower proportion of sarcomas (8–14%), compared to their irradiated counterparts (50%) [26, 32].

Hodgkin Lymphoma (HL)

Lymphomas represent approximately 15% of childhood cancers. HL diagnosed during childhood and adolescents has a 5-year survival rate of over 90%, and is most often treated with combination chemotherapy and radiation therapy. Survivors have an established risk for subsequent malignancies with a 25-year cumulative incidence of 19%, and no foreseeable plateau in incidence of solid tumors with continued follow-up [33, 34]. The most frequently observed solid secondary malignancies are breast cancer, thyroid cancer, and bone/soft tissue sarcomas [6, 12, 33–38]. With extended follow-up of cohorts of young HL survivors, increased risks of common adult carcinomas including colorectal, lung, and gastric types have emerged, and these cancers are diagnosed at younger ages than observed in the general population [34]. Established independent risk factors for secondary solid malignancies are younger age at HL diagnosis (12–16 years), increasing radiation dose, and female gender [33, 34]. In the study by Constine et al. [33], the relative risks for second malignancy in female versus male childhood HL survivors were 19.9 and 8.4, respectively ($p < 0.0001$). The higher risk in female survivors may in part be driven by breast cancer risk, although the difference in second malignancy risk by gender persisted after excluding breast cancer as a second malignancy.

The risk of secondary female breast cancer has been extensively studied in large cohorts of childhood HL survivors. These studies report a 15–55 fold increased risk of radiation-associated secondary female breast cancer compared to the age-matched general population [34–44]. Risk estimates vary by characteristics of the cohort studied including mediastinal radiation dose, age at therapy, duration of follow-up, and completeness of follow-up. The cumulative incidence of secondary breast cancer is as high as 12–35%, 20 years after therapy for HL, and like most secondary malignancies, the incidence does not plateau with longer duration of follow-up [34–43]. The typical latency of radiation-associated breast cancer in young survivors of HL is 10–15 years after therapy; however, secondary breast cancer has been reported in women as young as 20 years of age and as soon as 6 years after therapy [39]. Female HL survivors at greatest risk for secondary breast cancer are those treated between age 10–30 years with mediastinal radiation doses >25 Gy [43, 45]. Similar to other radiation associated secondary malignancies, a dose-response relationship between radiation dose and risk of secondary breast cancer has been established, with higher mediastinal doses associated with greater relative risk [33, 43, 44].

Survivors of childhood HL treated with neck and upper thorax radiation are at increased risk for radiation-associated secondary thyroid cancers. Large cohort studies of survivors of childhood cancer exposed to neck irradiation report the relative risks of secondary thyroid cancer to be between 10–35 [34, 35, 46–49]. At 30 years, the cumulative incidence in HL survivors is 4.4% [34]. Although the minimum latency period for secondary thyroid carcinoma is 5 years [34, 49, 50], the incidence of thyroid carcinoma remains increased beyond 40 years after irradiation for primary cancer [34, 51, 52]. Secondary thyroid cancer is more common in females, and young age at treatment is an independent risk factor [34]. The risk of thyroid cancer is related to radiation dose, but unlike most other radiation-induced second cancers, it is greatest at doses 20–29 Gy but declines at doses >30 Gy [48, 53]. A case control study of 69 cases showed an increased risk with radiation doses as high as 29 Gy (OR=9.8; 95% CI, 3.2 to 34.8), but a decrease in risk at doses >30 Gy [48]. This finding supports the “cell-kill” hypothesis, suggesting that higher doses of radiation cause thyroid cell death which reduces the initiation of carcinogenesis observed at lower doses. Finally, chemotherapy does not appear to modify risk of secondary thyroid cancer [48, 54].

Overview of Second Malignancy Risks After Selected Adult-Onset Tumors

In this section, the focus is on several adult-onset primary malignancies in which considerable data on the risk of second malignancies have accrued. These include HL and testicular cancer, both of which are typified by a relatively young age at diagnosis, high cure rate, and the historical use of large-field radiation therapy. In recent years, a growing amount of data has also emerged on the risk of second malignancies after several more common cancers, such as breast and prostate, which are also included in this section.

