Chapter 18
New Malignancies Following Childhood Cancer

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Synopsis

The incidence of subsequent primary cancers was evaluated in a cohort of 23,819 2-month survivors of childhood cancer diagnosed at ages less than 18 years during 1973-2000 and followed for an average of 8.3 years. The most common types of childhood cancers were leukemias, lymphomas, cancers of the central nervous system (CNS), and bone and soft tissue sarcomas. Childhood cancer survivors were at more than 6-fold increase in risk of developing a new cancer relative to the general population (O/E=6.07, O=352, EAR=15 per 10,000 person-years), and the cumulative incidence of second cancers after 25 years was 3.5%. Most common were subsequent primary cancers of the female breast, brain, bone, thyroid gland, and soft tissue, as well as melanoma of the skin and acute non-lymphocytic leukemia (ANLL). The greatest risks of subsequent cancers occurred among patients previously diagnosed with Ewing sarcoma (O/E=14.84, EAR=44), Hodgkin lymphoma (O/E=9.55, EAR=39), primitive neuroectodermal tumor of the CNS (O/E=12.54, EAR=26), and retinoblastoma (O/E=14.71, EAR=24). Risk of second solid cancers was significantly higher among persons whose initial treatment for childhood cancer included radiotherapy, whereas the excess of subsequent ANLL was more closely related to chemotherapy. Childhood cancer survivors are at markedly increased risk of developing a variety of new primary cancers compared with the general population, but the magnitude of excess risk and specific types of second cancers vary widely by type of first cancer.

Childhood Cancers

Childhood cancers are a heterogeneous group of diseases that vary widely in incidence, age at diagnosis, type of treatment, survival, and, most probably, etiology. Leukemia, lymphoma, and central nervous system (CNS) tumors account for nearly 60% of the total number of cases. In 1998, an estimated 12,400 children younger than age 20 years were diagnosed with cancer, and 2,500 children died due to their cancer (Ries et al, 1999). Incidence rates for most, but not all, types of childhood cancer are higher among males than females and among whites than blacks (Ries et al, 1999, 2004). Because of dramatic improvements in the therapy for many types of childhood cancers, survival is far better today than it was 30 or 40 years ago, and the population of long-term childhood cancer survivors is growing. Current 5-year relative survival rates for childhood acute lymphocytic leukemia (ALL), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), germ cell tumors, Wilms tumor, and retinoblastoma range between 70% and 93% (Ries et al, 1999). Treatment gains have been less dramatic for acute non-lymphocytic leukemia (ANLL), CNS cancer, neuroblastoma first diagnosed at age 5 years or older, Ewing sarcoma, and rhabdomyosarcoma (Ries et al, 1999, 2004). Five-year survival rates for most types of childhood cancers are somewhat better in whites than in blacks (Ries et al, 1999).

Treatment regimens have varied widely by type of first cancer and have changed over time. Historically, radiation was commonly used as part of initial therapy for CNS cancers, HL, rhabdomyosarcoma, and Ewing sarcoma; it was used much less often for osteosarcoma, fibrosarcoma, and germ cell cancers. Multidrug chemotherapy regimens, including alkylating agents, were introduced in the 1960s and modified during the ensuing decades (Friedman and Meadows, 1999; Ebb et al, 2005; Weinstein and Tarbell, 2005). As the medical community came to better understand the adverse late effects of radiation, it sought ways to lower radiation exposures without compromising survival. These included reducing the usage of prophylactic CNS irradiation in patients with ALL, avoiding or deferring the use of cranial radiotherapy in very young children with brain tumors, and reducing dose and field size in children with HL (Pollack, 1994; Kalapurakal and Thomas, 1997; Shusterman and Meadows, 2000; Donaldson, 2002; Bhatia, 2003; Bhatia et al, 2003). In light of the leukemogenic effects of alkylating agents (Tucker et al, 1987a), there have been parallel efforts to identify new drugs that are equally or more effective with less associated toxicity (Friedman and Meadows, 1999).

The etiology of childhood cancers is largely unknown. For very-early-age-at-onset cancers, such as retinoblastoma, neuroblastoma, Wilms tumor, and ALL of infancy,

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; O/E=ratio of observed to expected cancers; CI=confidence interval; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

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Table 18.A: Descriptive characteristics of persons diagnosed with different histopathologic types of childhood cancer, both sexes, SEER 1973-2000.

Histopathologic type*	Total	Number		Median		Initial therapy (%)	
		Female	Male	Age at DX	PYR	RT	Surgery
All first cancers	23,819	10,964	12,855	8.2	5.8	38.1	49.6
Leukemia	6,440	2,833	3,607	5.2	4.8	26.6	0.3
Acute lymphocytic	4,905	2,122	2,783	4.8	5.8	29.4	0.2
Acute non-lymphocytic	1,007	498	509	8.5	1.5	13.8	0.7
Hodgkin lymphoma	1,744	838	906	15.1	10.4	64.2	23.1
Non-Hodgkin lymphoma	1,038	322	716	12.1	5.7	39.4	23.6
Brain, CNS	4,344	1,948	2,396	7.6	4.8	57.3	75.4
Ependymoma	374	151	223	4.2	3.4	63.4	94.4
Astrocytoma	2,242	1,059	1,183	8.8	6.5	45.6	78.6
PNET (brain, CNS)	859	327	532	6.4	3.5	81.3	92.9
Neuroblastoma	1,461	691	770	1.6	4.0	31.6	64.1
Retinoblastoma	581	301	280	1.3	8.2	27.5	88.1
Wilms tumor	1,188	625	563	3.2	8.8	49.9	95.4
Bone, joints	1,352	584	768	13.7	4.0	27.7	68.4
Osteosarcoma	752	337	415	13.9	3.9	6.5	80.5
Ewing sarcoma	479	198	281	13.3	3.4	62.0	46.6
Soft tissue sarcoma	1,759	807	952	10.3	5.9	45.4	76.6
Rhabdomyosarcoma	769	309	460	6.6	4.8	64.5	62.3
Fibrosarcoma†	448	237	211	12.8	9.0	17.9	92.4
Other‡	538	259	279	12.5	4.5	41.3	84.0
Germ cell tumors§	1,206	601	605	14.6	7.0	21.7	86.2
Carcinomas/epithelial‖	1,606	1,017	589	15.5	9.3	24.5	89.9
Other¶	1,100	397	703	7.9	3.6	26.1	47.5

Notes: Includes children surviving 2 months or more after diagnosis.

Abbreviations: DX=diagnosis; PYR=person-years at risk; RT=initial radiation; CNS=central nervous system; PNET=primitive neuroectodermal tumor.

*Categories and ordering based on International Classification of Childhood Cancer (ICCC) (Kramarova and Stiller, 1996).

†Also includes neurofibrosarcoma.

‡Does not include Kaposi sarcoma.

§Includes intracranial and intraspinal germ cell tumors, other or unspecified nongonadal germ cell tumors, gonadal germ cell tumors, gonadal carcinomas, other or unspecified malignant gonadal tumors.

‖Includes adrenocortical carcinoma (N=38), thyroid carcinoma (N=592), nasopharyngeal carcinoma (N=77), malignant melanoma (N=466), skin carcinoma other than melanoma (N=3), and other or unspecified carcinoma (N=430).

¶Includes Burkitt lymphoma (N=335), unspecified lymphoma (N=143), miscellaneous lymphoreticular cancers (N=55), other tumors of sympathetic nervous system (N=55), non-central nervous system PNET (N=48), renal carcinoma (N=53), hepatoblastoma (N=191), hepatic carcinoma (N=61), and other or unspecified cancers (N=159).

prenatal exposures or genetic factors may play predominant roles. Ionizing radiation is known to induce leukemia, sarcomas, and CNS cancers but probably explains only a small minority of childhood tumors (Inskip, 1999). Congenital anomalies have been associated with Wilms tumor and leukemia, while infectious agents and immune factors may be related to certain types of leukemia and lymphoma (Ries et al, 1999). A strong genetic component has been identified in retinoblastoma, while leukemia, CNS cancer, and bone and soft tissue sarcomas may arise as part of the Li-Fraumeni familial cancer syndrome (Malkin et al, 1992; Hisada et al, 1998; Eng and Maher, 1999; Nichols et al, 2001). In addition, leukemia, CNS cancer, and soft tissue sarcoma occur in association with neurofibromatosis type 1 (Heyn et al, 1993; Eng and Maher, 1999).

Results and Discussion

Characteristics of Study Population

A total of 23,819 children (age <18 years) with cancer who survived 2 or more months following diagnosis were observed for an average of 8.3 years (median, 5.8 years) (Table 18.A). There were 12,951 5-year survivors, 8,424 10-year survivors, and 2,637 20-year survivors. ALL was the most common type of first cancer, accounting for 21% of the total, while cancers of the CNS accounted for an additional 18%. Fifty-four percent of the study population was male and 46% female, but there was a female predominance among cases of retinoblastoma, Wilms tumor, fibrosarcoma, cutaneous melanoma, and carcinomas. Eighty-one percent of the cohort was white, 10% black, and 9% other or of unknown race. Blacks were overrepresented among cases with osteosarcoma, retinoblastoma, soft tissue sarcoma, and Wilms tumor

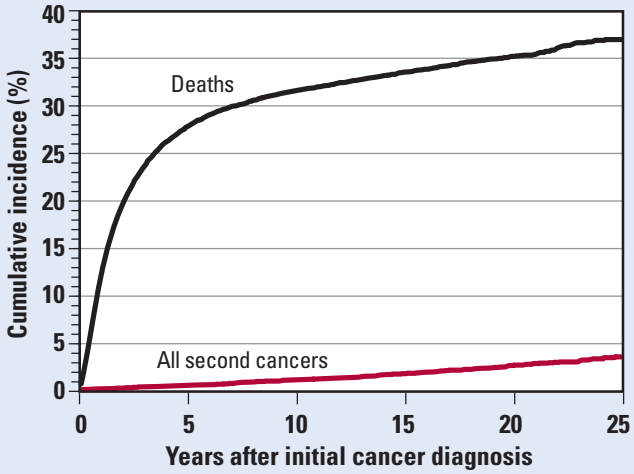
relative to their frequency in the cohort as a whole (data not shown). The median age at diagnosis was less than 5 years for retinoblastoma, neuroblastoma, Wilms tumor, ALL, and ependymoma; 5 to 9 years for ANLL, astrocytoma, primitive neuroectodermal tumor (PNET), and rhabdomyosarcoma; and 10 to 16 years for lymphoma, bone sarcoma, fibrosarcoma, germ cell tumors, various carcinomas, and melanoma. Patients diagnosed at very young ages often were followed into adolescence, and those diagnosed as teenagers were often followed into early adulthood. The maximum age at the end of follow-up was 44 years. Radiation was part of the initial course of therapy for a high proportion (>60%) of patients with HL, PNET, Ewing sarcoma, and rhabdomyosarcoma but rarely was given for osteosarcoma, fibrosarcoma, ANLL, or germ cell cancers. Initial treatment commonly included surgery, except for leukemia and lymphoma.

