Rare Subsequent Primary Cancers in Pediatric Cancer Survivors

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46.1 Introduction

Advances in cancer therapy during the past four decades have resulted in remarkable increases in survival for most cancers of childhood and adolescence. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program show that the overall 5-year survival rate for childhood cancer has increased from 45% in 1970 to over 80% in 2005 (Ries et al. 1999). It is estimated that one in every 640 young adults is now a survivor of childhood cancer, and that at least 328,000 persons in the USA alone have survived cancer diagnosed before the age of 20 years (Mariotto et al. 2009). Because of the relatively young age of these survivors, and their potential longevity, the delayed consequences of therapy may have a significant impact on their lives, and on society at large, over an extended period of time.

Also with this success has come the realization that a substantial proportion of childhood cancer survivors will experience late-occurring adverse health effects resulting from their disease and treatment. As pediatric cancer survivors are being followed long-term, nearly 73% of adult survivors of pediatric cancer have chronic health conditions, many of which are severe or disabling (Oeffinger et al. 2006). Numerous reports and reviews of late effects of chemotherapy and radiation have been published, describing sequelae present at, or shortly following, the end of therapy, as well as the occurrence of selected late complications. Most studies of late sequelae have focused on medical outcomes (Oeffinger and Hudson 2004). These studies have shown that the type and intensity of therapy, as well as the age at therapy, are important factors in both overall survival as well as late effects outcomes. Children who

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are younger at diagnosis and treatment are more severely affected than older children, particularly if treatment is administered at a significant time of development and growth.

One of the most devastating late effects is the development of a subsequent primary cancer that originates in a new primary site or tissue. Over the past 30 years, numerous reports and reviews of late effects of chemotherapy and radiation have been published, describing an increased risk of developing subsequent malignant neoplasms in survivors of childhood cancers. The incidence of subsequent primary cancers has been primarily linked to treatment, which is demonstrated in higher rates in certain types of cancer who receive these multimodal treatments (Ng et al. 2010). Other primary subsequent cancer has been linked to genetic predisposition to multiple cancers and sensitivity to radiogenic cancer, which has been demonstrated in children diagnosed with retinoblastoma (Kleinerman et al. 2005).

46.2 Study Findings

Information we have on the development of rare subsequent cancer in pediatric cancer survivors comes from two major sources: reports from the Surveillance, Epidemiology, and End Results (SEER) Program; and three large studies that have followed pediatric cancer survivors into adulthood. From these studies, it is clear that the major types of subsequent cancers are due to radiation exposure and certain chemotherapies, particularly alkylating agents. Recent studies have also indicated that the incidence of basal cell carcinoma is also very high in the survivor population. However, this is more difficult to enumerate since there are no record keeping of these cancers in the general population. The more rare cancers in this pediatric cancer survivor population are described below.

46.2.1 Surveillance, Epidemiology, and End Results (SEER) Program

SEER data is a compilation of population-based registries allowing for objective assessments and now covers 26% of the US population. In a recent monograph published through SEER looking at New Malignancies Among Cancer Survivors, descriptive analysis on new malignancies following childhood cancer was highlighted (Curtis et al. 2006). This study population included 23,819 children diagnosed with cancer before the age of 18, who had survived 2 or more months following diagnosis. This population was observed for an average of 8.3 years (median, 5.8 years). Within this population, there were 12,951 5-year survivors, 8,424 10-year survivors, and 2,637 20-year survivors. The maximum age at the end of follow-up was 44 years.

During this follow-up period, 352 new primary cancers were diagnosed in 327 individuals, accounting for a sixfold increase in incidence relative to the general population (observed/expected (O/E) = 6.07, 95% CI = 5.45–6.74, excess absolute risk (EAR) = 15 per 10,000 person-years). Of particular concern in this cohort is the occurrence of new primary cancers in this young population of longer-term survivors. The pattern of cancer incidence in this group patterned the cancer incidence seen more commonly in older adults. The more rare but significant subsequent primary cancers were diagnosed in the buccal cavity, digestive, respiratory, male genital, urinary, and central nervous system. Within these systems, increased risk of subsequent primary cancers due to radiation exposure were noted in cancers found in the salivary gland (O/E = 27.13), stomach (O/E = 35.89), pancreas (O/E = 69.36), and lung (O/E = 14.20).