Hodgkin Lymphoma

As in childhood HL, adult HL is associated with a high cure rate, and among patients with favorable-prognosis, early-stage disease, cure can be achieved in >90% of patients [55]. However, survivors of HL are at significantly increased risk for mortality from other causes, with second malignancy being the leading cause of death [56, 57]. A number of host-related and treatment-related factors contribute to or modify the risk of second malignancy after HL. However, while female gender has been shown to be a risk factor for development of second malignancy among childhood HL survivors [33, 58], the effect of gender in adult HL survivors is more complex [4]. Other differences in second malignancy risks between childhood and adult HL survivors will be discussed in a later section in the context of several distinct types of second cancers. These differences are summarized in Table 1.

Among various types of second malignancy after HL, solid tumors account for up to 75–80% of second malignancies after HL [36, 47, 59]. Radiotherapy-associated solid tumors usually develop after a longer latency period (at least 5 to 9 years) after treatment, and the increased risks persist for at least 30 years [60]. Cancers of the breast, lung, and gastrointestinal sites result in the largest excess absolute risks after HL. In a population-based study of solid tumor risk among 18,862 5-year HL survivors reported to 13 cancer registries, cancers at these three sites accounted for almost two-thirds of estimated excess number of cases [60]. For breast cancer, many studies have shown that risk is significantly higher among women who received radiation therapy at a young age. Relative risks compared to the general population appear to be particularly low for women treated after age 35. Travis et al [45] developed estimates of cumulative absolute risk for use in counseling of patients. For example, the cumulative absolute risks for a HL survivor who was treated at age 25 years with a chest radiation dose of 40 Gy without alkylating agents were estimated to be 1.4% after 10 years, 11% after 20 years, and 29% after 30 years.

Case-control studies conducted in several of these registries have shown significant dose-response relationships for the development of both breast cancer and lung cancer after radiotherapy for HL [42, 43, 61, 62]. For breast cancer after HL, there appears to be a protective effect of early menopause either as a result of alkylating chemotherapy or radiation dose >5 Gy to the ovaries, suggesting that ovarian hormones play an important role in promoting tumorigenesis once an initiating event has been produced by radiation [42, 43].

While alkylating agent chemotherapy for HL is associated with a subsequently reduced risk of breast cancer through a deleterious effect on ovarian function [42, 43], increased risks of lung cancer risk ensue. In a large international case-control study of lung cancer after HL in which the roles of radiation dose and amount of tobacco use were taken into account [61], a strong lung cancer dose-response relationship was observed for increasing cumulative dose of either mechlorethamine or procarbazine (P trend < 0.001), and with the number of cycles of alkylating agent chemotherapy, a grouping which included not only mechlorethamine or procarbazine, but other agents as well [61]. Other studies, albeit not as well controlled for radiation and tobacco use [63], have reported similar results for alkylating agent administration and the risk of subsequent lung cancer.

Tobacco use is an important modifying factor for treatment-related lung cancer after HL. In the international case-control study of lung cancer after HL [61, 62], patients who received either alkylating agent chemotherapy alone or 5 or more Gy of radiation therapy alone to the region of the lung in which cancer developed experienced 4.3-fold and 7.2-fold increased risks of lung cancer, respectively, compared to patients with minimal treatment exposures and who were non-smokers or light smokers. These relative risks increased to 16.8-fold and 20.2-fold, respectively, among patients who also smoked at least one pack of cigarettes per day. For cigarette smokers (at least one pack per day) also given alkylating agent chemotherapy and 5 Gy of radiation therapy to the area of the lung in which cancer developed, the relative risk of subsequent lung cancer was almost 50-fold. Further analysis indicated that these data were consistent with a multiplicative effect of smoking and treatment.

The risk of second primary cancers for HL patients treated in the modern era will likely be lower than those documented in current reports, in view of the decreased use of alkylating agent chemotherapy, the trend towards the application of smaller radiation fields, and lower doses and the availability of conformal radiation treatment techniques. It is important to institute long-term follow-up of these HL patients in order to accurately monitor and quantify the associated risks of second cancers and other late effects.