Overall Results

During the period of follow-up, 352 new primary cancers were diagnosed in 327 individuals. This represents a more than 6-fold increase in incidence relative to the general population (O/E=6.07, 95% CI=5.45-6.74, EAR=15 per 10,000 person-years) (Table 18.B), which is similar to risks reported for 3 other large cohorts from North America (Neglia et al, 2001), Great Britain (Jenkinson et al, 2004), and Nordic countries (Olsen et al, 1993) for contemporaneous periods. Eighteen childhood cancer patients developed 2 new malignancies, and 3 developed 3 or more new malignancies. Risks were similar for females (O/E=5.80, O=176, EAR=15) and males (O/E=6.36, O=176, EAR=15) but were somewhat higher for blacks (O/E=8.38, O=33, EAR=16) than whites (O/E=5.72, O=287, EAR=14). Subsequent cancer risks varied by age at diagnosis of the first cancer; however, patterns depended on type of first cancer and latency (or attained age). For all new cancers combined, the relative risk increased over the first 10 years following diagnosis of the initial cancer to nearly 8-fold and then decreased to less than 4-fold among 20-year survivors (Table 18.B). In contrast, the excess absolute risk increased with time, from 7 excess cancers per 10,000 person-years in the first year of follow-up to 26 among persons surviving more than 20 years. The cumulative incidence of developing a second cancer at 25 years, adjusted for the competing risk of death due to other causes, was 3.5% (95% CI=3.0%-4.1%) (Figure 18.1). In comparison, the 25-year cumulative competing risk of death, based on all deaths excluding deaths among patients with a second cancer, was 37.6% (95% CI=36.7%-38.5%). Most of the deaths due to other causes were attributed to the first cancer (data not shown).

Numerous types of subsequent primary cancers occurred significantly more often than expected among childhood cancer patients, and the patterns of excess risk for specific cancer sites changed over time (Table 18.B). The most common types were cancers of the female breast, brain/CNS, bone, thyroid gland, and soft tissue, as well as melanoma and ANLL. Significantly high rates also were noted for new malignancies of the buccal cavity, digestive system, respiratory system, testis, urinary tract, eye, and CNS other than brain, as well as NHL. Relative and excess absolute risks for specific types of cancer generally were similar for males and females, with some exceptions (data not shown). The excess of urinary tract cancers occurred exclusively among males. The relative and excess absolute risks for ANLL and the relative (but not absolute) risk for thyroid cancer were higher among males than females, whereas the relative and absolute risks of subsequent bone cancer were higher in females.

Figure 18.1: Cumulative incidence of developing a second cancer and cumulative probability of death due to competing causes among children with any primary cancer, SEER 1973-2000.



Note: The competing cause of death is based on all deaths excluding deaths among patients with a second cancer.

Elevated O/E ratios for some new primary cancers (notably ANLL, melanoma, and cancers of the female and male genital tracts) were apparent within the first 5 years after diagnosis of the first cancer (Table 18.B). For other cancers (including those of the buccal cavity, stomach, female breast, urinary tract, soft tissues, and cranial nerves or spinal cord), the relative risk appeared greater for long-term survivors. In particular, there was a late-emerging excess of stomach cancer, 15 or more years after initial therapy. Observed-to-expected ratios for NHL and cancers of the bone, brain, and thyroid gland varied erratically with time. The relative risks for all latency intervals combined were similar for new primary solid cancers and leukemia, but the absolute risk was decidedly higher for subsequent solid cancers (Table 18.B). Solid cancers accounted for 81% of all subsequent cancers, and the temporal change in risk since initial diagnosis resembled that for all subsequent cancers combined. For subsequent leukemia, both the O/E and EAR peaked between 1 and 5 years after the first cancer, and no cases were observed 15 or more years after initial diagnosis. As childhood cancer survivors mature to the ages at which cancer incidence rates in the population increase sharply, it remains to be

Table 18.B: Risk of subsequent primary cancers following childhood cancer (ages 0-17 years), by time since diagnosis of first cancer, both sexes.

	Years after first primary cancer diagnosis															
	<1 yr		1-4 yr		5-9 yr		10-14 yr		15-19 yr		≥20 yr		Total			
Number starting interval	23,819		20,415		12,951		8,424		5,234		2,637		23,819			
Person-years in interval	18,350		63,463		52,583		33,856		19,330		9,003		196,585			
Subsequent primary cancer	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**O**	**E**	**O/E**	**EAR**
All subsequent cancers	16	5.39*	83	7.74*	92	7.83*	72	5.77*	57	4.98*	32	3.71*	352	58.00	6.07*	14.96
All solid cancers	13	7.46*	53	8.15*	75	9.52*	63	6.77*	54	5.93*	27	3.70*	285	41.84	6.81*	12.37
Buccal cavity, pharynx	0	0.00	2	11.83*	4	18.19*	6	25.32*	4	18.73*	1	5.54	17	1.06	16.06*	0.81
Tongue	0	0.00	1	60.15	0	0.00	1	23.32	1	21.94	0	0.00	3	0.18	16.38*	0.14
Salivary gland	0	0.00	1	16.08	2	24.68*	3	36.97*	2	32.79*	0	0.00	8	0.34	23.37*	0.39
Digestive system	1	9.77	4	12.94*	5	15.29*	4	8.30*	8	12.95*	3	4.65	25	2.48	10.07*	1.15
Stomach	0	0.00	0	0.00	0	0.00	0	0.00	3	41.78*	3	43.34*	6	0.25	23.61*	0.29
Small intestine	0	0.00	1	148.04*	1	79.34*	1	49.82	0	0.00	0	0.00	3	0.09	32.79*	0.15
Colon	1	106.96*	1	19.66	0	0.00	0	0.00	1	4.42	0	0.00	3	0.79	3.78	0.11
Rectum, rectosigmoid junction	0	0.00	0	0.00	3	60.24*	0	0.00	0	0.00	0	0.00	3	0.43	7.02*	0.13
Pancreas	0	0.00	1	68.97	1	43.38	0	0.00	3	70.63*	0	0.00	5	0.16	30.31*	0.25
Respiratory system	0	0.00	1	6.21	3	17.72*	2	10.20*	1	4.16	1	3.37	8	1.11	7.19*	0.35
Nose, nasal cavity, ear	0	0.00	0	0.00	2	65.46*	0	0.00	0	0.00	0	0.00	2	0.13	15.08*	0.09
Lung, bronchus	0	0.00	1	22.20	1	13.86	2	18.65*	1	6.01	0	0.00	5	0.64	7.82*	0.22
Female breast	0	0.00	0	0.00	2	8.92*	13	18.42*	16	12.38*	8	4.64*	39	3.99	9.78*	3.69
Female genital system	1	12.85	4	9.06*	3	3.55	1	0.80	1	0.78	0	0.00	10	4.91	2.04	0.54
Cervix uteri	0	0.00	1	11.19	1	3.19	0	0.00	0	0.00	0	0.00	2	2.11	0.95	-0.01
Corpus uteri	0	0.00	0	0.00	0	0.00	1	12.54	1	8.14	0	0.00	2	0.41	4.87	0.17
Ovary	1	17.63	2	6.95	1	2.35	0	0.00	0	0.00	0	0.00	4	2.03	1.97	0.21
Male genital system	1	10.45	5	9.08*	5	4.76*	0	0.00	1	0.95	0	0.00	12	4.59	2.61*	0.73
Testis	1	11.34	5	9.49*	4	3.88*	0	0.00	1	0.97	0	0.00	11	4.48	2.46*	0.64
Urinary system	0	0.00	2	4.66	1	4.25	1	4.44	4	15.82*	0	0.00	8	1.58	5.07*	0.33
Urinary bladder	0	0.00	0	0.00	0	0.00	0	0.00	2	16.19*	0	0.00	2	0.52	3.82	0.08
Kidney parenchyma	0	0.00	2	5.46	0	0.00	1	9.83	2	16.29*	0	0.00	5	1.03	4.86*	0.20
Melanoma of skin†	5	61.74*	3	5.72*	6	5.54*	5	3.41*	3	2.10	3	2.85	25	5.63	4.44*	0.99
Eye, orbit	1	11.54	1	5.61	1	22.88	1	30.01	0	0.00	0	0.00	4	0.39	10.16*	0.18
Brain	2	4.20	7	4.43*	14	11.27*	6	7.25*	2	3.84	1	3.5	32	4.93	6.49*	1.38
Other central nervous system	0	0.00	2	12.83*	2	18.70*	2	29.27*	0	0.00	2	88.13*	8	0.45	17.90*	0.38
Thyroid	1	11.04	4	7.24*	8	7.90*	11	9.16*	3	2.78	3	4.1	30	4.67	6.43*	1.29
Bone, joints	1	6.84	12	20.94*	11	20.20*	7	19.40*	2	11.85*	2	32.04*	35	1.86	18.86*	1.69
Osteosarcoma	0	0.00	8	26.71*	7	25.06*	5	28.24*	1	14.40	0	0.00	21	0.92	22.79*	1.02
Chondrosarcoma	1	117.72*	1	27.45	2	43.48*	2	41.33*	1	24.69	0	0.00	7	0.20	34.78*	0.35
Soft tissue including heart	0	0.00	5	8.99*	10	21.35*	4	10.72*	8	31.38*	2	14.39*	29	1.97	14.75*	1.38
(Neuro)Fibrosarcoma	0	0.00	2	17.80*	7	57.01*	2	19.57*	4	55.20*	1	25.07	16	0.48	33.43*	0.79
Non-Hodgkin lymphoma	2	10.95*	3	4.03	4	4.64*	1	1.10	3	3.59	3	5.39*	16	4.09	3.91*	0.61
Hodgkin lymphoma	0	0.00	2	1.72	2	1.29	0	0.00	0	0.00	0	0.00	4	5.58	0.72	-0.08
Leukemia	0	0.00	24	10.87*	9	6.63*	5	6.32*	0	0.00	0	0.00	38	5.88	6.46*	1.63
Acute lymphocytic	0	0.00	3	1.89	3	3.73	2	5.94	0	0.00	0	0.00	8	3.50	2.29	0.23
Acute non-lymphocytic	0	0.00	19	38.66*	6	14.31*	3	9.44*	0	0.00	0	0.00	28	1.72	16.28*	1.34
Chronic myeloid	0	0.00	2	23.78*	0	0.00	0	0.00	0	0.00	0	0.00	2	0.47	4.24	0.08

Notes: EAR for female sites is based on 94,789 PYR and for male sites on 101,795 PYR.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

†Ten of 25 subsequent melanomas occurred among children with an initial melanoma.

seen whether the excess cancer risk will broaden to include the common adult carcinomas and increase in proportion to the background risk.