In addition, childhood cancer patients whose initial treatment included radiotherapy were at higher risk of developing a subsequent cancer than those not given radiotherapy, as reflected by the high O/E ratios and absolute risks seen (Table 46.1). Subsequent cancer sites showing the greatest increased risk following radiotherapy among 5-year survivors included breast, brain, bone and soft tissue, thyroid gland, digestive system, and lung. Also of interest is the increased risk of melanoma and the female and male genital system in patients without radiotherapy.

46.2.2 Population-Based Studies

In the synopsis of current data on subsequent primary cancers, two large population-based studies are highlighted due to the long average follow-up period of pediatric cancer survivors into adulthood. Both studies, using age-, sex-, and calendar time-specific comparisons with the general population, demonstrate that the risk of a subsequent cancer is substantially higher than that seen in the general population.

Table 46.1 Risk of subsequent primary cancers following childhood cancer by initial treatment with radiation

	Any radiation ($n=9,063$)				No radiation ($n=13,905$)			
Subsequent primary cancer	Observed	Expected	O/E	EAR	Observed	Expected	O/E	EAR
Buccal cavity, pharynx	7	0.47	15.03*	0.80	10	0.55	18.25*	0.87
Salivary gland	4	0.15	27.13*	0.47	4	0.18	22.03*	0.35
Digestive system	14	1.08	12.99*	1.59	10	1.29	7.74*	0.80
Stomach	4	0.11	35.89*	0.48	2	0.13	15.24*	0.17
Pancreas	5	0.07	69.36*	0.61	0	0.08	0.00	−0.01
Respiratory system	6	0.48	12.38*	0.68	2	0.57	3.48	0.13
Lung, bronchus	4	0.28	14.20*	0.46	1	0.32	30.9	0.06
Female breast	29	1.71	16.91*	7.14	10	2.08	4.81	1.48
Female genital system	3	2.14	1.40	0.22	7	2.56	2.73*	0.83
Male genital system	2	2.15	0.93	−0.03	10	2.24	4.46*	1.41
Urinary system	2	0.64	3.12	0.17	3	0.87	3.44	0.20
Melanoma of the skin	6	2.57	2.34	0.42	19	2.82	6.74	1.49
Brain, CNS	27	2.19	12.32*	30.5	12	3.00	4.00*	0.83
Thyroid	17	20.8	8.18*	1.83	12	2.41	4.99*	0.89
Bone, joints	23	0.80	28.83*	2.73	12	0.99	12.07*	1.02
Soft tissue	19	0.81	23.48*	2.23	7	1.09	6.45*	0.55
Hodgkin lymphoma	3	2.51	1.20	0.06	1	2.85	0.35	−0.17
Non-Hodgkin lymphoma	9	1.81	4.97*	0.88	6	2.11	2.85*	0.36
Acute lymphocytic leukemia	5	1.30	3.85*	0.45	3	2.09	1.44	0.08
Acute nonlymphocytic leukemia	12	0.72	16.66*	1.39	14	0.94	14.93*	1.21

O observed number of subsequent primary cancers, *E* expected number of subsequent primary cancers, *EAR* excess absolute risk (excess cancers per 10,000 person-years)
* $p<0.05$

Table 46.2 Risk of subsequent malignant neoplasms (SMN) after nonretinoblastoma childhood cancer by duration of follow-up from original diagnosis

	Follow-up period from diagnosis (years)			
	3–9	10–19	20–29	30 or more
Number of persons at risk	15,452	7,862	2,806	808
Observed number of SMN	92	64	34	11
SIR (95% CI)	10.2 (8.3–12.6)	5.7 (4.4–7.3)	3.5 (2.4–4.9)	2.4 (1.2–4.3)

SIR standardized incidence ratio, *95% CI* 95% confidence interval

The first is a cohort of 16,541 3-year survivors of childhood cancer treated in Britain between 1962 and 1987 (Jenkinson et al. 2004). Within this cohort of children diagnosed before the age of 15, 245 subsequent malignancies were identified, yielding an overall standardized incidence ratio (SIR) of 6.2 (95% confidence interval = 5.5–7.1). Of note, a statistically significant excess SIR was found within each decade of follow-up, with the overall SIR declining with successive decades from diagnosis (Table 46.2).