Testicular Cancer

Second malignancies observed after testicular cancer include contralateral testicular cancer, leukemia, and a number of solid tumors including malignant mesothelioma, and cancers of the lung, thyroid, esophagus, stomach, pancreas, colon, rectum, kidney, bladder, and connective tissue [64]. In a population-based study of 29,515 U.S. testicular cancer survivors, the 15-year cumulative risk of contralateral testicular cancer was 1.9% and 12.4-fold higher than that expected in the general population [65]. The increased risk of contralateral testicular cancer is likely due to underlying predisposition rather than treatment.

Chemotherapeutic agents that have been associated with the development of leukemia after testicular cancer include cisplatin and etoposide [66–68]. Large-field radiation therapy regimens of the past which incorporated mediastinal fields also contribute to excess risks. In a leukemia case-control study of 18,567 one-year survivors of testicular cancer, Travis et al. [66], found that risk increased significantly with total dose to active bone marrow. As the authors pointed out, this finding reflected the additional use of mediastinal radiotherapy, which is no longer applied. Subdiaphragmatic radiation alone was associated with a non-significant three-fold risk of leukemia.

The largest study of solid tumor risk following testicular cancer was conducted by Travis et al. [64]. In this international population-based survey, site-specific solid tumor risk among 40,576 testicular cancer survivors who were followed for an average of 11.8 years was reported. Men diagnosed with seminomas or nonseminomatous tumors at age 35 years demonstrated cumulative risks of solid cancer of 36% and 31%, respectively by age 75. The excess relative risk of solid tumors, however, decreased with increasing age at testicular cancer diagnosis. The relative risks of developing a solid tumor were significantly increased after both radiation therapy alone and chemotherapy alone (RR, 2.0 and 1.8, respectively). Although the relative risk was somewhat higher among patients who received both chemotherapy and radiation therapy (RR, 2.9), it did not differ significantly from those patients treated with single-modality therapy. Among patients treated with radiotherapy alone, relative risks for sites in typical infradiaphragmatic radiotherapy fields (stomach, pancreas, kidney, bladder) were higher than those for remaining sites (RR, 2.7, [95% CI =

2.4 to 3.0] vs RR, 1.6, [95% CI = 1.4 to 1.8]). For in-field sites, the significantly increased relative risks persisted for 35 years or more with no evidence of decline over time.

Recent changes in treatment approaches for testicular cancer will likely alter the profile of second malignancies. Treatment has evolved from large field radiation therapy, to radiation treatment limited to para-aortic fields and lower doses, to an alternative approach of surveillance for patients with early stage disease. However, results of studies on testicular cancer patients treated in earlier eras remain highly valuable, as therapies were effective and resulted in long-term survivors. For these patients, it is important to develop recommendations with regard to appropriate follow-up and screening guidelines [69].

Breast Cancer

Breast cancer is the most common malignancy in women in the United States [70]. Contralateral breast cancer accounts for 40% of all second tumors among women with breast cancer, with a twenty-five year cumulative risk of 6.9% [4]. While these excesses are largely related to pre-existing breast cancer risk factors, prior radiation therapy, especially treatment at a young age, may contribute to increased risk [71–74].

In early case-control studies by Boice et al. and Storm et al. [73, 75], the overall relative risk of contralateral breast cancer was not significantly increased after radiation therapy (RR, 1.2, 95% CI, 0.94, 1.2) [73]. However, among women age <45 years at the time of irradiation, the relative risk in the Boice et al. study was 1.6 (95% CI, 1.1–2.4). In a recent Dutch study of 7,425 1-year survivors of breast cancer, the overall relative risk for contralateral breast cancer for those who received radiation therapy compared to those who did not was not significantly elevated [76]. When the dose-response analyses were focused on patients <45 years of age when irradiated, women treated with postlumpectomy radiation (which was associated with higher doses to the contralateral breast) had a significantly 1.5-fold increased risk of contralateral breast cancer compared with patients treated with postmastectomy radiation therapy. A dose-response relationship was observed for any contralateral breast cancer, with a stronger relationship for medially located cancers. The joint effects of tangential breast fields and a strong family history of breast cancer on the risk of contralateral breast cancer was greater than expected when individual risks were summed.

