original reports abstract

Bone and Soft-Tissue Sarcoma Risk in Long-Term Survivors of Hereditary Retinoblastoma Treated With Radiation

Ruth A. Kleinerman, PhD[1]; Sara J. Schonfeld, PhD[1]; Byron S. Sigel, BA[1]; Jeannette R. Wong-Siegel, MD, MPH[1]; Ethel S. Gilbert, PhD[1]; David H. Abramson, MD[2]; Johanna M. Seddon, MD, ScM[3]; Margaret A. Tucker, MD[1]; and Lindsay M. Morton, PhD[1]

PURPOSE Survivors of hereditary retinoblastoma have excellent survival but substantially increased risks of subsequent bone and soft-tissue sarcomas, particularly after radiotherapy. Comprehensive investigation of sarcoma risk patterns would inform clinical surveillance for survivors.

PATIENTS AND METHODS In a cohort of 952 irradiated survivors of hereditary retinoblastoma who were originally diagnosed during 1914 to 2006, we quantified sarcoma risk with standardized incidence ratios (SIRs) and cumulative incidence analyses. We conducted analyses separately for bone and soft-tissue sarcomas occurring in the head and neck (in/near the radiotherapy field) versus body and extremities (out of field).

RESULTS Of 105 bone and 124 soft-tissue sarcomas, more than one half occurred in the head and neck (bone, 53.3%; soft tissue, 51.6%), one quarter in the body and extremities (bone, 29.5%; soft tissue, 25.0%), and approximately one fifth in unknown/unspecified locations (bone, 17.1%; soft tissue, 23.4%). We noted substantially higher risks compared with the general population for head and neck versus body and extremity tumors for both bone (SIR, 2,213; 95% CI, 1,671 to 2,873 *v* SIR, 169; 95% CI, 115 to 239) and soft-tissue sarcomas (SIR, 542; 95% CI, 418 to 692 *v* SIR, 45.7; 95% CI, 31.1 to 64.9). Head and neck bone and soft-tissue sarcomas were diagnosed beginning in early childhood and continued well into adulthood, reaching a 60-year cumulative incidence of 6.8% (95% CI, 5.0% to 8.7%) and 9.3% (95% CI, 7.0% to 11.7%), respectively. In contrast, body and extremity bone sarcoma incidence flattened after adolescence (3.5%; 95% CI, 2.3% to 4.8%), whereas body and extremity soft-tissue sarcoma incidence was rare until age 30, when incidence rose steeply (60-year cumulative incidence, 6.6%; 95% CI, 4.1% to 9.2%), particularly for females (9.4%; 95% CI, 5.1% to 13.8%).

CONCLUSION Strikingly elevated bone and soft-tissue sarcoma risks differ by age, location, and sex, highlighting important contributions of both radiotherapy and genetic susceptibility. These data provide guidance for the development of a risk-based screening protocol that focuses on the highest sarcoma risks by age, location, and sex.

J Clin Oncol 37:3436-3445. © 2019 by American Society of Clinical Oncology

INTRODUCTION

Children who are diagnosed with hereditary retinoblastoma, a rare eye cancer caused by a germline mutation in the *RB1* tumor suppressor gene, have excellent prognosis in high-income countries but have substantially increased risks for developing and dying of subsequent bone and soft-tissue sarcomas.[1-10] Previous studies have established that radiotherapy is a major cause of sarcoma after hereditary retinoblastoma and that systemic chemotherapy may also contribute.[4,11-15]

Little is known, however, about the long-term risk of sarcoma after hereditary retinoblastoma and whether the risks vary by specific tumor characteristics, including location (ie, proximity to the radiation field), histologic subtype, or age at diagnosis. Better understanding of the patterns and characteristics of sarcomas after retinoblastoma can provide insight into etiology and have implications for the long-term clinical surveillance of survivors. We therefore conducted a comprehensive analysis of the risk factors for bone and soft-tissue sarcomas by anatomic location and histologic subtype in a large-scale, long-term cohort study of survivors of retinoblastoma who received radiotherapy, evaluating the roles of systemic chemotherapy, age and calendar year of retinoblastoma diagnosis, family history of retinoblastoma, attained age, and sex.

PATIENTS AND METHODS

Patients for this analysis were derived from a long-term cohort study of 2,136 individuals who were diagnosed

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 27, 2019 and published at jco.org on October 17, 2019: DOI https://doi.org/10.1200/JCO.19.01096

or treated for retinoblastoma from 1914 to 2006 at two medical centers in New York, NY, and Boston, MA.[10] For each participant, we reviewed medical records to systematically ascertain detailed information on patient characteristics, retinoblastoma diagnosis, treatment, and family history of retinoblastoma. We restricted the study population for this analysis to patients with hereditary retinoblastoma who were irradiated and survived without developing a subsequent sarcoma for at least 1 year. Hereditary retinoblastoma was defined as bilateral retinoblastoma or unilateral retinoblastoma with a family history of retinoblastoma in a first- or second-degree relative (excluding offspring, because family history was defined systematically based on medical record data at the time of retinoblastoma diagnosis). Nonhereditary survivors and nonirradiated hereditary survivors were excluded because low incidence of sarcomas in these groups prevented detailed analysis. Exclusions are described in the Data Supplement. Reflecting treatment changes over time, the proportion of all 1-year hereditary survivors who were irradiated declined from more than 85% before 1990 to approximately 67% thereafter (Data Supplement).

Subsequent Bone Sarcoma and Soft-Tissue Sarcoma Diagnoses

We ascertained subsequent sarcomas through medical record review, questionnaires administered to the cohort (telephone and online; Data Supplement) between 1987 and 2016, and periodic linkages with the National Death Index through 2016. Self-reported sarcomas from patient questionnaires were confirmed by pathology reports.