The second population-based study reported on a cohort of 47,697 children diagnosed before the age of 20 years, from the cancer registries of the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) during 1943–2005 (Olsen et al. 2009). Over this time period, 1,180 subsequent cancers were observed in 1,088 persons. The overall SIR was 3.3 (95% CI = 3.1–3.5). The relative risks were statistically significant at all ages, including cohort members up to the age of 70 years. Cohort members who were treated during the

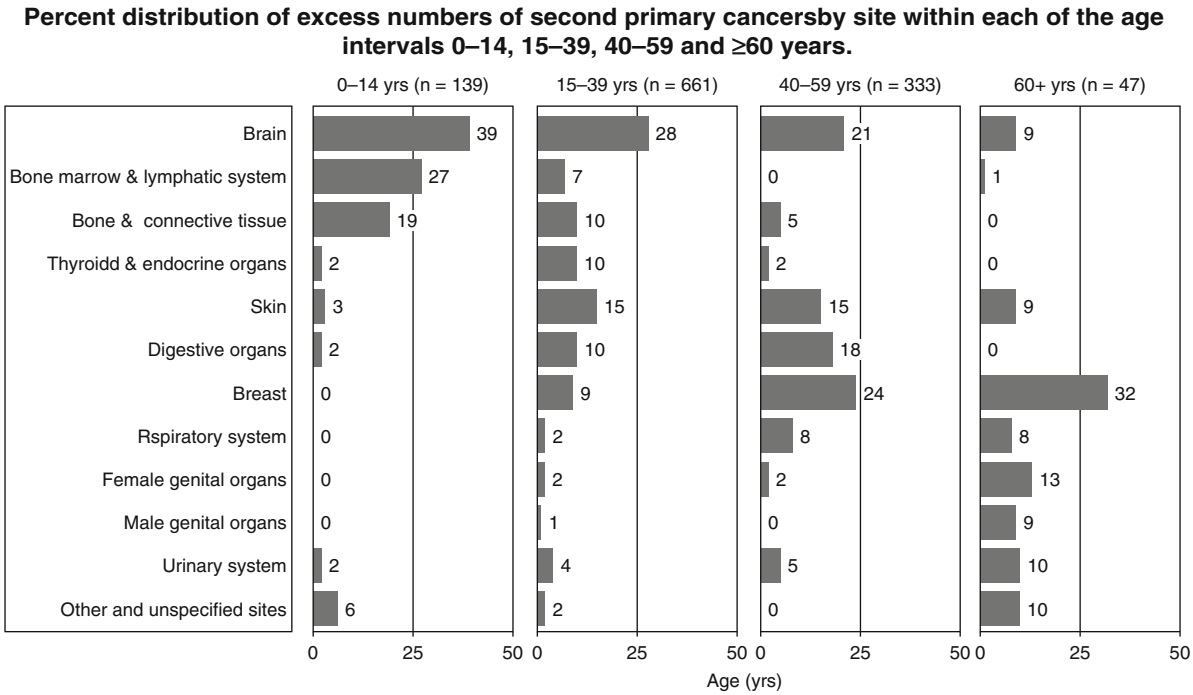

Fig. 46.1 Percent distribution of excess numbers of second primary cancers by site within each of the age intervals 0–14, 15–39, 40–59 and ≥60 years (Olsen et al. (2009))

multimodal treatment era (1975–2005) had the highest age-specific incidence rate of a subsequent cancer. Among survivors, the cumulative risks for second cancers before the age of 50 were 8.6% in the 1943–1959 subcohort (prechemotherapy era), 12.2% for the 1960–1974 subcohort (first-generation chemotherapy era), and 13.3% for the 1975–2005 subcohort (combination chemotherapy era). The number of excess second primary cancers observed by age is shown in Fig. 46.1, demonstrating continued increased risk decades of life after the original cancer diagnosis.

46.2.3 Childhood Cancer Survivor Study (CCSS)

The CCSS is a multi-institutional study of individuals who survived for 5 or more years after treatment for cancer diagnosed during childhood or adolescence. Eligibility criteria for CCSS are: diagnosis of leukemia, central nervous system (CNS) malignancies (all histologies), Hodgkin disease, non-Hodgkin lymphoma, malignant kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; diagnosis and initial treatment at one of the 26 collaborating CCSS institutions; and diagnosis between 1970 and 1986 (Robison et al. 2002).