The patterns of excess risk over time in the SEER cohort are similar to those observed in previous studies of multiple primary cancers in children (Little et al, 1991, 1998a; Olsen et al, 1993; de Vathaire et al, 1999a; Jenkinson et al, 2004). The wave-like temporal pattern for excess leukemia fits the pattern commonly observed following acute exposure to leukemogens and strongly suggests an effect of treatment. A decreasing relative risk for solid cancers with increasing follow-up time may reflect increases in background incidence rates unrelated to the initial childhood cancer or its treatment. However, part of

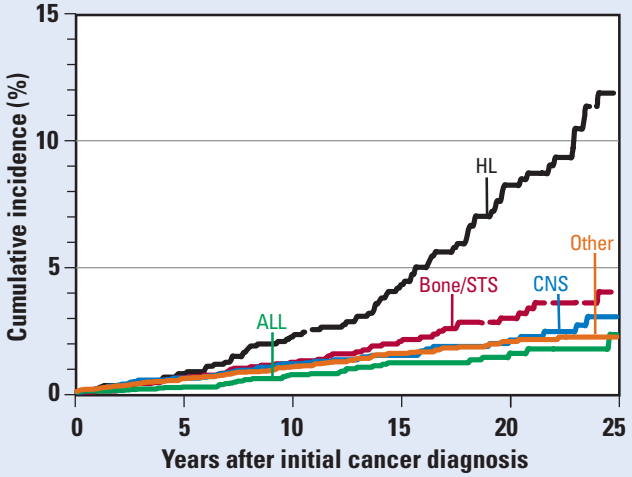
the decrease in relative risk in later follow-up intervals may reflect underascertainment of new cancers among long-term survivors. An estimated 14% of childhood cancer cases are lost to follow-up by SEER (Ries et al, 1999). In addition, new primary cancers occurring among persons who moved outside of geographic areas covered by SEER registries would not be recorded in SEER files.

Childhood cancer patients whose initial treatment included radiotherapy were at higher risk of developing a new cancer than those not given radiotherapy (Table 18.C). 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 (especially stomach and pancreas), and lung. Because subsequent courses of radiotherapy were often given for several types of initial cancer (particularly HL), and because prophylactic craniospinal irradiation for ALL was not coded as radiation treatment until 1988, some of the persons classified in the "no radiation" group probably did receive radiation. This would imply that actual differences in O/E ratios for the irradiated and nonirradiated groups are greater than indicated in Table 18.C, for some types of subsequent cancers. Previous epidemiologic studies have documented excesses of cancers of the female breast, thyroid gland, brain and CNS, salivary gland, bone, and stomach associated with radiotherapy during childhood (Tucker et al, 1987a,b, 1991; Ron et al, 1988, 1995; Neglia et al, 1991; Newton et al, 1991; Hancock et al, 1993; Bhatia et al, 1996; Hawkins et al, 1996; Kuttesch et al, 1996; Wong et al, 1997; Karlsson et al, 1998; Le Vu et al, 1998; Little et al, 1998b; Schneider et al, 1998; Walter et al, 1998; de Vathaire et al, 1999b; Garwicz et al, 2000; Metayer et al, 2000; Bhatia and Sklar, 2002; Sigurdson et al, 2005).

The O/E ratios for ANLL and cancer of the buccal cavity differed little by radiotherapy history, while the O/E ratios for cancers of the female and male genital tract and for cutaneous melanoma were higher among persons not known to have received radiation. Chemotherapy likely was more important than radiotherapy in causing subsequent ANLL. At least 23 of the 28 ANLL cases were known to have received chemotherapy for their childhood cancer. Chemotherapy probably contributed to the increased risks of other subsequent cancers, because previous studies have linked alkylating agents with second primary bone and soft tissue sarcomas (Tucker et al, 1987b; Newton et al, 1991; Hawkins et al, 1996; Le Vu et al, 1998), lung cancer (Kaldor et al, 1992; Swerdlow et al, 1992; Travis et al, 2002), and bladder cancer (Travis et al, 1995). Melanoma has not been clearly linked to radiotherapy or chemotherapy, although a recent small study of childhood cancer survivors reported increased risks associated with radiation doses greater than 15 Gy or treatment with alkylating agents and spindle inhibitors combined (Guérin et al, 2003).

The largest relative risks for all types of subsequent cancers combined were seen among patients with initial diagnoses of Ewing sarcoma, retinoblastoma, and PNET, while the largest absolute risks were seen following

Figure 18.2: Cumulative incidence of developing a second cancer among children with selected first primary cancers: Hodgkin lymphoma (HL), bone and soft tissue sarcomas (Bone/STS), brain and other central nervous system cancers (CNS), acute lymphocytic leukemia (ALL) and other cancer sites (Other).



Ewing sarcoma, HL, and PNET (Table 18.D). The cumulative incidence of second cancer at 25 years after HL was 11.8% (95% CI=9.1%-14.9%), decidedly higher than for most other types of childhood cancers (Figure 18.2). (Because of the small numbers of second cancers, PNET is grouped with other brain and CNS cancers, and Ewing sarcoma with other bone sarcomas.) Patients with Ewing sarcoma, HL, and PNET were frequently treated with both radiotherapy and chemotherapy. Patients diagnosed with lymphomas, bone sarcomas, and carcinomas plus melanomas also tended to be older, and to have attained ages at which background incidence rates for many cancers are higher. The high relative risk of cancer in patients with retinoblastoma probably reflects the combination of genetic predisposition to multiple cancers, sensitivity to radiogenic cancer, and very low background cancer risk in the general population during the early years of life. Overall, females and males had similar excess risks of subsequent cancer after most types of first cancer (Table 18.D). However, risks following HL and fibrosarcoma were higher in females, and risks following a first Wilms tumor, retinoblastoma, carcinoma, or ependymoma were higher among males. A large part of the sex difference in subsequent cancer after HL can be explained by the occurrence of radiation-related breast cancer (discussed later in this chapter).

The EAR for new primary solid cancers was higher among persons whose first cancer was diagnosed between the ages of 10 and 17 years than at younger ages (Table 18.E); however, it was difficult to separate the effects of age at initial cancer diagnosis from the effects related to the type of first cancer, its treatment, and time since initial diagnosis (or attained age). HL rarely occurs before the age of 10 years, but it accounted for a large part of the excess risk for the group aged 10-17 years

Table 18.C: Risk of subsequent primary cancers following childhood cancer (ages 0-17 years), by time since diagnosis of first cancer and by initial treatment with radiation, both sexes.

	Years after first primary cancer diagnosis															
	<1 yr		1-4 yr		5-9 yr		10-14 yr		15-19 yr		≥20 yr		Total			
Radiation, no. pts	9,063		7,670		4,940		3,607		2,492		1,359		9,063			
Radiation, PYR	6,971		23,726		21,142		15,269		9,629		4,695		81,432			
No radiation, no. pts	13,905		12,054		7,577		4,530		2,555		1,172		13,905			
No radiation, PYR	10,764		37,596		29,691		17,405		8,998		3,857		108,311			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
All subsequent cancers																
Any radiation	4	3.69	37	9.39*	56	11.69*	43	7.67*	36	6.50*	21	5.02*	197	25.14	7.84*	21.10
No radiation	12	6.72*	41	6.41*	34	5.21*	28	4.38*	16	2.94*	11	2.79*	142	30.48	4.66*	10.30
All solid cancers																
Any radiation	2	3.17	23	9.68*	45	14.06*	38	9.16*	34	7.77*	18	5.13*	160	18.24	8.77*	17.41
No radiation	11	10.44*	27	6.94*	29	6.62*	24	5.01*	16	3.67*	9	2.68*	116	21.83	5.31*	8.69
Buccal cavity, pharynx																
Any radiation	0	0.00	2	30.97*	1	11.15	1	9.47	3	29.07*	0	0.00	7	0.47	15.03*	0.80
No radiation	0	0.00	0	0.00	3	24.52*	5	40.81*	1	9.82	1	12.37	10	0.55	18.25*	0.87
Salivary gland																
Any radiation	0	0.00	1	42.37	1	31.06	0	0.00	2	67.91*	0	0.00	4	0.15	27.13*	0.47
No radiation	0	0.00	0	0.00	1	21.75	3	70.11*	0	0.00	0	0.00	4	0.18	22.03*	0.35
Digestive system																
Any radiation	1	29.01	1	9.46	3	22.73*	2	9.45*	5	17.19*	2	6.59	14	1.08	12.99*	1.59
No radiation	0	0.00	2	10.40*	2	10.94*	2	7.95	3	9.95*	1	3.35	10	1.29	7.74*	0.80
Stomach																
Any radiation	0	0.00	0	0.00	0	0.00	0	0.00	2	60.12*	2	61.83*	4	0.11	35.89*	0.48
No radiation	0	0.00	0	0.00	0	0.00	0	0.00	1	28.08	1	30.81	2	0.13	15.24*	0.17
Pancreas																
Any radiation	0	0.00	1	191.15*	1	112.06*	0	0.00	3	151.26*	0	0.00	5	0.07	69.36*	0.61
No radiation	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.08	0.00	-0.01
Respiratory system																
Any radiation	0	0.00	1	16.81	1	14.10	2	22.51*	1	8.81	1	7.45	6	0.48	12.38*	0.68
No radiation	0	0.00	0	0.00	2	21.78*	0	0.00	0	0.00	0	0.00	2	0.57	3.48	0.13
Lung, bronchus																
Any radiation	0	0.00	1	56.44	0	0.00	2	42.30*	1	13.05	0	0.00	4	0.28	14.20*	0.46
No radiation	0	0.00	0	0.00	1	25.56	0	0.00	0	0.00	0	0.00	1	0.32	3.09	0.06
Female breast																
Any radiation	0	0.00	0	0.00	2	22.91*	11	37.47*	11	19.21*	5	6.71*	29	1.71	16.91*	7.14
No radiation	0	0.00	0	0.00	0	0.00	2	5.21	5	7.48*	3	3.44	10	2.08	4.81*	1.48
Female genital system																
Any radiation	0	0.00	0	0.00	1	2.99	1	1.85	1	1.67	0	0.00	3	2.14	1.40	0.22
No radiation	1	21.97	4	15.49*	2	4.18	0	0.00	0	0.00	0	0.00	7	2.56	2.73*	0.83
Male genital system																
Any radiation	0	0.00	0	0.00	1	2.22	0	0.00	1	1.86	0	0.00	2	2.15	0.93	-0.03
No radiation	1	18.03	5	16.03*	4	7.19*	0	0.00	0	0.00	0	0.00	10	2.24	4.46*	1.41
Urinary system																
Any radiation	0	0.00	0	0.00	1	10.74	0	0.00	1	8.28	0	0.00	2	0.64	3.12	0.17
No radiation	0	0.00	1	3.66	0	0.00	1	8.65	1	8.25	0	0.00	3	0.87	3.44	0.20
Melanoma of skin																
Any radiation	0	0.00	1	4.93	1	2.25	1	1.52	3	4.28	0	0.00	6	2.57	2.34	0.42
No radiation	5	107.52*	2	6.68	5	8.41*	4	5.34*	0	0.00	3	6.48*	19	2.82	6.74*	1.49
Brain, CNS																
Any radiation	1	5.19	4	6.40*	12	22.54*	5	12.41*	2	7.16	3	18.88*	27	2.19	12.32*	3.05
No radiation	1	3.14	5	4.75*	4	5.18*	2	4.34	0	0.00	0	0.00	12	3.00	4.00*	0.83
Thyroid																
Any radiation	0	0.00	2	9.48*	5	12.33*	7	13.27*	0	0.00	3	8.12*	17	2.08	8.18*	1.83
No radiation	1	19.31	1	3.14	3	5.29*	4	6.36*	3	5.83*	0	0.00	12	2.41	4.99*	0.89

Table 18.C: Continued.