Bone and soft-tissue sarcomas were classified according to the International Classification of Childhood Cancers,[16] with minor modifications (Data Supplement). We used pathology or medical record reports to code incident sarcomas according to the International Classification of Diseases of Oncology.[17] Diagnoses reported on death certificates were coded according to the International Classification of Diseases version in use at the time of death. Sarcomas with a topography code that corresponded to bone or soft tissue but no available morphology code were classified as unknown histologic type. We distinguished sarcomas that occurred in the head and neck (ie, likely in/near the radiation field) from those that occurred in the body and extremities (ie, likely out of field; Data Supplement). Tumors with poorly specified or unknown locations were categorized as unknown and excluded from location-specific analyses.

The Special Studies Institutional Review Board at the National Cancer Institute approved the study, including informed consent for past questionnaires from survivors or their legal guardians for survivors younger than age 18 years.

Statistical Analysis

We conducted analyses separately for bone and soft-tissue sarcomas. Follow up began 1 year after retinoblastoma diagnosis and ended at the earliest of date of first report of sarcoma diagnosis, death, or last known contact. Individuals who developed both bone and soft-tissue sarcomas were included until the outcome of each analysis and thus contributed events to both bone and soft-tissue sarcomas.

To compare sarcoma risks in the study cohort versus the US general population, we estimated standardized incidence ratios (SIRs; observed/expected cases) and 95% CIs. Expected numbers were obtained from 5-year age, sex, and calendar year (1973-1974, 1975-1979, . . . 2010-2015)–specific incidence rates from the SEER program nine registries, 1973 to 2015,[18] multiplied by the stratum-specific person-years at risk. SEER rates from 1973 to 1974 were applied to earlier years of follow up. We also calculated absolute excess risks (AER; [observed-expected]/person-years $\times$ 10,000). SIRs and AERs were calculated for bone and soft-tissue sarcomas overall and by subtypes defined by histology, location, and attained age (age at sarcoma diagnosis or exit).

To identify potential sarcoma risk factors within the cohort, we computed relative risks (RRs) and 95% profile likelihood CIs in mutually adjusted multivariable Poisson regression models. We fitted models separately for sarcomas that occurred in the head and neck and in the body and extremities and included age and year of retinoblastoma diagnosis, attained age, sex, family history of retinoblastoma, and use of systemic chemotherapy for retinoblastoma. We assessed the statistical significance (two-sided $P < .05$) of each factor using a likelihood ratio test, comparing model fit with and without the factor of interest. Heterogeneity of risk factor patterns between sarcomas that occurred in the head and neck versus the body and extremities was assessed using likelihood ratio tests in fully parameterized interaction models (location $\times$ each risk factor). We conducted analyses using SEER*Stat (version 8.3.5), SAS software (version 9.4; SAS Institute, Cary, NC), and Epicure.[19]

To understand the clinical impact of sarcoma occurrence, we calculated the cumulative incidence of bone and soft-tissue sarcomas up to 60 years after retinoblastoma diagnosis by location and sex, accounting for the competing risk of death.[20] Because most survivors of hereditary retinoblastoma were diagnosed by age 1 year, attained age and latency from retinoblastoma diagnosis are approximately equivalent.

Lastly, because the use of follow-up questionnaires and National Death Index searches may have led to the underascertainment of some sarcomas, particularly nonfatal cases, we evaluated the potential for ascertainment bias (Data Supplement).

RESULTS

Among 952 irradiated, 1-year survivors of hereditary retinoblastoma, median age at retinoblastoma diagnosis was 8.0 months and median year of diagnosis was 1968

(Table 1). One half of patients in the overall cohort were female, although both bone and soft-tissue sarcoma diagnoses were more common among males. Nearly all patients received external beam radiotherapy and 44% received chemotherapy for retinoblastoma. Median age at diagnosis was 15.5 years (range, 1.5 to 72.3 years) for bone sarcomas and 33.5 years (range, 2.0 to 74.1 years) for soft-tissue sarcomas.

Bone Sarcoma

Among 105 bone sarcomas, 56 (53.3%) occurred in the head and neck; 31 (29.5%) in the body and extremities, especially the long bones; and 18 (17.1%) in unknown/unspecified locations (Data Supplement). Osteosarcoma was the most common histologic type (72.4%), with nearly all the remaining bone sarcomas of unknown histology.

Compared with the general population, risk was increased more than 2,000-fold for bone sarcomas in the head and neck (SIR, 2,213; 95% CI, 1,671 to 2,873) and 169-fold (95% CI, 115 to 239) for sarcomas in the body and extremities, corresponding to AERs of 21.7 and 12.0 cases per 10,000 person-years, respectively (Data Supplement). The majority of subsequent bone sarcomas in the head and all in the body and extremities were diagnosed before age 30 years in the cohort and SIRs decreased with increasing

TABLE 1. Characteristics of Survivors of Hereditary Retinoblastoma Who Received Radiotherapy as Part of Their Initial Treatment (N = 952)