In a report from the Early Breast Cancer Trialists' Collaborative Group [77], a significantly increased risk of contralateral breast cancer was found after radiotherapy, largely during the period 5–14 years after randomization (RR, 1.4, $p=0.00001$). In this study, small excess risks after irradiation were evident even among women aged >50 years at treatment (RR, 1.3, $p=0.002$). In contrast, in a recent multi-institutional study of 708 women with contralateral breast cancer, Stovall et al. found no evidence of dose-response in women >40 years of age at treatment [78]. However, women <40 years of age who received >1 Gy of absorbed radiation dose to the specific quadrant of the contralateral breast had a 2.5-fold greater risk for cancer than unexposed women (RR = 2.5; 95% CI 1.5 – 4.5). For women < 40 years of age followed for >5 years, a 3-fold risk was observed, with a significant dose-response.

Tamoxifen has been shown to reduce the risk of contralateral breast tumors by 30–40% [79]. However, a number of large investigations have clearly demonstrated a 2- to 4-fold increased risk of endometrial cancer after tamoxifen therapy [80, 81]. Whereas earlier studies indicated that endometrial cancer after tamoxifen therapy might have a more favorable prognosis compared with *de novo* tumors, more recent data have suggested that tamoxifen-related endometrial cancers may demonstrate more aggressive behavior [82–84]. It should be noted, however, that most cases of secondary endometrial cancer are detected at an early stage and are thus able to be surgically resected [84]. Consequently, endometrial

cancer after tamoxifen therapy does not appear to be associated with poorer endometrial cancer-specific survival.

Other solid tumors that have been linked to radiotherapy for breast cancer include lung cancer, esophageal cancer, and soft tissue sarcoma [4, 71, 85–90]. In several studies [71, 86, 87], women who received radiation had a 1.5- to 3-fold increased risk of developing lung cancer compared to women who did not receive radiation therapy. These excesses appeared to be more clearly related to post-mastectomy radiation therapy, in which the target volume often also includes the supraclavicular, axillary, and/or internal mammary nodal region, thus exposing a larger volume of underlying lung tissue to radiation, while the existence of any increased risk after post-lumpectomy radiation therapy is less certain [88, 89, 91]. The observation that lung cancer after breast cancer therapy is more frequently found in the ipsilateral lung also supports a contributing role of radiation therapy to the elevated risk [88]. Several studies showed an even greater increase in lung cancer risk among smokers given breast irradiation [92, 93]. In a population-based case control study of lung cancer after breast cancer, 119 cases of lung cancer were matched with 380 controls without lung cancer [94]. Compared with nonsmoking women who did not receive postmastectomy radiation therapy, nonsmoking women who received postmastectomy radiation therapy had no higher risk of lung cancer. However, the adjusted odds ratios were 5.9 (95% CI, 2.7 to 12.8) for ever-smokers who did not receive postmastectomy radiation therapy and 18.9 (95% CI, 7.9 to 45.4) for ever-smokers who received postmastectomy radiation therapy. Adjusted odds ratios for the joint effects of smoking and postmastectomy radiation therapy were 10.5 (95% CI, 2.9 to 37.8) for the contralateral lung and 37.6 (95% CI, 10.2 to 139.0) for the ipsilateral lung.