The CCSS represents the largest cohort of relatively long-term survivors of childhood cancer and has contributed significantly because of the extensive medical record review of survivors and pathology validation of reported subsequent primary cancers. Because of the continued surveillance in this population, the 30-year cumulative incidence of the development of a subsequent primary cancer has been estimated to be 9.3% compared with the 20-year incidence in this cohort of 3.2% (Meadows et al. 2009). These data highlight the fact that the standardized incidence ratio continues to increase as this cohort ages.

A recent analysis within the CCSS cohort documented 802 subsequent malignant cancers among 732 survivors with a median time of follow-up since the primary cancer diagnosis of 22.9 years (range = 5.0–36.7 years) (Friedman et al. 2010). Associations between the primary cancer and subsequent cancers are shown in Table 46.3. The diagnosis of Hodgkin disease showed a disproportionate number of subsequent

Table 46.3 Original and subsequent malignant neoplasm diagnoses

Subsequent diagnosis		Leukemia			Lymphoma			CNS			Solid organ					Skin
		ALL	AML	Other	HL	NHL	Other	Glial	Medullo PNET	Other	Breast	Bone	STS	Thyroid	Other	Melanoma
Primary diagnosis	Number in cohort (%)															
Leukemia	4830 (33.6)	3	6		2	3	2	30	2	8	16	4	12	28	50	20
CNS tumors	1877 (13.1)		2	1	1		2	13	1	1	4	5	12	15	22	10
Hodgkin lymphoma	1927 (13.4)		8	6		10	6	4	1	3	161	6	26	42	69	13
Non-Hodgkin lymphoma	1080 (7.5)	2	2		3	1		2		5	6	2	4	10	16	2
Kidney	1256 (8.7)	2							1		7	4	8	3	12	3
Neuroblastoma	955 (6.7)	1	3		1			2			2		5	10	17	
Soft tissue sarcoma	2434 (17.0)		1	3	2			1		5	16	13	18	8	22	8
Bone tumors	1246 (8.7)	2	2	1				2		2	35	10	7	12	22	8
Total		10	24	11	9	14	10	54	5	24	247	44	92	128	230	64

Table 46.4 Observed and expected numbers of invasive second malignant neoplasms by second malignancy diagnosis

Second malignancy diagnosis	Cases observed	Cases expected	Standardized incidence ratio (95% C.I.)	Median time to SMN occurrence (years)
All invasive second malignancies	802	130	6.2 (5.7, 6.7)	17.8
Leukemia	41	130	6.2 (4.5, 8.4)	8.9
Acute lymphoblastic leukemia	10	7	3.7 (2.0, 6.8)	11.5
Acute myeloid leukemia	21	3	9.5 (6.2, 14.5)	7.4
Central nervous system	77	7	10.6 (8.5, 13.3)	13.2
Glial	52	6	9.0 (6.9, 11.9)	11.7
Medulloblastoma, PNET	6	0.6	7.6 (3.1, 18.3)	11.6
Meningioma (malignant)	11	0.04	91.3 (27.5, 302.8)	22.9
Breast cancer	188	17	10.7 (9.1, 12.6)	21.3
Melanoma	48	14	3.4 (2.5, 4.6)	18.9
Thyroid cancer	128	11	11.2 (9.4, 13.4)	18.6
Bone cancer	45	2	19.2 (14.4, 25.7)	9.8
Osteosarcoma	35	1	30.2 (21.4, 42.4)	9.3
Ewing sarcoma	4	0.6	6.7 (2.5, 17.9)	14.0
Lymphoma	33	18	1.8 (1.3, 2.6)	18.5
Hodgkin lymphoma	9	9	1.0 (0.5, 1.9)	18.5
Non-Hodgkin lymphoma	21	8	2.6 (1.6, 4.1)	21.6
Soft tissue sarcoma	73	9	8.2 (6.5, 10.4)	15.2
Kidney cancer	20	3	7.7 (4.8, 12.1)	19.6
Head and neck cancer	38	3	11.2 (8.1, 15.5)	15.6
Small intestine and colorectal cancer	27	6	4.9 (3.3, 7.1)	23.1
Lung and bronchus cancer	11	3	2.6 (2.0, 6.5)	20.3
Female genital cancer	23	10	2.2 (1.5, 3.3)	19.5
Other cancers	50	19	2.7 (2.0, 3.5)	21.0

cancers, with 35% of the reported subsequent malignant cancers in this group that only comprises 13% of the cohort. Standardized incidence ratios, using age-, sex-, and race-specific rates, found the highest risks were observed for subsequent bone cancer, thyroid cancer, head and neck cancer, CNS malignancies, and breast cancer (Table 46.4). Of particular interest is the increased risk of solid organ malignancies typically seen in older adults, such as head and neck tumors, small intestine and colorectal cancer, cancer of the lung and bronchus, and cancer of the female genital tract.