Characteristic	Bone Sarcoma Only	Soft-Tissue Sarcoma Only	Bone and Soft-Tissue Sarcoma	No Bone or Soft-Tissue Sarcoma
Total	96 (100)	115 (100)	9 (100)	732 (100)
Age at retinoblastoma, months				
0-11	66 (68.8)	66 (57.4)	5 (55.6)	440 (60.1)
12-23	22 (22.9)	37 (32.2)	3 (33.3)	190 (26.0)
≥ 24	8 (8.3)	12 (10.4)	1 (11.1)	102 (13.9)
Year of retinoblastoma diagnosis				
1914-1959	29 (30.2)	47 (40.9)	2 (22.2)	167 (22.8)
1960-1969	26 (27.1)	38 (33.0)	4 (44.4)	201 (27.5)
1970-2006	41 (42.7)	30 (26.1)	3 (33.3)	364 (49.7)
Sex				
Male	55 (57.3)	63 (54.8)	4 (44.4)	361 (49.3)
Female	41 (42.7)	52 (45.2)	5 (55.6)	371 (50.7)
Family history of retinoblastoma				
No/unknown	74 (77.1)	98 (85.2)	9 (100)	573 (78.3)
Yes	22 (22.9)	17 (14.8)	0 (0.0)	159 (21.7)
Type of radiotherapy				
External beam	82 (85.4)	101 (87.8)	9 (100)	602 (82.2)
Brachytherapy	1 (1.0)	1 (0.9)	0 (0.0)	31 (4.2)
Both	11 (11.5)	12 (10.4)	0 (0.0)	84 (11.5)
Unknown type	2 (2.1)	1 (0.9)	0 (0.0)	15 (2.1)
Chemotherapy for retinoblastoma				
No	45 (46.9)	59 (51.3)	3 (33.3)	411 (56.2)
Yes	48 (50.0)	54 (47.0)	6 (66.7)	311 (42.5)
Unknown	3 (3.1)	2 (1.7)	0 (0.0)	10 (1.4)
Age at bone/soft-tissue sarcoma diagnosis or exit, years*				
< 15	48 (50.0)	25 (21.7)	2 (22.2)	216 (29.5)
15-29	37 (38.5)	22 (19.1)	4 (44.4)	151 (20.6)
30-44	6 (6.3)	42 (36.5)	3 (33.3)	186 (25.4)
≥ 45	5 (5.2)	26 (22.7)	0 (0.0)	179 (24.5)

NOTE. Data presented as No. (%) unless otherwise indicated.

*Age at exit for the first sarcoma. Among seven survivors who were diagnosed with a bone sarcoma followed by a soft-tissue sarcoma, ages at sarcoma (bone/soft-tissue sarcoma) were: 44/57, 30/33, 16/17, 18/41, 14/23, 15/17, and 17/21 years. Among two survivors who were diagnosed with a soft-tissue sarcoma followed by a bone sarcoma, ages at sarcoma (soft tissue/bone sarcoma) were 31/40 and 3/15 years.

age, in striking contrast to patterns in the general population (Fig 1).

Corresponding to the age patterns described above, analyses within the cohort were consistent with a decreasing risk for head and neck bone sarcomas with increasing attained age (RR ≥ 30 *v* < 15 years = 0.39; 95% CI, 0.16 to 0.84; P_{trend} = .030; Table 2). Risk was also higher among patients who were diagnosed with retinoblastoma before 12 months compared with older ages (P_{trend} = .033), whereas year of retinoblastoma diagnosis, sex, family history of retinoblastoma, and use of chemotherapy were not statistically significantly associated with head and neck bone sarcoma risk. For body and extremity bone sarcomas, risk also was decreased with increasing attained age (P_{trend} = .006), with no cases observed after age 25 in our cohort. When comparing risk factor patterns between bone sarcomas in the head and neck versus body and extremities, the only statistically significant difference was for the year of retinoblastoma diagnosis ($P_{heterogeneity}$ = .028), with risks declining nonsignificantly in more recent calendar years for head and neck tumors and increasing nonsignificantly for body and extremity tumors.

Cumulative incidence analyses demonstrated the varying clinical burden of bone sarcomas by age and location (Fig 2A). For head and neck bone sarcomas, the cumulative incidence increased dramatically after age 5 years through adolescence, then increased more modestly, reaching 6.8% (95% CI, 5.0% to 8.7%) at 60 years after retinoblastoma. For body and extremity bone sarcomas, the cumulative incidence also increased dramatically after age 5 through adolescence, but then remained at 3.5% (95% CI, 2.3% to 4.8%).

Soft-Tissue Sarcoma

We identified 124 soft-tissue sarcomas, including 64 (51.6%) in the head and neck; 31 (25.0%) in the body and extremities, particularly the abdomen and pelvis; and 29 (23.4%) in unknown/unspecified locations (Data Supplement). Fibrosarcoma/malignant fibrous histiocytoma were the most commonly diagnosed histologies in the head and neck (n = 25; 39.1%), whereas leiomyosarcoma was the most common histology reported for other body regions (n = 21; 67.7%).

Compared with the general population, risk was increased more than 500-fold for soft-tissue sarcomas in the head and neck (SIR, 542; 95% CI, 418 to 692) and 45.7-fold (95% CI, 31.1 to 64.9) for other regions of the body, corresponding to AERs of 25.0 and 11.9 cases per 10,000 person-years, respectively (Data Supplement). The distribution of soft-tissue sarcomas in the cohort differed substantially from SEER with respect to age and histology (Fig 1 and Data Supplement). For example, rhabdomyosarcomas, which occurred predominantly in childhood (age < 15 years), were diagnosed only in the head and neck in our cohort but throughout the body in SEER. Fibrosarcomas also occurred predominantly at younger ages (< 30 years) and only in the head and neck in our cohort but occurred more frequently at older ages and in other body regions in SEER. Head and neck tumors accounted for approximately 35% of leiomyosarcomas in our cohort, but this location was exceedingly rare in SEER.