	Years after first primary cancer diagnosis															
	<1 yr		1-4 yr		5-9 yr		10-14 yr		15-19 yr		≥20 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
Bone, joints																
Any radiation	0	0.00	8	35.36*	8	34.82*	5	30.09*	1	11.85	1	30.39	23	0.80	28.83*	2.73
No radiation	1	12.13	4	12.26*	3	10.08*	2	10.94*	1	12.76	1	37.89	12	0.99	12.07*	1.02
Soft tissue including heart																
Any radiation	0	0.00	3	15.17*	8	42.94*	2	12.04*	4	31.91*	2	27.90*	19	0.81	23.48*	2.23
No radiation	0	0.00	2	5.90	1	3.76	2	10.32*	2	16.64*	0	0.00	7	1.09	6.45*	0.55
Hodgkin lymphoma																
Any radiation	0	0.00	1	2.13	2	3.05	0	0.00	0	0.00	0	0.00	3	2.51	1.20	0.06
No radiation	0	0.00	1	1.55	0	0.00	0	0.00	0	0.00	0	0.00	1	2.85	0.35	-0.17
Non-Hodgkin lymphoma																
Any radiation	2	27.79*	1	3.48	2	5.65	0	0.00	2	4.90	2	7.15	9	1.81	4.97*	0.88
No radiation	0	0.00	2	4.65	2	4.19	1	2.17	0	0.00	1	4.12	6	2.11	2.85*	0.36
Acute lymphocytic leukemia																
Any radiation	0	0.00	2	3.71	2	6.48	1	6.60	0	0.00	0	0.00	5	1.30	3.85*	0.45
No radiation	0	0.00	1	1.00	1	2.12	1	5.73	0	0.00	0	0.00	3	2.09	1.44	0.08
Acute non-lymphocytic leukemia																
Any radiation	0	0.00	8	44.63*	3	17.69*	1	6.97	0	0.00	0	0.00	12	0.72	16.66*	1.39
No radiation	0	0.00	10	33.92*	2	8.51	2	12.26*	0	0.00	0	0.00	14	0.94	14.93*	1.21

Notes: EAR for female sites is based on 38,218 (any radiation) and 53,447 (no radiation) PYR, and for male sites on 43,214 (any radiation) and 54,864 (no radiation) PYR. Patients with unknown treatment, unknown radiation, or no known treatment were excluded (N=851, O=13).

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000); pts=patients; CNS=central nervous system.

*P <0.05.

at first diagnosis. For this age group, O/E ratios for subsequent solid cancers were similar among patients with HL and those with other forms of cancer through the first 10 years of follow-up; only among patients who survived more than 10 years was the O/E clearly higher for those diagnosed with HL. This temporal pattern may be explained by the frequent use of extended field radiotherapy in HL patients and a latency period of 10 years or more before most radiation-related solid cancers begin to appear. The excess of subsequent leukemia occurred entirely within the first 15 years of follow-up, regardless of age at diagnosis and type of the first cancer (Table 18.E).

Risks of Specific Subsequent Primary Cancers by Type of First Primary Cancer

Acute Lymphocytic Leukemia

Children diagnosed with ALL had a nearly 5-fold relative risk of developing a new cancer (O/E=4.70, O=39); however, the overall excess absolute risk (EAR=8) was low compared with risks following most other childhood cancers (Tables 18.D and 18.F). The relative risk grew to 8-fold for the 5- to 9-year follow-up interval, then declined. Most of the absolute excess was due to subsequent cancers of the salivary glands, brain and other CNS, bone, and thyroid gland, with the temporal patterns of relative risk generally consistent with a radiation effect. Previous studies of ALL have found that cranial irradiation, given to prevent or treat CNS involvement, is related to a particularly high risk of subsequent primary brain cancer, as well as new cancers of the head and neck (Neglia et al, 1991; Bhatia et al, 2002; Bhatia, 2003), whereas excess leukemias have been linked to the use of epipodophyllotoxins (Pui et al, 1989, 2003). It is possible that genetic predisposition related to neurofibromatosis type 1 or Li-Fraumeni syndrome played a role in the excess cancer incidence after ALL (Hisada et al, 1998; Eng and Maher, 1999).

Hodgkin Lymphoma

In our survey, HL was the initial cancer associated with 87 of the 352 new primary cancers following childhood cancers (O/E=9.55, EAR=39) (Tables 18.D and 18.G). A strong increasing trend over time was apparent, with the EAR rising to more than 90 among children surviving 15 years or more (data not shown). Risks were higher among females, mainly due to a notably high risk of breast cancer (O/E=24.61, EAR=23) (Table 18.G). In addition, significantly elevated risks of more than 9-fold were seen for subsequent cancers of the salivary gland, stomach, pancreas, lung, bone, soft tissue, and thyroid gland, as well as for ANLL and NHL, based on smaller numbers. Radiotherapy clearly contributed to the excess risk of solid cancers among 5-year survivors. The increased risk of breast cancer after mantle radiotherapy for HL is well established (Tucker et al, 1988; Hancock et al, 1993; van Leeuwen et al, 1994a, 2000, 2003; Bhatia et al, 1996, 2003; Travis et al, 1996, 2003; Metayer et al, 2000). Radiation also may have contributed to the increases seen for

Table 18.D: Risk of subsequent primary cancers of all types combined following childhood cancer (ages 0-17 years), by type of first cancer, both sexes.

Number starting interval Person-years in interval	Females 10,964 94,789			Males 12,855 101,795			Total 23,819 196,584			
Type of first cancer	O	O/E	EAR	O	O/E	EAR	O	E	O/E	EAR
All first cancers	176	5.80*	15.37	176	6.36*	14.57	352	58.00	6.07*	14.96
Leukemia	20	4.23*	6.93	26	4.78*	8.05	46	10.17	4.52*	7.53
Acute lymphocytic	18	4.80*	7.83	21	4.61*	7.60	39	8.30	4.70*	7.70
Acute non-lymphocytic	1	1.69	1.74	2	4.65	8.28	3	1.02	2.93	4.66
Hodgkin lymphoma	59	11.74*	56.72	28	6.86*	22.82	87	9.11	9.55*	38.95
Non-Hodgkin lymphoma	4	4.74*	12.43	9	5.29*	12.85	13	2.54	5.11*	12.72
Brain, CNS	21	5.00*	11.53	35	7.76*	17.28	56	8.71	6.43*	14.68
Ependymoma	0	0.00	-2.63	4	14.47*	28.68	4	0.51	7.79*	15.86
Astrocytoma	11	4.11*	9.40	16	5.66*	12.84	27	5.50	4.91*	11.25
PNET (brain, CNS)	6	10.56*	23.83	9	14.32*	26.91	15	1.20	12.54*	25.61
Neuroblastoma	7	7.87*	12.06	4	4.10*	5.72	11	1.87	5.90*	8.82
Retinoblastoma	6	11.60*	17.59	9	17.92*	30.17	15	1.02	14.71*	23.56
Wilms tumor	5	4.07*	5.81	9	8.56*	14.32	14	2.28	6.14*	9.73
Bone, joints	13	7.08*	23.87	13	8.46*	23.36	26	3.37	7.71*	23.61
Osteosarcoma	5	4.46*	14.36	5	6.08*	15.87	10	1.94	5.14*	15.10
Ewing sarcoma	7	13.79*	42.74	8	15.90*	45.92	15	1.01	14.84*	44.39
Soft tissue including heart	16	6.80*	19.78	12	5.10*	12.12	28	4.71	5.95*	15.67
Rhabdomyosarcoma	5	7.88*	18.19	6	6.81*	14.40	11	1.52	7.26*	15.93
Fibrosarcoma†	7	7.95*	25.32	2	2.74	5.79	9	1.61	5.59*	16.03
Other	4	4.90*	15.53	4	5.45*	14.89	8	1.55	5.16*	15.20
Germ cell tumors	8	3.50*	9.87	9	4.68*	13.34	17	4.21	4.04*	11.53
Carcinomas/epithelial‡	15	2.67*	8.33	15	6.06*	20.85	30	8.10	3.71*	12.69
Other§	2	2.44	4.16	7	6.32*	12.82	9	1.93	4.67*	9.52

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000); CNS=central nervous system; PNET=primitive neuroectodermal tumor.

*P <0.05.

†Also includes neurofibrosarcoma.

‡Includes adrenocortical carcinoma (N=38), thyroid carcinoma (N=592), nasopharyngeal carcinoma (N=77), malignant melanoma (N=466), skin carcinoma other than melanoma (N=3), and other or unspecified carcinoma (N=430).

§Includes Burkitt lymphoma (N=335), unspecified lymphoma (N=143), miscellaneous lymphoreticular cancers (N=55), other tumors of sympathetic nervous system (N=55), non-CNS PNET (N=48), renal carcinoma (N=53), hepatoblastoma (N=191), hepatic carcinoma (N=61), and other or unspecified cancers (N=159).

cancers of the digestive system, thyroid, lung, bone, and soft tissue among long-term survivors, as observed in other HL study populations (Tucker et al, 1988; van Leeuwen et al, 1994a; Metayer et al, 2000; Dores et al, 2002; Travis et al, 2002). The high relative risk for subsequent ANLL, reaching an increase of 75-fold during the first 15 years of follow-up, is consistent with previous studies linking excess ANLL following HL to treatment with alkylating agents (Tucker et al, 1987a, 1988; Kaldor et al, 1990; Swerdlow et al, 1992, 1997; van Leeuwen et al, 1994a,b). Misclassification of the original HL or depressed cell-mediated immunity associated with HL (Slivnick et al, 1990) may be related to the excess of NHL. Recent trends toward use of lower radiation doses, smaller radiation fields, and less toxic chemotherapy may reduce the risk of new malignancies in the future (Moppett et al, 2001; Donaldson, 2002).

Non-Hodgkin Lymphoma

The risk of developing a new malignancy following childhood NHL (O/E=5.11, O=13, EAR=13) was decidedly lower than that for HL (Table 18.G). However, significantly elevated risks were seen for ANLL and cancers of the female breast and thyroid, based on small numbers of cases. For breast cancer, the excess was confined to 15-year survivors (O/E=29.62) and is probably related to initial treatment with radiation. Radiation is no longer part of standard therapy for many patients with childhood NHL (Kalapurakal and Thomas, 1997). The increased risk of ANLL among NHL survivors within the first 5 years after initial diagnosis appears related to treatment with chemotherapy, including alkylating agents and/or epipodophyllotoxins (Hawkins et al, 1992; Travis et al, 1994a; Leung et al, 2001). The excess thyroid cancer occurred within the first 5 years after diagnosis of NHL and may reflect increased detection due to close medical surveillance.

Central Nervous System Cancers

Relative and excess absolute risks of developing a new cancer were highest following a first PNET (O/E=12.54, O=15, EAR=26), intermediate following ependymoma

Table 18.E: Risk of subsequent primary solid cancers and leukemia following a first childhood cancer, by age at first cancer diagnosis, type of first cancer (Hodgkin lymphoma, other) and years after first primary cancer diagnosis, both sexes.