Elevated risks of esophageal cancer after breast cancer have been reported in several studies [4, 93]. Although the roles of treatment, smoking habits, and alcohol use have not been simultaneously addressed, Curtis et al. [4] and Brown et al. [85] noted that the pattern of excess risks of esophageal cancer were consistent with a radiation effect. Zablotska et al. examined the risk of squamous cell esophageal cancer after adjuvant radiation therapy for breast cancer [95], reporting a significantly increased relative risk only among women who received post-mastectomy radiation therapy, but not among those who received post-lumpectomy radiation therapy, who presumably received lower doses. In an ongoing NCI-international study of breast cancer patients initiated by Travis and colleagues, the relationship between radiation dose to the esophagus and the subsequent risk of both esophageal adenocarcinoma and squamous cell cancer is being quantified; in addition, the possible modifying effects of tobacco use, alcohol, and chemotherapy are being examined.

The 15-year cumulative incidence of sarcoma after breast cancer is low (<0.5%), although the relative risk has been estimated to be as high as 7-fold, given the low background incidence in the general population [71, 96–98]. In an Italian study of breast cancer survivors by Rubino et al [99], all subsequent sarcomas were either localized to previously irradiated fields or to the upper extremity of the arm ipsilateral to the treated breast among women initially given radiotherapy. By estimating the initial radiation dose to the site of sarcoma development, using a dose of 14 Gy as reference, women who received 14–44 Gy had a 1.6 fold increased risk of sarcoma while those who received ≥45 Gy to the site had a 30.6 fold increased risk (p trend for dose <0.001). Angiosarcoma after breast cancer was initially shown to be associated with chronic lymphedema following radical mastectomy [100]. Given the increasing use of radiotherapy with breast-conserving surgery, a growing number of reports document the occurrence of cutaneous angiosarcoma of the breast arising in the radiation field [98, 101–103]. Unlike other radiation-associated soft tissue sarcomas, breast angiosarcoma can have a short latency period of just the first 5 years after therapy.

The increased risk of leukemia has been related to antecedent chemotherapy and radiation therapy [73, 104–106]. In a population-based, nested case-control study of women treated for breast cancer between 1973 and 1985 [4], Curtis et al. showed in a case-control study that, compared to women who did not receive alkylating chemotherapy or radiation therapy, the relative risk of acute myelogenous leukemia after radiation therapy alone, alkylating chemotherapy alone, and both chemotherapy and radiation therapy were 2.4, 10.0 and 17.4, respectively. A significant dose-response relation for subsequent leukemia risk was observed for melphalan, cyclophosphamide and cumulative radiation dose to the active bone marrow. Recent data demonstrate that the risk of secondary acute leukemia is more strongly related to the dose-intensity of cyclophosphamide than with cumulative dose [107], which may be of particular relevance given the increasing trend toward the use of dose-intensified regimens for breast cancer.

Evolutions in systemic chemotherapy for breast cancer, including targeted therapy, may eventually affect the risk of second malignancies. In addition, recent advances in radiation therapy, including the use of intensity modulated radiation therapy (IMRT), and the growing interest in partial breast irradiation [108], may also influence the risk profile. The degree to which second cancer risk will be affected by these newer radiation therapy approaches and techniques will need to be established through long-term follow-up of large cohorts of breast cancer survivors with sufficient statistical power to detect increased site-specific risks.

Prostate Cancer

Prostate cancer is the most common malignancy among men in the United States [70], with increasing amounts of data available on the risk of second malignancies. Curtis et al. [4] evaluated the risk of subsequent primary malignancies among over 308,000 patients reported to the population-based SEER Program (1973 – 2000). Prostate cancer survivors experienced increased risks for malignant melanoma and subsequent cancers of the small intestine, soft tissue, bladder, thyroid, and thymus [4]. It was concluded that treatment with radiotherapy appeared to be associated with increased risks for selected solid cancers that occurred within the abdominal and pelvic fields, especially bladder cancer.

Other series have compared the risk of second malignancies among prostate cancer patients initially given radiation therapy with the risk among those who did not receive radiation therapy. Associations have been reported between radiation therapy and subsequently increased risks of cancers of the bladder and rectum [4, 109]. Notably, Curtis et al. did not observe increased risks of rectal cancer (O/E = 0.98) among over 90,000 prostate cancer survivors initially treated with radiotherapy in their report [4]. Similarly, Kendal et al. found no excess rectal cancers after prostate irradiation [110].