Within the cohort, there was statistically significant heterogeneity between sarcomas of the head and neck versus the body and extremities with respect to several risk factors (Table 2). For body and extremity soft-tissue sarcoma, risk increased substantially with increasing attained age, reaching 35.4-fold (95% CI, 6.28 to 668) increased risk for age ≥ 45 years versus < 15 years of age (P_{trend} < .001), whereas there was no association with attained age for head and neck soft tissue sarcomas (P_{trend} = .461; $P_{heterogeneity}$ < .001). The highest risks for head and neck soft-tissue sarcoma were observed for patients who were diagnosed with hereditary retinoblastoma before age 12 months (P_{trend} = .028), whereas age at retinoblastoma diagnosis was not statistically significantly associated with body and extremity soft-tissue sarcoma (P_{trend} = .478; $P_{heterogeneity}$ = .061). Patterns of soft-tissue sarcoma occurrence also varied by sex, with females less likely to be diagnosed with head and neck soft-tissue sarcoma than males (RR, 0.59; 95% CI, 0.35 to 0.97), but approximately twice as likely to be diagnosed with body and extremity soft-tissue sarcoma (RR, 2.09; 95% CI, 1.00 to 4.66; $P_{heterogeneity}$ = .005). This pattern was likely driven by the 16 patients—13 female and three male—who were diagnosed with soft-tissue sarcoma in the uterus, pelvis, and retroperitoneum (Data Supplement). Soft-tissue sarcoma risk, regardless of location, did not seem to be related to the calendar year of retinoblastoma diagnosis, family history of retinoblastoma, or chemotherapy.

As with bone sarcomas, cumulative incidence analyses demonstrated a different clinical burden of soft-tissue sarcomas by age and location (Fig 2B). Incidence of head and neck soft-tissue sarcoma rose steadily throughout the entire duration of follow up (60 years: cumulative incidence, 9.3%; 95% CI, 7.0% to 11.7%), whereas soft-tissue sarcoma in other body regions rarely occurred before the fourth decade of life, at which point the incidence increased steeply (60 years: cumulative incidence, 6.6%; 95% CI, 4.1% to 9.2%). This pattern was even more pronounced when stratified by sex, with a higher cumulative incidence of soft-tissue sarcoma in other body regions for females (cumulative incidence, 9.4%; 95% CI, 5.1% to 13.8%) than males (cumulative incidence, 4.1%; 95% CI, 1.2% to 7.0%; Fig 3).

Analyses for Potential Ascertainment Bias

Although the overall response status to the follow-up interviews/questionnaires decreased from 79% in 1993 to 44% in 2015, responders and nonresponders were largely comparable with respect to potential sarcoma risk factors