Age at diagnosis of first cancer (yr)	First cancer	Years after first primary cancer diagnosis															
		<1 yr		1-4 yr		5-9 yr		10-14 yr		15-19 yr		≥20 yr		Total			
		O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
Subsequent primary solid cancer																	
<5	Hodgkin lymphoma	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.04	0.00	-1.19
	Other	2	2.73	11	5.66*	21	17.58*	17	14.92*	12	10.31*	2	2.06	65	7.14	9.10*	8.43
	All 1st cancers	2	2.72	11	5.64*	21	17.50*	17	14.85*	12	10.24*	2	2.04	65	7.18	9.05*	8.38
5-9	Hodgkin lymphoma	0	0.00	1	25.71	0	0.00	1	12.04	1	11.99	0	0.00	3	0.33	9.13*	12.36
	Other	1	4.71	11	14.22*	6	6.37*	11	9.67*	3	2.52	1	1.11	33	5.16	6.39*	7.51
	All 1st cancers	1	4.52	12	14.77*	6	5.98*	12	9.83*	4	3.14	1	1.05	36	5.49	6.56*	7.78
10-17	Hodgkin lymphoma	0	0.00	6	8.24*	11	8.98*	13	8.12*	22	13.66*	10	7.31*	62	6.66	9.31*	31.62
	Other	10	15.18*	24	7.97*	37	8.13*	21	3.94*	16	3.17*	14	3.50*	122	22.50	5.42*	14.04
	All 1st cancers	10	12.69*	30	8.03*	48	8.46*	34	4.90*	38	5.70*	24	4.47*	184	29.16	6.31*	17.52
Subsequent leukemia																	
<5	Hodgkin lymphoma	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.01	0.00	-0.34
	Other	0	0.00	7	5.96*	2	3.44	2	7.05	0	0.00	0	0.00	11	2.71	4.06*	1.21
	All 1st cancers	0	0.00	7	5.95*	2	3.43	2	7.01	0	0.00	0	0.00	11	2.72	4.05*	1.20
5-9	Hodgkin lymphoma	0	0.00	0	0.00	2	127.20*	1	92.46*	0	0.00	0	0.00	3	0.06	50.62*	13.60
	Other	0	0.00	2	5.48	1	4.11	0	0.00	0	0.00	0	0.00	3	1.00	2.99	0.54
	All 1st cancers	0	0.00	2	5.22	3	11.58*	1	6.32	0	0.00	0	0.00	6	1.06	5.65*	1.26
10-17	Hodgkin lymphoma	0	0.00	2	17.44*	2	19.71*	2	26.80*	0	0.00	0	0.00	6	0.42	14.43*	3.19
	Other	0	0.00	13	24.43*	2	4.85	0	0.00	0	0.00	0	0.00	15	1.69	8.90*	1.88
	All 1st cancers	0	0.00	15	23.19*	4	7.79*	2	5.75	0	0.00	0	0.00	21	2.10	9.99*	2.14

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

(O/E=7.79, O=4, EAR=16), and lowest following an astrocytoma (O/E=4.91, O=27, EAR=11) (Table 18.D). This result parallels the use of radiation to treat the primary tumor (Tables 18.A and 18.H). Risk of subsequent CNS cancer (mostly brain cancer) was significantly increased following a first CNS cancer, with the excesses among those surviving 5 or more years, possibly related to radiotherapy. In the absence of radiotherapy, chemotherapy has not been related to subsequent primary CNS tumors (Little et al, 1998b; Garwicz et al, 2000). However, chemotherapy, which was commonly used for childhood brain cancer (Black, 1991a,b; Pollack, 1994), is likely to account for the excess of leukemia. It is noteworthy that the only 2 cases of subsequent chronic myelogenous leukemia observed in the entire cohort of childhood cancer survivors occurred among patients diagnosed previously with astrocytoma. Craniospinal radiation fields were more commonly used for PNETs than for astrocytomas because of the greater tendency of PNETs to spread throughout the CNS (Black, 1991a,b; Pollack, 1994; Fine et al, 2005), so that radiation exposure covered more extensive volumes of tissue. In a prior study of second cancers in PNET (medulloblastoma) patients, which partially overlapped with the present study, excesses of ALL were seen, along with cancers of the salivary glands, uterine cervix, CNS, and thyroid gland, with a majority of the solid cancers arising in or near the radiation fields (Goldstein et al, 1997). In the present study, bone and soft tissue sarcomas were increased following astrocytoma, possibly due to a combination of treatment and genetic susceptibility (Inskip, 2003). Recent trends in the treatment of childhood CNS cancer include less use of cranial radiotherapy and greater use of chemotherapy (Moppett et al, 2001).

Bone Sarcoma

The large risk of subsequent cancer following Ewing sarcoma (O/E=14.84, O=15, EAR=44) was due mostly to new cancers of the bone, soft tissue, and breast, as well as ANLL (Table 18.I). Several studies of Ewing sarcoma have reported an increased risk of subsequent osteosarcoma and soft tissue sarcomas related to high radiation doses (41-60 Gy) and alkylating agents (Suit, 1975; Tucker et al, 1987b; Travis et al, 1994b; Hawkins et al, 1996; Kuttesch et al, 1996; Le Vu et al, 1998). Notably high risks of leukemia have been associated with multiagent chemotherapy for Ewing sarcoma (Dunst et al, 1998). A similar constellation of excess cancers was observed after osteosarcoma in our survey (Table 18.I), although relative and absolute risks (O/E=5.14, O=10, EAR=15) were lower than for Ewing sarcoma. The risk of subsequent breast cancer was increased markedly among patients with

Table 18.F: Risk of subsequent primary cancers among 4,905 children (ages 0-17 years) diagnosed with acute lymphocytic leukemia, by years after diagnosis of initial cancer, both sexes.

	Years after first primary cancer diagnosis									
	<5 yr		5-9 yr		≥10 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
All subsequent cancers	7	2.73*	14	8.16*	18	4.47*	39	8.30	4.70*	7.70
Any radiation†	1	1.28	8	12.31*	5	2.3	14	3.60	3.89*	6.93
All solid cancers	6	4.08*	13	12.31*	17	5.78*	36	5.47	6.58*	7.66
Any radiation†	1	2.25	8	19.88*	5	3.13*	14	2.45	5.72*	7.70
Buccal cavity, pharynx	1	31.99	1	30.54	2	25.34*	4	0.14	27.98*	0.97
Salivary gland	1	95.60*	1	75.88	1	36.99	3	0.05	59.20*	0.74
Digestive system	1	12.83	0	0.00	1	6.17	2	0.28	7.19	0.43
Brain, CNS	1	1.87	7	24.27*	3	10.22*	11	1.12	9.86*	2.48
Thyroid	1	18.27	2	20.97*	5	12.58*	8	0.55	14.61*	1.87
Bone, joints	1	8.06	1	8.12	2	15.41*	4	0.38	10.61*	0.91
Osteosarcoma	0	0.00	0	0.00	2	31.18*	2	0.19	10.33*	0.45
Soft tissue including heart	1	6.98	1	11.69	0	0.00	2	0.36	5.56	0.41
Melanoma of skin	0	0.00	0	0.00	2	4.25	2	0.62	3.20	0.35
Other	1	0.65	2	2.10	3	1.27	6	4.86	1.24	0.29

Notes: Number of patients (PYR at risk in interval) for <5, 5-9, and ≥10 time intervals are: 4,905 (17,699), 2,723 (10,742), and 1,688 (11,403), respectively.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000); CNS=central nervous system.

*P <0.05.

†Radiotherapy data are known to be incomplete for patients with acute leukemia because cranial irradiation given to prevent CNS involvement was not reportable to SEER before 1988.

Ewing sarcoma or osteosarcoma, probably due in part to thoracic radiotherapy for lung metastases, although genetic predisposition may have played a role. A recent study showed that breast cancer incidence was increased among survivors of bone or soft tissue sarcoma who did not receive chest radiotherapy, and that a family history of sarcoma was predictive of breast cancer risk among childhood cancer survivors (Kenney et al, 2004). Germline mutations in p53, which underlie most cases of Li-Fraumeni syndrome, have been found in up to 3% of children with osteosarcomas (McIntyre et al, 1994). Unlike osteosarcoma, Ewing sarcoma is not considered part of Li-Fraumeni syndrome.

Soft Tissue Sarcoma

Six-fold increased risks of subsequent cancers were observed among children with soft tissue sarcoma, with 28 new cancers observed among 27 children (O/E=5.95) (Table 18.D). Significant elevations in risk were seen among children with rhabdomyosarcoma (O/E=7.26, O=11, EAR=16), fibromatous neoplasms (O/E=5.59, O=9, EAR=16), and other soft tissue sarcomas (O/E=5.16, O=8, EAR=15) (Table 18.J). Excesses were found for subsequent ANLL, melanoma, bone and soft tissue sarcomas, and cancers of the female breast and buccal cavity. A more detailed analysis of SEER data found that combined modality treatment with radiation and chemotherapeutic agents was associated with a significantly higher risk of subsequent malignancies than initial treatment with surgery alone, with risks being especially high for subsequent ANLL, melanoma, breast cancer, and sarcomas (Cohen et al, 2005). Our results are consistent with clinical surveys of second cancers following combined modality treatment for childhood rhabdomyosarcoma (Heyn et al, 1993, 1994). In these trials, the observed excess of ANLL was attributed to therapy with alkylating agents and topoisomerase II inhibitors (doxorubicin, etoposide). Previous studies have shown that germline mutations in p53 occur in up to 10% of children with soft tissue sarcomas (Hartley et al, 1993) and that genetic susceptibility greatly increases the risk of second cancers among children treated for soft tissue sarcomas (Heyn et al, 1993; Kenney et al, 2004).

Retinoblastoma

Retinoblastoma patients had a high relative risk of developing a new cancer (O/E=14.71, O=15, EAR=24) (Table 18.K). Risks were greater among those who received radiation as part of their initial treatment (O/E=44.08, O=12) than among those who did not (O/E=4.2, O=3). The risks of subsequent cancer were most pronounced for cancers of the bone, soft tissue, and eye/orbit, as well as ALL, consistent with the exceptional risks of second cancer reported among children with familial or bilateral retinoblastoma (Draper et al, 1986; Eng et al, 1993; Wong et al, 1997; Kleinerman et al, 2005). Although subsequent cancer risks are elevated in heritable cases both with and without exposure to radiotherapy, the relative risks of sarcomas associated with radiotherapy are substantially higher for heritable than for nonheritable (sporadic) cases, indicating gene-environment interaction (Wong et al, 1997; Moll et al, 2001; Fletcher et al, 2004; Kleinerman et al, 2005). The array of second cancers reported after retinoblastoma includes cancers of the nasal cavity, brain,

Table 18.G: Risk of subsequent primary cancers among children (ages 0-17 years) diagnosed with lymphoma, by years after diagnosis of initial cancer, both sexes.