Chrouser et al. showed that excess bladder cancers were limited to patients who received adjuvant radiation therapy after a radical prostatectomy [111], which may reflect the larger volume of bladder tissue exposed to radiation in the post-operative setting. In a survey of prostate cancer patients reported to the British Columbia Tumor Registry, an increased relative risk of bladder cancer was observed only in the non-irradiated cohort (RR, 1.3; $p < 0.01$), but not among irradiated patients [112].

In studies that report significant cancer excesses after radiotherapy for prostate cancer, the overall risk appears to be low. In an early investigation of men with prostate cancer reported to the SEER program conducted by Brenner et al. [113], the risk of developing a second malignancy was estimated at 1 in 290. In the last few years, IMRT has been increasingly utilized to treat prostate cancer in order to permit more conformal dose distribution and dose escalation [114]. Depending on treatment energy, IMRT is associated with a 3- to 5- fold higher number of monitor units (1 monitor unit gives an absorbed dose of 1 cGy at a depth

of maximum dose for a field size of 10×10 cm for a source-to-axis distance of 100 cm) as compared with conventional treatment. Applying risk coefficients from the National Council of Radiation Protection and Measurements for specific anatomic sites to this configuration, the risks of second malignancies using IMRT techniques have been estimated to be 2–3 times higher than that after conventional radiation therapy [115]. This is due to exposure of larger volumes of normal tissue to low doses of radiation with IMRT as compared to conventional conformal techniques. These preliminary estimates remain to be confirmed in epidemiologic studies which include large numbers of patients given IMRT who have been followed for sufficient periods of time to permit detection of any increased radiotherapy-associated risks.

In the interim, conflicting observations with regard to the contribution of radiotherapy to various second malignancies after prostate cancer may reflect a number of factors, including the practice of most registries to gather data only on initial course of therapy, the incomplete registration of initial treatment, misclassification of therapy, and the absence of data on subsequent treatment. Moreover, selection bias may be present in decisions to administer surgery or radiation therapy to treat prostate cancer, and the limited data available in most population-based registries do not allow for the identification of confounding factors. Patients with significant comorbid illnesses and/or a history of heavy tobacco use may not be treated with surgery and may be more likely to be given radiation therapy. Further, radiation therapy and treatment-related sequelae such as cystitis, hematuria, proctitis, and rectal bleeding may lead to additional cystoscopies or colonoscopies which can then result in an apparently increased incidence of urologic and colorectal cancers.

Second Malignancy Risk Across the Age Spectrum

The patterns of second primary malignancies in survivors of pediatric cancer and adult-onset cancer differ in terms of the observed types of second tumors, magnitude of risks, latency periods, and the influence of modifying factors. Possible explanations for these variations include the genetic underpinnings and etiology of the first cancer diagnosis in different age groups, and variations in treatment approaches for children compared with adults (e.g. different chemotherapeutic regimens and doses, radiation fields, doses and techniques). In addition, the susceptibility of specific organs or tissues to radiocarcinogenesis likely varies depending on developmental stage and the microenvironment. The differences may also be influenced by the strong dependence of baseline risks on attained age, the period of time needed to reach an attained age for certain malignancies, and the contributions and modifying effects of exposures to environmental factors (e.g. tobacco or alcohol). Moreover, treatment outcomes for similar diagnoses differ in children and adults, e.g. ALL has a better prognosis in children than in adults [116]. Highlighted below are examples of several types of second malignancies where differences in incidence according to age at first primary cancer diagnosis have been consistently reported.