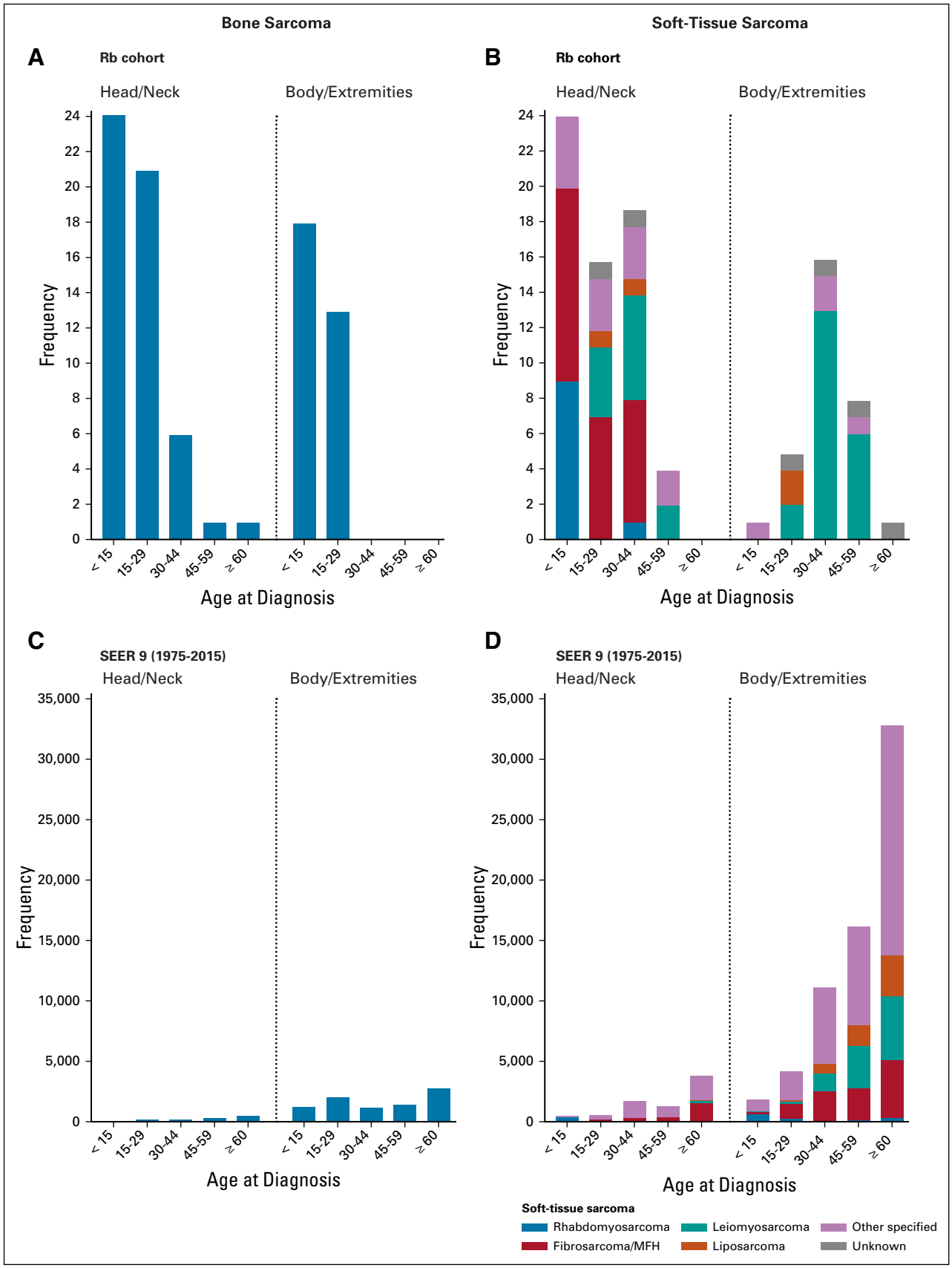

FIG 1. Frequency of histology of subsequent sarcomas after retinoblastoma (Rb) and in the SEER program by age and location. (A) Bone after Rb, (B) soft-tissue after Rb, (C) bone in SEER, and (D) soft-tissue in SEER. The distribution of other soft-tissue sarcomas in Rb and SEER are presented in the Data Supplement. MFH, malignant fibrous histiocytoma.

TABLE 2. Risks for Bone and Soft-Tissue Sarcomas by Location (head/neck *v* body/extremities) Among Survivors of Hereditary Retinoblastoma (N = 952)

	Bone Sarcoma								Soft-Tissue Sarcoma							
		Head and Neck			Body and Extremities					Head and Neck			Body and Extremities			
Characteristic	Person-Years* (25,770)	No.	RR†	(95% CI)	No.	RR†	(95% CI)	P_{het}‡	Person-Years* (25,520)	No.	RR†	(95% CI)	No.	RR†	(95% CI)	P_{het}‡
Age at sarcoma, years																
< 15	10,139	27	1.00	REF	18	1.00	REF		10,171	25	1.00	REF	1	1.00	REF	
15-29	8,382	21	0.95	(0.53 to 1.69)	13	0.95	(0.45 to 1.93)		8,407	16	0.80	(0.42 to 1.48)	5	5.85	(0.94 to 112)	
30-44§	7,250	8	0.39	(0.16 to 0.84)	0				5,041	19	1.60	(0.86 to 2.96)	16	28.1	(1.73 to 511)	
≥ 45									1,901	4	0.85	(0.24 to 2.31)	9	35.4	(6.28 to 668)	
P_{trend}‖				.030			.006	.277				.461			< .001	< .001
Age at retinoblastoma, months																
0-11¶	14,956	41	1.00	REF	20	1.00	REF		14,884	43	1.00	REF	14	1.00	REF	
12-23	7,346	10	0.49	(0.23 to 0.95)	8	0.96	(0.39 to 2.15)		7,293	18	0.83	(0.46 to 1.42)	10	1.10	(0.47 to 2.49)	
≥ 24	3,468	5	0.53	(0.18 to 1.23)	3	0.74	(0.17 to 2.22)		3,342	3	0.29	(0.07 to 0.8)	7	1.43	(0.53 to 3.50)	
P_{trend}‖				.033			.664	.348				.028			.478	.061
Year of retinoblastoma diagnosis																
< 1960	7,721	21	1.00	REF	6	1.00	REF		7,503	22	1.00	REF	16	1.00	REF	
1960-69	9,028	18	0.68	(0.36 to 1.27)	8	0.98	(0.34 to 2.98)		9,014	21	0.73	(0.4 to 1.34)	11	0.74	(0.33 to 1.63)	
≥ 1970	9,021	17	0.57	(0.29 to 1.12)	17	1.82	(0.73 to 5.15)		9,002	21	0.82	(0.43 to 1.56)	4	0.60	(0.16 to 1.79)	
P_{trend}‖				.101			.151	.028				.523			.321	.779
Sex																
Male	13,312	28	1.00	REF	18	1.00	REF		13,154	41	1.00	REF	10	1.00	REF	
Female	12,458	28	1.05	(0.62 to 1.78)	13	0.78	(0.37 to 1.59)		12,366	23	0.59	(0.35 to 0.97)	21	2.09	(1.00 to 4.66)	
P_{het}‖				.851			.498	.528				.036			.050	.005
Family history of retinoblastoma																
No/unknown	20,996	47	1.00	REF	23	1.00	REF		20,755	53	1.00	REF	27	1.00	REF	
Yes	4,774	9	0.77	(0.35 to 1.52)	8	1.30	(0.53 to 2.86)		4,765	11	0.89	(0.44 to 1.65)	4	0.94	(0.27 to 2.45)	
P_{het}‖				.473			.544	.381				.720			.907	.921
Chemotherapy for retinoblastoma																
No	15,034	30	1.00	REF	15	1.00	REF		14,856	37	1.00	REF	12	1.00	REF	
Yes	10,735	26	1.20	(0.69 to 2.06)	16	1.89	(0.91 to 3.98)		10,663	27	1.06	(0.63 to 1.76)	19	1.82	(0.88 to 3.92)	
P_{het}‖				.522			.089	.352				.817			.105	.201

Abbreviations: het, heterogeneity; REF, reference; RR, relative risk.

*As a result of rounding, sum across levels of each characteristic may exceed the total.

†Relative risks and 95% CIs estimated from multivariable Poisson regression models mutually adjusted for all variables in the table.

‡Two-sided likelihood ratio test for heterogeneity of the RR patterns between sarcomas occurring in the head and neck versus the body and extremities. Models were fully parameterized and included an interaction term for location × each factor, with ordinal categories of attained age, age at retinoblastoma diagnosis, and calendar year of retinoblastoma modeled continuously; and sex, family history, and chemotherapy modeled categorically.