	Years after first primary cancer diagnosis											
	<5 yr		5-9 yr		10-14 yr		≥15 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
First primary cancer: Hodgkin lymphoma (N=1,744)												
All subsequent cancers	11	7.55*	18	9.93*	20	9.33*	38	10.29*	87	9.11	9.55*	38.95
Any radiation	5	5.18*	14	10.80*	16	9.84*	33	11.36*	68	6.79	10.01*	42.74
All solid cancers	7	7.66*	11	8.51*	14	8.28*	33	10.53*	65	7.03	9.25*	28.99
Any radiation	3	4.96	9	9.73*	12	9.33*	29	11.74*	53	5.29	10.03*	33.32
Salivary gland	0	0.00	0	0.00	0	0.00	2	119.77*	2	0.05	39.47*	0.97
Digestive system	0	0.00	1	17.97	0	0.00	6	23.16*	7	0.44	15.87*	3.28
Stomach	0	0.00	0	0.00	0	0.00	4	146.34*	4	0.05	85.31*	1.98
Pancreas	0	0.00	1	262.44*	0	0.00	1	50.12	2	0.03	63.45*	0.98
Lung, bronchus	0	0.00	0	0.00	2	98.12*	1	11.03	3	0.13	22.26*	1.43
Female breast	0	0.00	2	38.01*	8	48.00*	13	18.43*	23	0.93	24.61*	23.19
Female genital	1	10.55	1	6.11	0	0.00	1	2.26	3	0.95	3.17	2.16
Bones, joints	3	32.88*	0	0.00	0	0.00	2	81.25*	5	0.20	25.06*	2.40
Osteosarcoma	2	42.17*	0	0.00	0	0.00	0	0.00	2	0.09	22.17*	0.95
Soft tissue including heart	1	15.42	2	34.69*	0	0.00	3	54.88*	6	0.22	26.76*	2.89
Fibrosarcoma	0	0.00	2	114.29*	0	0.00	2	121.01*	4	0.07	60.53*	1.97
Melanoma of skin	0	0.00	2	9.00*	1	3.45	1	2.14	4	1.10	3.65	1.45
Brain, CNS	0	0.00	2	15.30*	0	0.00	0	0.00	2	0.54	3.70	0.73
Thyroid	1	8.18	1	5.17	3	14.09*	3	9.98*	8	0.83	9.65*	3.59
Non-Hodgkin lymphoma	2	18.63*	2	16.75*	0	0.00	5	19.82*	9	0.63	14.33*	4.19
Acute non-lymphocytic leukemia	2	34.52*	4	77.57*	3	75.77*	0	0.00	9	0.19	46.19*	4.40
Other	1	1.75	1	1.45	3	4.14	1	1.11	6	2.89	2.08	1.56
First primary cancer: Non-Hodgkin lymphoma (N=1,038)												
All subsequent cancers	8	13.68*	2	3.40	0	0.00	3	3.91	13	2.54	5.11*	12.72
All solid cancers	3	8.56*	1	2.53	0	0.00	3	4.92	7	1.80	3.89*	6.33
Female breast	0	0.00	0	0.00	0	0.00	2	29.62*	2	0.10	20.75*	7.49
Thyroid	2	72.64*	0	0.00	0	0.00	0	0.00	2	0.18	11.26*	2.22
Hodgkin lymphoma	2	26.34*	0	0.00	0	0.00	0	0.00	2	0.28	7.25	2.10
Acute non-lymphocytic leukemia	2	74.65*	0	0.00	0	0.00	0	0.00	2	0.07	26.74*	2.34
Other	2	4.41	2	4.62	0	0.00	1	1.72	5	1.92	2.61	3.75

Notes: Number of patients (PYR in interval) for <5, 5-9, 10-14, and ≥15 time intervals are 1,744 (7,181), 1,261 (5,390), 910 (3,807), and 605 (3,620), respectively, for Hodgkin lymphoma; and 1,038 (3,450), 557 (2,285), 367 (1,445), and 205 (1,041), respectively, for non-Hodgkin lymphoma.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000); CNS=central nervous system.

*P <0.05.

pineal gland, uterine corpus, female breast, lung, and bladder, as well as melanoma (Kleinerman et al, 2005). However, these tumors were not observed in our study (except for 1 case of nasal cavity cancer), possibly due to the young attained age of the population.

Neuroblastoma

A nearly 6-fold elevation in subsequent cancer risk was observed among children with neuroblastoma (O/E=5.90, O=11, EAR=9), with the highest risks among those surviving 10 or more years (Table 18.K). Significantly elevated risks were seen for subsequent cancers of the kidney, digestive system, and thyroid gland, although based on small numbers. In a European cohort of 544 children who survived 5 or more years after neuroblastoma, the most common new malignancies involved the thyroid (O=5) and breast (O=3), with risks associated with radiotherapy but not chemotherapy (Rubino et al, 2003). The absence of breast cancer in our study may be related to the early onset of neuroblastoma, as most of the cohort has not yet reached the ages at which breast cancer tends to occur. It has been suggested that neuroblastoma patients may be prone to thyroid cancer independent of treatment (de Vathaire et al, 1992, 1999b), but this remains unclear.

Wilms Tumor

Risk of a new primary cancer was increased approximately 6-fold among children with Wilms tumor, who were followed for an average of 10 years (O/E=6.14, O=14, EAR=10) (Table 18.K). One-half of the new cancers consisted of soft tissue sarcoma, cancer of the urinary system (1 bladder and 1 kidney), or ANLL. In a study of 5,278 Wilms tumor patients diagnosed between

TABLE 18.H: Risk of subsequent cancers among children (ages 0-17 years) diagnosed with central nervous system cancer, by years after diagnosis of initial cancer, both sexes.

	Years after first primary cancer diagnosis									
	<5 yr		5-9 yr		≥10 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
First primary cancer: Astrocytoma (N=2,242)										
All subsequent cancers	14	11.43*	6	5.25*	7	2.23	27	5.50	4.91*	11.25
All radiation	9	17.51*	5	8.96*	3	1.63	17	2.92	5.83*	15.07
All solid cancers	10	13.72*	6	8.00*	6	2.46	22	3.92	5.61*	9.46
All radiation	6	19.72*	5	13.60*	3	2.09	14	2.11	6.64*	12.72
Digestive system	1	30.11	1	33.30	0	0.00	2	0.22	8.91*	0.93
Bone, joints	3	40.71*	1	16.60	0	0.00	4	0.19	20.97*	1.99
Soft tissue including heart	1	15.21	2	40.83*	0	0.00	3	0.19	15.75*	1.47
Melanoma of skin	1	19.63	0	0.00	1	2.52	2	0.55	3.65	0.76
Brain, CNS	4	18.41*	1	7.54	2	11.49*	7	0.52	13.36*	3.39
Brain	3	15.16*	0	0.00	1	6.20	4	0.48	8.32*	1.84
Other CNS	1	51.48	1	93.22*	1	77.58*	3	0.04	69.70*	1.55
Non-Hodgkin lymphoma	1	11.18	0	0.00	1	4.33	2	0.41	4.90	0.83
Leukemia	3	11.38*	0	0.00	0	0.00	3	0.55	5.49*	1.28
Chronic myelogenous leukemia	2	209.41*	0	0.00	0	0.00	2	0.05	43.52*	1.02
Other	0	0.00	1	1.82	3	1.59	4	2.87	1.39	0.59
First primary cancer: PNET of CNS (N=859)										
All subsequent cancers	3	8.02*	8	32.79*	4	6.92*	15	1.20	12.54*	25.61
Any radiation	2	6.26	8	35.80*	4	7.39*	14	1.08	12.91*	26.59
All solid cancers	2	9.27*	6	39.39*	4	9.14*	12	0.81	14.90*	20.77
Any radiation	2	10.86*	6	42.99*	4	9.80*	12	0.73	16.39*	23.20
Digestive system	1	94.88*	1	167.57*	1	35.66	3	0.04	67.35*	5.48
Pancreas	1	†	0	0.00	1	†	2	0.00	†	3.71
Bones, soft tissues	0	0.00	2	68.37*	0	0.00	2	0.10	19.29*	3.52
Brain, CNS	1	13.23	1	28.48	3	83.12*	5	0.15	34.06*	9.00
Brain	1	14.53	1	31.08	1	30.06	3	0.13	22.34*	5.32
Other CNS	0	0.00	0	0.00	2	†	2	0.01	159.71*	3.69
Leukemia	1	10.38	2	55.47*	0	0.00	3	0.17	18.00*	5.26
Acute lymphocytic leukemia	0	0.00	2	88.26*	0	0.00	2	0.11	18.40*	3.51
Other	0	0.00	2	14.53*	0	0.00	2	0.73	2.72	2.35

Notes: Includes children surviving 2 or more months after diagnosis. Number of patients (PYR in interval) for <5, 5-9, and ≥10 time intervals are 2,242 (7,828), 1,304 (5,259), and 842 (6,026), respectively, for astrocytoma; and 859 (2,570), 351 (1,382), and 212 (1,439), respectively, for PNET.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000); PNET=primitive neuroectodermal tumor; CNS=central nervous system.

*P <0.05.

†O/E >500.00.

1969 and 1991, abdominal irradiation and treatment of relapse with etoposide were associated with an increased risk of second cancer, with 7 of 43 second cancers being ANLL (Breslow et al, 1995; Shearer et al, 2001). Since Wilms tumor tends to occur at a very young age, relatively few survivors in the present study were followed into adulthood.

Germ Cell, Trophoblastic, or Other Gonadal Cancers

In this study, the most common first primary tumors in this category were cancer of the ovary (70%) among females and cancers of the testis (64%) and pineal gland (14%) among males. The risk of subsequent cancer was increased approximately 4-fold (O/E=3.50 in females and 4.68 in males) (Tables 18.D and 18.K). Among females, this was attributable mainly to 3 cases of cancer of the reproductive system (O/E=7.23), 2 of which arose in the contralateral ovary. The increased risk of subsequent cancer among males was attributable to 7 cases of contralateral testicular cancer (O/E=19.06), consistent with the tendency to bilateral disease reported in the literature (Buetow, 1995).

Table 18.I: Risk of subsequent cancers among children (ages 0-17 years) diagnosed with bone sarcomas, by years after diagnosis of initial cancer, both sexes.