Breast Cancer as a Second Malignancy

The radiosensitivity of the breast at age <40 years has been well-established [117]. Most of the data has been reported in survivors of childhood cancer [34, 39, 118], young adult HL (most of these studies also included a small proportion of pediatric patients) [42, 43], and of breast cancer [73, 75–78]. For radiation-related breast cancer in survivors of adult cancer, a decreasing risk with increasing age at radiation therapy has generally been noted, with little risk for patients exposed at >40 years old [36, 60, 73]. In pediatric cancer survivors, the risk of breast cancer appears less affected by age at treatment possibly because of the more limited age range. In a report by Bhatia et al. from the Late Effects Study Group on second malignancy risk after childhood HL [34], age at diagnosis was not significantly associated with subsequent breast cancer risk. Travis et al. focused on women given radiotherapy for

HL before age 30 [42], where no trend with age was detected, although the range was relatively narrow at 13 – 30 years (median 22 years). Similarly, Inskip et al. found that in female 5-year survivors of childhood cancer, the radiation sensitivity of the breast in girls ages 10–20 was confirmed [118]. However, a strong effect of age at exposure was not demonstrated within this narrow range. The age at initial cancer diagnosis was <13 years in only 15/107 cases. Kenney et al. published one of the most comprehensive studies on breast cancer risk in childhood cancer survivors [39]. Based on data from the CCSS, among 6,068 eligible female childhood cancer survivors, 95 women (68% of whom were survivors of pediatric HL) had 111 confirmed cases of breast cancer. After adjustment for chest irradiation, age at treatment was not significantly associated with risk of breast cancer. Girls who were treated between ages 5–9 did not experience a significantly increased risk of subsequent breast cancer, while the risk became significantly increased after age 10. These findings suggest that in contrast to pre-pubertal breast tissues, proliferating and developing breast tissues may be more sensitive to the tumorigenic effect of radiation. However, breast cancer has been linked with radiation exposure at very young ages (<5) in other settings [117]. Another possible explanation may be due to the relatively narrow age range, and that the length of follow-up time may not be long enough for younger survivors to reach an attained age when the breast cancer risk rises.

As noted above, the studies by Travis [42] and van Leeuwen [43] have shown the importance of hormonal stimulation in the development of radiation-associated breast cancer in women treated during young adulthood. A protective effect of alkylating agents or radiation dose to the ovary at >5 Gy was not found in the study by Inskip et al [118], who pointed out that ovaries in adolescent girls have a larger reserve of eggs and follicles relative to older women and are less likely to experience loss of function for a given dose of alkylating agent or radiation. Similarly, Kenney et al [39] did not observe a protective effect of alkylating chemotherapy, even at the highest dose level. Finally, in the CCSS study, almost one quarter of the breast cancer cases were diagnosed in women who had not been exposed to previous chest radiation. Thus, in selected younger patients, familial cancer syndromes may play a critical role in breast cancer risk, a finding that may influence breast cancer screening recommendations.

Thyroid Cancer as a Second Malignancy

In a CCSS study of 13,581 childhood cancer survivors followed for at least 5 years (median follow-up 15.4 years) [3], thyroid cancer was the second most common subsequent malignant neoplasm after breast cancer. Thyroid cancer (43 cases) represented 15% of all solid tumors, with a significantly elevated 11-fold risk compared to the matched normal population. Thyroid cancer as a second malignancy in survivors of adult-onset cancer has been reported predominantly after adult HL. In Hodgson et al.'s study on solid tumor risk after HL [60], 40 cases of thyroid cancer were diagnosed among 1,490 solid tumors, with a strong decline in the relative risk with increasing age at HL diagnosis. While the risk of thyroid cancer was significantly elevated at RR = 3.1 (95% CI, 1.8–5.2) for patients diagnosed at age 30, cancers of this site were far less common than breast, lung, head and neck, and genitourinary cancers, and represented only 2.7% of all reported cases of solid tumors. There were an estimated 29 excess number of cases of thyroid cancer in this cohort, as compared to 175 and 226 excess cases of breast and lung cancer, respectively. These differences between survivors of adult and childhood cancer likely reflect the well-documented radiosensitivity of the thyroid in younger patients [34, 48]. Unlike radiation-related breast cancer, lung cancer and sarcoma, for thyroid cancer, there appears to be a reduction in the radiation dose-response at doses >30Gy, consistent with a cell-killing effect [48].