§Attained age 30-44 and ≥ 45 years combined for bone sarcoma.

‖Two-sided likelihood ratio test for heterogeneity (sex, family history, and chemotherapy modeled categorically) and trend (ordinal categories of attained age, age at retinoblastoma, and calendar year of retinoblastoma modeled continuously) of the RRs within each type of sarcoma (eg, within bone sarcomas occurring in the head and neck).

¶Relative risks for ages 6 to < 12 months versus 0 to < 6 months at retinoblastoma diagnosis were as follows: head and neck bone sarcoma (RR, 0.56; 95% CI, 0.28 to 1.07); body and extremity bone sarcoma (RR, 0.96; 95% CI, 0.37 to 2.36); head and neck soft-tissue sarcoma (RR, 0.85; 95% CI, 0.45 to 1.56); and body and extremity soft-tissue sarcoma (RR, 0.75; 95% CI, 0.24 to 2.17).

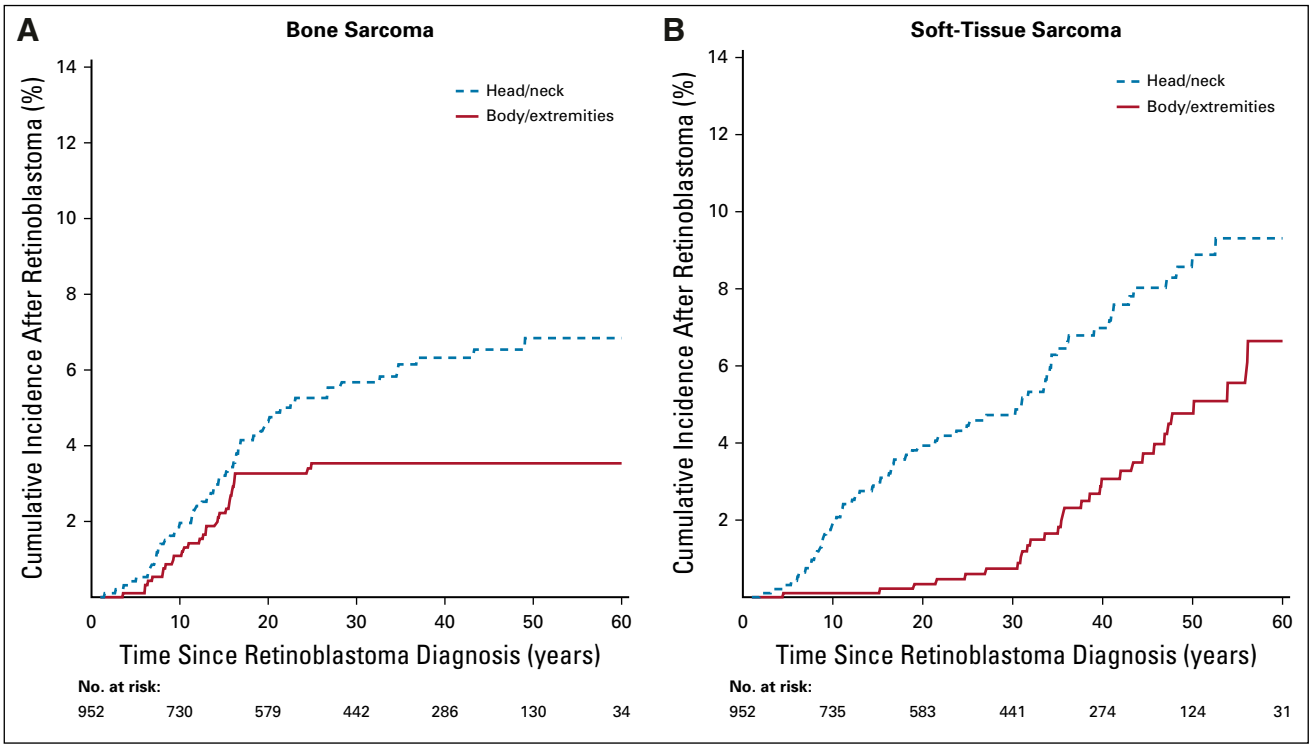

FIG 2. Cumulative incidence of subsequent sarcomas after retinoblastoma by location (head/neck *v* body/extremities). (A) Bone and (B) soft tissue.

(Data Supplement) and subsequent mortality (a measure of health status; Data Supplement).

DISCUSSION

In this long-term, large-scale follow-up study, we show that the substantially elevated risks of bone and soft-tissue sarcoma in survivors of hereditary retinoblastoma who were treated with radiotherapy vary by sarcoma type, histology, location, age at sarcoma, age at retinoblastoma, and sex. Approximately two thirds of bone sarcomas and soft-tissue sarcomas diagnosed with known location in our cohort occurred in the head and neck, representing an incidence rate of more than 2,000-fold and 500-fold, respectively, higher than that expected in the general population. Head and neck bone and soft-tissue sarcomas were diagnosed in early childhood and continued well into adulthood. In contrast, bone and soft-tissue sarcomas that were diagnosed elsewhere in the body were increased 169-fold and 45.7-fold, respectively, compared with the general population, with bone sarcomas primarily occurring in the long bones during adolescence and soft-tissue sarcomas mainly occurring in the abdomen and pelvis beginning in the fourth decade of life, particularly leiomyosarcomas in females. These contrasting incidence patterns by tumor location, age, and sex indicate the importance of both radiotherapy and genetic predisposition in the etiology of sarcomas after retinoblastoma and provide guidance for the long-term clinical management of survivors of hereditary retinoblastoma.