	Years after first primary cancer diagnosis									
	<5 yr		5-9 yr		≥10 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
First primary cancer: Osteosarcoma (N=752)										
All subsequent cancers	3	7.15*	0	0.00	7	6.28*	10	1.94	5.14*	15.10
All solid cancers	2	7.71	0	0.00	7	7.62*	9	1.46	6.15*	14.13
Female breast	0	0.00	0	0.00	3	16.93*	3	0.19	15.96*	10.41
Bone and soft tissue sarcoma	1	18.69	0	0.00	2	64.43*	3	0.11	26.50*	5.41
Soft tissue	0	0.00	0	0.00	2	96.81*	2	0.06	35.15*	3.64
Other	2	5.49	0	0.00	2	2.21	4	1.64	2.44	4.42
First primary cancer: Ewing sarcoma (N=479)										
All subsequent cancers	3	11.40*	6	27.53*	6	11.33*	15	1.01	14.84*	44.39
Any radiation	1	6.27	6	45.94*	4	10.47*	11	0.67	16.37*	50.47
All solid cancers	1	6.26	4	26.80*	6	14.14*	11	0.73	15.00*	32.58
Any radiation	1	10.38	4	45.16*	4	13.03*	9	0.49	18.29*	41.58
Female breast	0	0.00	0	0.00	2	38.51*	2	0.06	35.79*	12.80
Bone, joints	1	51.22	1	110.44*	1	152.34*	3	0.04	85.37*	9.41
Osteosarcoma	1	99.91*	1	226.58*	1	403.59*	3	0.02	177.51*	9.47
Soft tissue including heart	0	0.00	3	381.44*	1	92.13*	4	0.03	126.37*	12.59
Fibrosarcoma	0	0.00	2	†	0	0.00	2	0.01	245.58*	6.32
Acute non-lymphocytic leukemia	2	171.82*	1	135.86*	0	0.00	3	0.03	105.37*	9.43
Other	0	0.00	1	5.25	2	4.44	3	0.86	3.49	6.80

Notes: Number of patients (PYR in interval) for <5, 5-9, and ≥10 time intervals are 752 (2,385), 346 (1,393), and 217 (1,556), respectively, for osteosarcoma; and 479 (1,510), 205 (791), and 114 (851), respectively, for Ewing sarcoma.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

†O/E >500.00.

Table 18.J: Risk of subsequent cancers among children (ages 0-17 years) diagnosed with soft tissue sarcomas, by years after diagnosis of initial cancer, both sexes.

	Years after first primary cancer diagnosis									
	<5 yr		5-9 yr		≥10 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
First primary cancer: Rhabdomyosarcoma (N=769)										
All subsequent cancers	3	8.05*	1	3.42	7	8.23*	11	1.52	7.26*	15.93
Any radiation	2	8.64	0	0.00	5	10.25*	7	0.90	7.76*	16.48
All solid cancers	1	4.59	1	5.40	6	9.26*	8	1.05	7.61*	11.67
Any radiation	1	7.41	0	0.00	4	11.00*	5	0.61	8.14*	11.85
Bone, soft tissue	1	24.80	1	31.89	2	46.25*	4	0.11	34.81*	6.53
Bone, joints	1	51.51	1	56.13	1	49.75	3	0.06	52.33*	4.94
Female breast	0	0.00	0	0.00	2	29.28*	2	0.07	27.91*	8.04
Acute non-lymphocytic leukemia	2	107.83*	0	0.00	0	0.00	2	0.05	40.20*	3.28
Other	0	0.00	0	0.00	3	4.17	3	1.28	2.34	2.89
First primary cancer: Fibrosarcoma (N=448)										
All subsequent cancers	4	13.32*	3	8.93*	2	2.05	9	1.61	5.59*	16.03
Any radiation	2	44.35*	3	65.48*	2	21.87*	7	0.18	38.38*	120.84
All solid cancers	3	16.15*	2	8.59	2	2.56	7	1.20	5.83*	12.58
Any radiation	1	34.98	2	60.57*	2	27.38*	5	0.13	37.14*	86.24
Bone, soft tissue	1	29.30	2	81.01*	0	0.00	3	0.09	32.38*	6.31
Bone, joints	1	54.34	1	80.50*	0	0.00	2	0.04	45.69*	4.25
Female genital system	1	57.71	0	0.00	1	9.27	2	0.16	12.90*	7.64
Other	2	8.04	1	3.55	1	1.20	4	1.36	2.93	5.72
First primary cancer: Other soft tissue sarcomas (N=538)										
All subsequent cancers	2	6.50	1	3.47	5	5.24*	8	1.55	5.16*	15.20
Any radiation	2	16.88*	0	0.00	5	13.58*	7	0.59	11.85*	40.61
All solid cancers	1	5.29	1	5.03	5	6.42*	7	1.17	6.00*	13.75
Any radiation	1	13.84	0	0.00	5	16.54*	6	0.45	13.47*	35.19
Buccal cavity, pharynx	0	0.00	0	0.00	2	103.43*	2	0.03	65.19*	4.64
Melanoma of skin	1	56.22	0	0.00	1	8.59	2	0.16	12.24*	4.33
Other	1	3.52	1	3.94	2	2.44	4	1.36	2.95	6.23

Notes: Number of patients (PYR in interval) for <5, 5-9, and ≥10 time intervals are 769 (2,484), 386 (1,587), and 263 (1,882), respectively, for persons with rhabdomyosarcoma; 448 (1,715), 301 (1,278), and 215 (1,615), respectively, for persons with fibrosarcoma (or neurofibrosarcoma); and 538 (1,763), 265 (1,079), and 172 (1,401), respectively, for those with other soft tissue sarcomas.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P < 0.05.

Table 18.K: Risk of subsequent cancers among children (ages 0-17 years) diagnosed with retinoblastoma, neuroblastoma, Wilms tumor, and germ cell tumors, by years after diagnosis of initial cancer, both sexes.

	Years after first primary cancer diagnosis									
	<5 yr		5-9 yr		≥10 yr		Total			
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	E	O/E	EAR
First primary cancer: Retinoblastoma (N=581)										
All subsequent cancers	4	10.55*	7	40.05*	4	8.59*	15	1.02	14.71*	23.56
Any radiation	3	26.04*	5	100.99*	4	37.22*	12	0.27	44.08*	72.45
All solid cancers	3	13.46*	6	60.84*	3	9.60*	12	0.63	18.93*	19.16
Any radiation	2	29.18*	5	179.69*	3	41.42*	10	0.17	59.24*	60.74
Bone and soft tissue	1	32.35	4	187.97*	3	63.52*	8	0.10	80.47*	13.32
Bone	1	166.88*	4	331.57*	0	0.00	5	0.04	114.35*	8.35
Soft tissue	0	0.00	0	0.00	3	139.13*	3	0.06	53.86*	4.96
Eye	1	45.85	1	†	0	0.00	2	0.02	81.09*	3.33
Acute lymphocytic leukemia	1	9.50	1	25.40	1	39.49	3	0.17	17.65*	4.77
Other	1	4.53	1	8.88	0	0.00	2	0.73	2.76	2.15
First primary cancer: Neuroblastoma (N=1,461)										
All subsequent cancers	3	3.86	2	6.23	6	7.81*	11	1.87	5.90*	8.82
Any radiation	0	0.00	2	21.02*	3	8.23*	5	0.67	7.49*	12.28
All solid cancers	2	4.39	2	10.99*	6	11.41*	10	1.16	8.59*	8.54
Any radiation	0	0.00	2	37.21*	3	11.90*	5	0.43	11.72*	12.96
Digestive system	0	0.00	0	0.00	3	124.97*	3	0.07	45.32*	2.83
Brain, CNS	1	6.44	1	12.44	0	0.00	2	0.31	6.36	1.63
Thyroid	0	0.00	1	130.58*	1	14.37	2	0.08	24.65*	1.85
Kidney	1	14.30	0	0.00	2	314.79*	3	0.09	33.60*	2.81
Other	1	1.96	0	0.00	0	0.00	1	1.31	0.76	-0.30
First primary cancer: Wilms tumor (N=1,188)										
All subsequent cancers	5	7.35*	1	2.31	8	6.87*	14	2.28	6.14*	9.73
Any radiation	2	6.40	0	0.00	4	5.35*	6	1.28	4.69*	7.49
All solid cancers	1	2.52	1	3.91	8	9.69*	10	1.48	6.77*	7.07
Any radiation	0	0.00	0	0.00	4	7.41*	4	0.85	4.70*	5.00
Bone, soft tissue	1	15.89	0	0.00	4	43.79*	5	0.21	23.66*	3.97
Soft tissue	1	23.80	0	0.00	3	66.77*	4	0.11	36.14*	3.23
Urinary system	0	0.00	0	0.00	2	98.08*	2	0.09	22.15*	1.59
Acute non-lymphocytic leukemia	3	83.80*	0	0.00	0	0.00	3	0.09	32.06*	2.41
Other	1	1.90	1	2.93	2	1.97	4	1.88	2.12	1.76
First primary cancer: Germ cell tumors (N=1,206)										
All subsequent cancers	8	8.99*	6	6.80*	3	1.23	17	4.21	4.04*	11.53
All solid cancers	8	14.19*	6	9.59*	3	1.51	17	3.17	5.36*	12.46
Female breast	0	0.00	0	0.00	2	6.02	2	0.36	5.53	2.83
Female genital system	1	19.74	2	25.80*	0	0.00	3	0.41	7.23*	4.46
Ovary	1	29.68	1	27.27	0	0.00	2	0.16	12.28*	3.17
Testis	5	71.67*	2	19.68*	0	0.00	7	0.37	19.06*	12.51
Other	2	2.62	2	2.95	1	0.62	5	3.06	1.63	1.75

Notes: Number of patients (PYR in interval) for <5, 5-9, and ≥10 time intervals are 581 (2,279), 381 (1,570), and 261 (2,085), respectively, for persons with retinoblastoma; 1,461 (4,489), 676 (2,696), and 419 (3,168), respectively, for those with neuroblastoma; 1,188 (4,650), 794 (3,346), and 549 (4,051), respectively, for persons with Wilms tumor; and 1,206 (4,470), 740 (2,964), and 477 (3,662), respectively, for persons with germ cell tumors.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected number of subsequent primary cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

†O/E >500.00.

References

Bhatia S, Robison LL, Oberlin O, et al. 1996. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 334(12):745-751.

Bhatia S, Sklar C. 2002. Second cancers in survivors of childhood cancer. Nat Rev Cancer 2(2):124-132.

Bhatia S, Sather HN, Pabustan OB, et al. 2002. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. Blood 99(12):4257-4264.

Bhatia S. 2003. Late effects among survivors of leukemia during childhood and adolescence. Blood Cells Mol Dis 31(1):84-92.

Bhatia S, Yasui Y, Robison LL, et al. 2003. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 21(23):4386-4394.

Black PM. 1991a. Brain tumors. Part 1. N Engl J Med 324(21):1471-1476.

Black PM. 1991b. Brain tumors. Part 2. N Engl J Med 324(22):1555-1564.

Breslow NE, Takashima JR, Whitton JA, et al. 1995. Second malignant neoplasms following treatment for Wilm's tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 13(8):1851-1859.

Buetow SA. 1995. Epidemiology of testicular cancer. Epidemiol Rev 17(2):433-449.

Cohen RJ, Curtis RE, Inskip PD, et al. 2005. The risk of developing second cancers among survivors of childhood soft tissue sarcoma. Cancer 103(11):2391-2396.

de Vathaire F, Francois P, Schlumberger M, et al. 1992. Epidemiological evidence for a common mechanism for neuroblastoma and differentiated thyroid tumour. Br J Cancer 65(3):425-428.

de Vathaire F, Hawkins M, Campbell S, et al. 1999a. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. Br J Cancer 79(11-12):1884-1893.

de Vathaire F, Hardiman C, Shamsaldin A, et al. 1999b. Thyroid carcinomas after irradiation for a first cancer during childhood. Arch Intern Med 159(22):2713-2719.

Donaldson SS. 2002. Pediatric Hodgkin's disease—up, up, and beyond. Int J Radiat Oncol Biol Phys 54(1):1-8.