Earlier nested case-control studies of specific subsequent cancers have yielded important information regarding the influence of radiation dose on the occurrence of the more common subsequent cancers. In a study of 69 cases with confirmed thyroid cancer, a significant dose response of radiation to the risk of thyroid cancer increase up to 20–29 Gy of radiation (odds ratio (OR) = 9.8, 95% CI = 3.2–34.8), with a fall in the dose–response relationship at greater than 30 Gy, suggesting a cell-killing effect (Sigurdson et al. 2005). In a study of subsequent CNS tumors, the dose response for excess relative risk from radiation exposure for 40 subsequent gliomas was linear and peaked for doses of 30–44.9 Gy (OR = 21.0, 95% CI = 2.1–42.3) (Neglia et al. 2006). Similarly for a study of 120 subsequent breast cancer in female survivors, the odds ratio for breast cancer increased linearly with radiation dose, with the highest at doses 40 Gy (OR = 10.9, 95% CI = 3.8–31.0) (Inskip et al. 2006). For each of these subsequent cancers, chemotherapy for the first cancer diagnosis, exposure to chemotherapy, showed no association for the observed increase in risk.

46.3 Synopsis of Above Data

The development of subsequent primary cancers in pediatric cancer survivors is a rare occurrence but nonetheless of particular concern to survivors and their families.

The most common of these occurrences are subsequent cancers of the bone and soft tissue sarcomas, epithelial cancers (e.g., breast, head, and neck), thyroid, and melanoma. Each of the studies reported above show similar patterns, regardless of the makeup of the cohort being followed. First, exposure to radiotherapy increases the risk of certain cancers; however, chemotherapy also plays an important role. Second, the risk of the development of these subsequent cancers does not appear to diminish over the lifetime of the cancer survivor and is shown to stay increased through older adulthood. And, third, the type of subsequent cancer that develops appears to be determined by the therapeutic treatment of the original cancer and years since diagnosis.

These studies clearly indicate the need for careful surveillance and monitoring of subsequent cancers, from the time of completion of treatment through subsequent decades of life in pediatric cancer survivors. Recommendations for cancer surveillance have been outlined in the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, a collaborative effort within the Children's Oncology Group (COG Guidelines). These evidence-based guidelines are organized by therapeutic exposure and include a cancer screening section that lists elements of the history, physical exam, radiology, and other specialized tests that are recommended to aid in the detection of subsequent cancers in survivors. It is important to point out that many adult survivors do not realize the health risks that are related to their childhood cancer, and do not have regular medical follow-up or practiced recommended cancer screening (Kadan-Lottick et al. 2002). Continued education of cancer survivors and their health care providers is critical, to ensure this continued surveillance. Furthermore, continued follow-up of these described cohorts will continue to provide further insight into this increased risk decades after the original diagnosis.

46.4 Treatment of Rare Tumors as Secondary Tumors

Most secondary tumors in survivors of childhood cancer do not occur in childhood but rather in adulthood at an earlier age. However, a few specific secondary tumors are frequently encountered in childhood. Examples include sarcomas in patients with retinoblastoma and acute myelogenous leukemia in patients treated with etoposide. In both cases, standard treatment strategies must be directed against the secondary treatment. There are some limitations. Previous treatment may reduce the ability to deliver full doses of therapy such as radiation and anthracyclines. In the case of rare secondary tumors, pediatric oncologists, internal medicine oncologists, and primary physicians caring for patients who were childhood cancer survivors should be aware that tumors may occur at significant earlier ages. One goal of childhood cancer survivorship programs is education. Patients are informed of the need for close monitoring of their health. That is often not adequate as childhood cancer survivors often tend to avoid medical care. Ongoing education of the medical community is essential.

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