Despite the very high risks for bone and soft-tissue sarcomas after retinoblastoma reported in this and other cohorts,[2,4-6] screening guidelines for survivors of hereditary retinoblastoma recommend only annual history and physical exam, as well as patient education regarding concerning signs and symptoms. Surveillance whole-body magnetic resonance imaging has not been shown to date to be effective,[21] despite its use in patients with other inherited cancer predisposition syndromes, such as Li Fraumeni syndrome.[22,23] Our results suggest that future studies could be designed to assess the utility of a risk-based magnetic resonance imaging screening protocol that focuses on the highest sarcoma risks by age, body location, and sex, such as regular, long-term screening restricted to the head and neck, and possible additional screening for bone sarcomas in the long bones only during adolescence and for soft-tissue sarcoma in the abdomen and pelvis only beginning in the fourth decade of life, particularly for females.

Results from this analysis extend previous reports on sarcoma after hereditary retinoblastoma with a larger sample size, longer-term follow up, and more detailed clinical data. Specifically, the age-specific incidence patterns that we observed for bone sarcomas confirmed a previous French study in which the three bone tumors diagnosed after age 25 years—oldest at age 30 years—occurred exclusively inside the radiotherapy field.[24] Our results also are consistent with the strong role of attained age in bone sarcoma risk reported in a European cohort of survivors of retinoblastoma,[5] although that study lacked information on

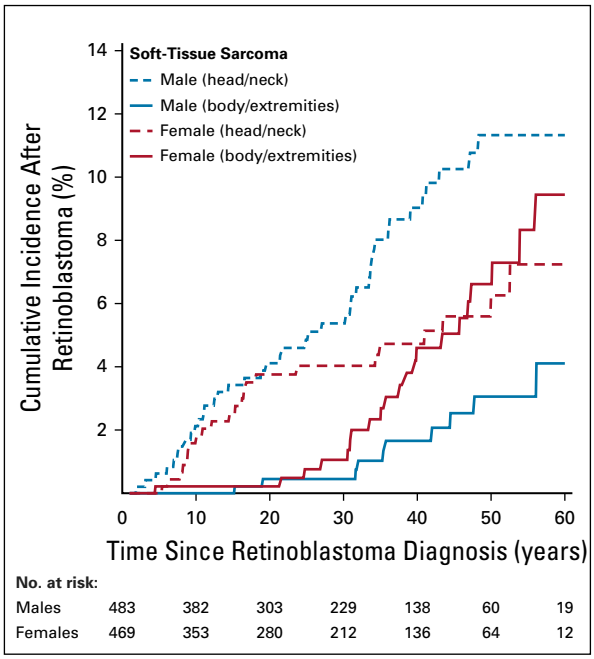

FIG 3. Cumulative incidence of subsequent soft-tissue sarcomas after retinoblastoma by location (head/neck *v* body/extremities) and sex.

hereditary status and retinoblastoma treatment. Results from the same European cohort also demonstrated that soft-tissue sarcoma risk was highest for leiomyosarcomas and for males.[6] Whereas we also found strongly elevated risks for leiomyosarcomas, we report that the sex-specific findings vary by location of the soft-tissue sarcoma, with strongly elevated risks for soft-tissue sarcoma outside the head and neck for females, likely associated with an increased risk for leiomyosarcomas of the uterus, pelvis, and retroperitoneum after age 30 years.[25,26]

Some,[14,27] but not all,[28] previous studies also have suggested that younger age at radiotherapy for retinoblastoma may be associated with a higher risk of second cancers compared with older age at exposure. Our results suggest that this pattern applies only to bone sarcomas and soft-tissue sarcoma diagnosed in the head and neck, which could account for the discrepant results in the literature. Finally, as we reported previously in our cohort,[13] chemotherapy was modestly associated with sarcoma risk after hereditary retinoblastoma, although it was most evident for bone and soft-tissue sarcoma that occurred outside the head and neck.[29]

Observed patterns of bone and soft-tissue sarcoma occurrence emphasize the importance of both radiotherapy and genetic susceptibility in their etiology after hereditary retinoblastoma. High-dose radiotherapy is an established risk factor for sarcoma after retinoblastoma[2,11,12] as well as other pediatric and adult malignancies.[30-32] In addition, the importance of *RB1* mutations in carcinogenesis is supported not only by the strikingly elevated sarcoma risks occurring outside the treatment field among irradiated survivors of hereditary retinoblastoma that we observed, but also by the importance of recurrent *RB1* somatic mutations in sporadic sarcomas.[33,34] Understanding whether specific *RB1* mutations or other genetic variants confer differential sarcoma risk, either in the presence or absence of radiation exposure, could provide insight into sarcoma etiology and identify individuals—even with low penetrance or mosaic *RB1* mutations—who might benefit the most from increased surveillance.[35,36]

The major strengths of this analysis include the large sample size, long-term follow up, and detailed clinical data, which enabled the investigation of specific risk factors by sarcoma type, histology, location, age at onset, and sex; however, several key limitations should be taken into account. We lacked *RB1* germline mutation data for the cohort as well as detailed histologic information on some sarcoma diagnoses, particularly those reported on death certificates, including some deaths that were attributed to cancer of an organ site other than soft tissue.[10] We may have missed some sarcoma diagnoses as a result of incomplete response to the periodic questionnaires, but the general similarity of responders and nonresponders with respect to baseline characteristics and mortality risk was reassuring (Data Supplement).