Dores GM, Metayer C, Curtis RE, et al. 2002. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol 20(16):3484-3494.

Draper GJ, Sanders BM, Kingston JE. 1986. Second primary neoplasms in patients with retinoblastoma. Br J Cancer 53(5):661-671.

Dunst J, Ahrens S, Paulussen M, et al. 1998. Second malignancies after treatment for Ewing's sarcoma: a report of the CESS-studies. Int J Radiat Oncol Biol Phys 42(2):379-384.

Ebb HD, Green, DM, Shamberger, RC, et al. 2005. Solid tumors of childhood (Section 2). *In* DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology, 7th ed. Philadelphia, Lippincott Williams & Wilkins, pp. 1898-1937.

Eng C, Li FP, Abramson DH, et al. 1993. Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst 85(14):1121-1128.

Eng C, Maher ER. 1999. Dominant genes and phakomatoses associated with multiple primary cancers. *In* Neugut AI, Meadows AT, Robinson E (eds): Multiple Primary Cancers. Philadelphia, Lippincott Williams & Wilkins, pp. 165-195.

Fine HA, Barker FG, Markert JM, et al. 2005. Neoplasms of the central nervous system. *In* DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer Principles and Practice of Oncology, 7th ed. Philadelphia, Lippincott Williams & Wilkins, pp. 1834-1887.

Fletcher O, Easton D, Anderson K, et al. 2004. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 96(5):357-363.

Friedman DL, Meadows AT. 1999. Pediatric tumors. *In* Neugut AI, Meadows AT, Robinson E (eds): Multiple Primary Cancers. Philadelphia, Lippincott Williams & Wilkins, pp. 235-256.

Garwicz S, Anderson H, Olsen JH, et al. 2000. Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. Int J Cancer 88(4):672-678.

Goldstein AM, Yuen J, Tucker MA. 1997. Second cancers after medulloblastoma: population-based results from the United States and Sweden. Cancer Causes Control 8(6):865-871.

Guérin S, Dupuy A, Anderson H, et al. 2003. Radiation dose as a risk factor for malignant melanoma following childhood cancer. Eur J Cancer 39(16):2379-2386.

Hancock SL, Tucker MA, Hoppe RT. 1993. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 85(1):25-31.

Hartley AL, Birch JM, Blair V, et al. 1993. Patterns of cancer in the families of children with soft tissue sarcoma. Cancer 72(3):923-930.

Hawkins MM, Wilson LM, Stovall MA, et al. 1992. Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. BMJ 304(6832):951-958.

Hawkins MM, Wilson LM, Burton HS, et al. 1996. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst 88(5):270-278.

Heyn R, Haeberlen V, Newton WA, et al. 1993. Second malignant neoplasms in children treated for rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. J Clin Oncol 11(2):262-270.

Heyn R, Khan F, Ensign LG, et al. 1994. Acute myeloid leukemia in patients treated for rhabdomyosarcoma with cyclophosphamide and low-dose etoposide on Intergroup Rhabdomyosarcoma Study III: an interim report. Med Pediatr Oncol 23(2):99-106.

Hisada M, Garber JE, Fung CY, et al. 1998. Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 90(8):606-611.

Inskip PD. 1999. Second cancers following radiotherapy. *In* Neugut AI, Meadows AT, Robinson E (eds): Multiple Primary Cancers. Philadelphia, Lippincott Williams & Wilkins, pp. 91-135.

Inskip PD. 2003. Multiple primary tumors involving cancer of the brain and central nervous system as the first or subsequent cancer. Cancer 98(3):562-570.

Jenkinson HC, Hawkins MM, Stiller CA, et al. 2004. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. Br J Cancer 91(11):1905-1910.

Kalapurakal JA, Thomas PR. 1997. Pediatric radiotherapy. An overview. Radiol Clin North Am 35(6):1265-1280.

Kaldor JM, Day NE, Clarke EA, et al. 1990. Leukemia following Hodgkin's disease. N Engl J Med 322(1):7-13.

Kaldor JM, Day NE, Bell J, et al. 1992. Lung cancer following Hodgkin's disease: a case-control study. Int J Cancer 52(5):677-681.

Karlsson P, Holmberg E, Lundell M, et al. 1998. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. Radiat Res 150(3):357-364.

Kenney LB, Yasui Y, Inskip PD, et al. 2004. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med 141(8):590-597.

Kleinerman RA, Tucker MA, Tarone RE, et al. 2005. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 23(10):2272-2279.

Kramarova E, Stiller CA. 1996. The international classification of childhood cancer. Int J Cancer 68(6):759-765.

Kuttesch JF Jr, Wexler LH, Marcus RB, et al. 1996. Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas. J Clin Oncol 14(10):2818-2825.

Leung W, Sandlund JT, Hudson MM, et al. 2001. Second malignancy after treatment of childhood non-Hodgkin lymphoma. Cancer 92(7):1959-1966.

Le Vu B, de Vathaire F, Shamsaldin A, et al. 1998. Radiation dose, chemotherapy and risk of osteosarcoma after solid tumours during childhood. Int J Cancer 77(3):370-377.

Little MP, Hawkins MM, Shore RE, et al. 1991. Time variations in the risk of cancer following irradiation in childhood. Radiat Res 126(3):304-316.

Little MP, de Vathaire F, Charles MW, et al. 1998a. Variations with time and age in the risks of solid cancer incidence after radiation exposure in childhood. Stat Med 17(12):1341-1355.

Little MP, de Vathaire F, Shamsaldin A, et al. 1998b. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. Int J Cancer 78(3):269-275.

Malkin D, Jolly KW, Barbier N, et al. 1992. Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. N Engl J Med 326(20):1309-1315.

McIntyre JF, Smith-Sorensen B, Friend SH, et al. 1994. Germline mutations of the p53 tumor suppressor gene in children with osteosarcoma. J Clin Oncol 12(5):925-930.

Metayer C, Lynch CF, Clarke EA, et al. 2000. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 18(12):2435-2443.

Moll AC, Imhof SM, Schouten-van Meeteren AY, et al. 2001. Second primary tumors in hereditary retinoblastoma: a register-based study, 1945-1997: is there an age effect on radiation-related risk? Ophthalmology 108(6):1109-1114.

Moppett J, Oakhill A, Duncan AW. 2001. Second malignancies in children: the usual suspects? Eur J Radiol 38(3):235-248.

Neglia JP, Meadows AT, Robison LL, et al. 1991. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 325(19):1330-1336.

Neglia JP, Friedman DL, Yasui Y, et al. 2001. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 93(8):618-629.

Newton WA Jr, Meadows AT, Shimada H, et al. 1991. Bone sarcomas as second malignant neoplasms following childhood cancer. Cancer 67(1):193-201.

Nichols KE, Malkin D, Garber JE, et al. 2001. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 10(2):83-87.

Olsen JH, Garwicz S, Hertz H, et al. 1993. Second malignant neoplasms after cancer in childhood or adolescence. Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries. BMJ 307(6911):1030-1036.

Pollack IF. 1994. Brain tumors in children. N Engl J Med 331(22):1500-1507.

Pui CH, Behm FG, Raimondi SC, et al. 1989. Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. N Engl J Med 321(3):136-142.

Pui CH, Cheng C, Leung W, et al. 2003. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med 349(7):640-649.

Ries LG, Smith MA, Gurney JG, et al (eds). 1999. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. NIH Pub. No. 99-4649. Bethesda, MD, National Cancer Institute.

Ries LG, Eisner MP, Kosary CL, et al (eds). 2004. SEER Cancer Statistics Review, 1975-2001. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2001.

Ron E, Modan B, Boice JD Jr, et al. 1988. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 319(16):1033-1039.

Ron E, Lubin JH, Shore RE, et al. 1995. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 141(3):259-277.

Rubino C, Adjadj E, Guérin S, et al. 2003. Long-term risk of second malignant neoplasms after neuroblastoma in childhood: role of treatment. Int J Cancer 107(5):791-796.

Schneider AB, Lubin J, Ron E, et al. 1998. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. Radiat Res 149(6):625-630.

Shearer P, Kapoor G, Beckwith JB, et al. 2001. Secondary acute myelogenous leukemia in patients previously treated for childhood renal tumors: a report from the National Wilms Tumor Study Group. J Pediatr Hematol Oncol 23(2):109-111.

Shusterman S, Meadows AT. 2000. Long term survivors of childhood leukemia. Curr Opin Hematol 7(4):217-222.

Sigurdson AJ, Ronckers CM, Mertens AC, et al. 2005. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 365(9476):2014-2023.

Slivnick DJ, Ellis TM, Nawrocki JF, et al. 1990. The impact of Hodgkin's disease on the immune system. Semin Oncol 17(6):673-682.

Suit HD. 1975. Role of therapeutic radiology in cancer of bone. Cancer 35(3 suppl):930-935.

Swerdlow AJ, Douglas AJ, Hudson GV, et al. 1992. Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. BMJ 304(6835):1137-1143.

Swerdlow AJ, Barber JA, Horwich A, et al. 1997. Second malignancy in patients with Hodgkin's disease treated at the Royal Marsden Hospital. Br J Cancer 75(1):116-123.

Travis LB, Curtis RE, Stovall M, et al. 1994a. Risk of leukemia following treatment for non-Hodgkin's lymphoma. J Natl Cancer Inst 86(19):1450-1457.

Travis LB, Curtis RE, Hankey BF, et al. 1994b. Second cancers in patients with Ewing's sarcoma. Med Pediatr Oncol 22(4):296-297.

Travis LB, Curtis RE, Glimelius B, et al. 1995. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst 87(7):524-530.

Travis LB, Curtis RE, Boice JD Jr, et al. 1996. Late effects of treatment for childhood Hodgkin's disease. N Engl J Med 335(5):352-353.

Travis LB, Gospodarowicz M, Curtis RE, et al. 2002. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 94(3):182-192.

Travis LB, Hill DA, Dores GM, et al. 2003. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 290(4):465-475.

Tucker MA, Meadows AT, Boice JD Jr, et al. 1987a. Leukemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 78(3):459-464.

Tucker MA, D'Angio GJ, Boice JD Jr, et al. 1987b. Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 317(10):588-593.

Tucker MA, Coleman CN, Cox RS, et al. 1988. Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 318(2):76-81.

Tucker MA, Jones PH, Boice JD Jr, et al. 1991. Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res 51(11):2885-2888.

van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. 1994a. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol 12(2):312-325.

van Leeuwen FE, Chorus AM, van den Belt-Dusebout AW, et al. 1994b. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 12(5):1063-1073.

van Leeuwen FE, Klokman WJ, Veer MB, et al. 2000. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 18(3):487-497.

van Leeuwen FE, Klokman WJ, Stovall M, et al. 2003. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 95(13):971-980.

Walter AW, Hancock ML, Pui CH, et al. 1998. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. J Clin Oncol 16(12):3761-3767.

Weinstein HJ, Tarbell NJ. 2005. Leukemias and lymphomas in childhood. *In* DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology, 7th ed. Philadelphia, Lippincott Williams & Wilkins, pp. 1939-1957.

Wong FL, Boice JD Jr, Abramson DH, et al. 1997. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278(15):1262-1267.