Lung Cancer as a Second Malignancy

An increased risk of lung cancer as a second malignancy is seen after a number of adult-onset primary malignancies, including HL, non-Hodgkin's lymphoma, head and neck cancers, cervical cancer, and breast cancer. In fact, lung cancer is one of the most common second malignancies in survivors of adult HL [60]. Although analytic studies have linked excess second primary lung cancers to antecedent chest irradiation and alkylating chemotherapy in patients with HL [61, 62], and to radiation in women with breast cancer [87], it is clear that smoking plays a major role. In a review of 2 million cancer survivors reported to the NCI SEER Program, Curtis et al. concluded that tobacco or alcohol-related cancer sites accounted for about 35% of the total excess risk of subsequent cancers [4]. While lung cancer represents a sizable proportion of second malignancies after selected adult-onset tumors, it is less commonly observed in pediatric cancer survivors. In an early report from the CCSS, at a median follow-up time of 15.4 years, second primary lung cancers had not yet been observed [3]. In a later publication from the same group that included additional information from a follow-up questionnaire [54], 4 cases of lung cancer were reported, 3 of which were in survivors of HL. This suggests that most pediatric cancer survivors have not reached the attained age at which lung cancer rates increase. Moreover, any effects of tobacco use have not yet become manifest, and a longer follow-up time will be needed to document any increased risks. In the interim, it is critical to continue to both undertake measures to both prevent smoking onset and to encourage smoking cessation in survivors of both adult-onset and childhood cancers [119].

Conclusions

Efforts to characterize differences in the long-term, site-specific patterns of excess second malignancies between survivors of childhood cancer and adult-onset cancer may eventually permit insights into mechanisms of carcinogenesis, including the roles of contributing etiologic factors and interactions between influences (including gene-environment and gene-gene interactions). Moreover, an improved understanding of the impact of age at treatment and attained age on second cancer risks should facilitate customization of screening and prevention strategies as well as the identification of high-risk patients for intensified efforts. Although differences exist in the risk of second malignancies across the age spectrum, lessons learned from one age group may potentially be applicable to other age groups as treatments evolve, follow-up time increases, and our understanding of secondary carcinogenesis improves.

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Table 1

Comparison of Second Malignancy in Survivors of Childhood versus Adult Hodgkin's Lymphoma*

	Childhood HL	Adult HL	Comments
Overall risks	Higher RR (15–55)	Lower RR (3–6)	Related to lower background cancer risks with younger age and higher susceptibility of developing organs to radiation- associated carcinogenesis
Female gender as a risk factor	Yes	Unclear	In childhood HL survivors, increased SM in female survivors persist despite excluding breast cancer
Breast cancer after HL	RRs increase with increasing age at HL diagnosis Risk not affected by exposure to alkylating agents	RRs decrease with increasing age at HL diagnosis Reduced risk with exposure to alkylating agents in a dose-related manner	Difference may be due to: <ul style="list-style-type: none"> • higher susceptibility to radiation- related carcinogenesis in proliferating and developing breast tissue, compared to pre-pubertal or mature breast tissue • differences in breast cancer risk by attained age at follow-up Difference may be due to: <ul style="list-style-type: none"> • larger reserve of eggs and follicles in girls • differences in types of alkylating agents and doses between pediatric and adult patients
Lung cancer after HL	Represents a minority of cases	Represents one of the most common SM	Lung cancer representing a higher proportion of SM in adult HL survivors may be due to: <ul style="list-style-type: none"> • shorter time to reach the attained age in which increased lung cancer risks emerge • higher likelihood of antecedent or concurrent tobacco use in adults
Thyroid cancer after HL	Represents one of the most common SM	Represents a minority of cases	Thyroid cancer representing a higher proportion of SM in childhood HL survivors may be due to: <ul style="list-style-type: none"> • higher susceptibility to radiation- related carcinogenesis of the thyroid in younger patients • larger number of other cancers at an older attained age

* Table represents a synthesis of current evidence. With the continued follow-up of both pediatric and adult HL survivors, taken together with the evolution of treatments, these observations may change

Abbreviations: HL, Hodgkin's lymphoma; RR, relative risk; SM, second malignancy