We assumed on the basis of previous dosimetry work in this cohort that head and neck sarcomas were likely in/near the treatment field and thus received high radiation doses,[12] especially patients who were treated with orthovoltage radiotherapy before 1960 who would have been exposed to more scatter radiation to the head than individuals irradiated in the following decades. Use of radiotherapy to treat hereditary retinoblastoma has declined in the United States[37] and other high-income countries in favor of the use of intra-arterial chemotherapy—ophthalmic artery chemosurgery—and intravitreal injections of chemotherapy.[38] However, our results are still relevant for survivors of hereditary retinoblastoma who were treated with radiotherapy in the past. Of note, it is unclear whether the nonstatistically significant decreasing trends observed for bone sarcoma—head and neck only—and soft-tissue sarcomas reflect reduced sarcoma risk in more recent calendar years or younger attained ages.

In conclusion, we provide the first comprehensive evidence that the strikingly elevated risks of bone and soft-tissue sarcomas treated with radiotherapy for hereditary retinoblastoma vary by sarcoma type, histology, location, age at onset, age at retinoblastoma, and sex. These findings suggest a risk-based design for future studies of the utility of sarcoma surveillance in this high-risk patient population.

AFFILIATIONS

[1]National Cancer Institute, Bethesda, MD
[2]Memorial Sloan Kettering Cancer Center, New York, NY
[3]University of Massachusetts Medical School, Worcester, MA

CORRESPONDING AUTHOR

Ruth A. Kleinerman, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 9609 Medical Center Dr, Room 7E456, Rockville, MD 20892; e-mail: kleinerr@mail.nih.gov.

SUPPORT

Supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01096.

AUTHOR CONTRIBUTIONS

Conception and design: Ruth A. Kleinerman, Margaret A. Tucker, Lindsay M. Morton

Financial support: Lindsay M. Morton

Provision of study materials or patients: David H. Abramson, Johanna M. Seddon

Collection and assembly of data: Ruth A. Kleinerman, Jeanette R. Wong-Siegel, Johanna M. Seddon, Margaret A. Tucker, Lindsay M. Morton

Data analysis and interpretation: Ruth A. Kleinerman, Sara J. Schonfeld, Byron S. Sigel, Ethel S. Gilbert, David H. Abramson, Margaret A. Tucker, Lindsay M. Morton

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Kleinerman RA, Schonfeld SJ, Tucker MA: Sarcomas in hereditary retinoblastoma. Clin Sarcoma Res 2:15, 2012
2. Marees T, Moll AC, Imhof SM, et al: Risk of second malignancies in survivors of retinoblastoma: More than 40 years of follow-up. J Natl Cancer Inst 100: 1771-1779, 2008
3. Reulen RC, Frobisher C, Winter DL, et al: Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 305:2311-2319, 2011
4. Temming P, Arendt M, Viehmann A, et al: Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center. Pediatr Blood Cancer 64:71-80, 2017
5. Fidler MM, Reulen RC, Winter DL, et al: Risk of subsequent bone cancers among 69 460 five-year survivors of childhood and adolescent cancer in Europe. J Natl Cancer Inst 110:183-194, 2018
6. Bright CJ, Hawkins MM, Winter DL, et al: Risk of soft-tissue sarcoma among 69 460 five-year survivors of childhood cancer in Europe. J Natl Cancer Inst 110: 649-660, 2018
7. Fujiwara T, Fujiwara M, Numoto K, et al: Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol 45:1139-1145, 2015
8. Fletcher O, Easton D, Anderson K, et al: Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 96:357-363, 2004
9. Acquaviva A, Ciccolallo L, Rondelli R, et al: Mortality from second tumour among long-term survivors of retinoblastoma: A retrospective analysis of the Italian Retinoblastoma Registry. Oncogene 25:5350-5357, 2006
10. Kleinerman RA, Tucker MA, Sigel BS, et al: Patterns of cause-specific mortality among 2053 survivors of retinoblastoma, 1914-2016. J Natl Cancer Inst 111: 961-969, 2019
11. Hawkins MM, Wilson LM, Burton HS, et al: Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst 88:270-278, 1996
12. Wong FL, Boice JD Jr, Abramson DH, et al: Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278:1262-1267, 1997
13. Wong JR, Morton LM, Tucker MA, et al: Risk of subsequent malignant neoplasms in long-term hereditary retinoblastoma survivors after chemotherapy and radiotherapy. J Clin Oncol 32:3284-3290, 2014
14. Rodjan F, Graaf P, Brisse HJ, et al: Second cranio-facial malignancies in hereditary retinoblastoma survivors previously treated with radiation therapy: Clinic and radiologic characteristics and survival outcomes. Eur J Cancer 49:1939-1947, 2013
15. Abramson DH, Ellsworth RM, Kitchin FD: Osteogenic sarcoma of the humerus after cobalt plaque treatment for retinoblastoma. Am J Ophthalmol 90:374-376, 1980
16. Steliarova-Foucher E, Stiller C, Lacour B, et al: International Classification of Childhood Cancer, third edition. Cancer 103:1457-1467, 2005
17. World Health Organization: International Classification of Diseases for Oncology, First Revision (ed 3). Geneva, Switzerland, World Health Organization, 2013
18. Noone A, Howlader N, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. https://seer.cancer.gov/csr/1975_2015/
19. Preston DL, Lubin J, Pierce DA, et al. Epicure User Guide. Ottawa, ON, Canada, Risk Sciences International, 2015
20. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 18:695-706, 1999
21. Friedman DN, Lis E, Sklar CA, et al: Whole-body magnetic resonance imaging (WB-MRI) as surveillance for subsequent malignancies in survivors of hereditary retinoblastoma: A pilot study. Pediatr Blood Cancer 61:1440-1444, 2014
22. Villani A, Tabori U, Schiffman J, et al: Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: A prospective observational study. Lancet Oncol 12:559-567, 2011
23. Ballinger ML, Best A, Mai PL, et al: Baseline surveillance in Li-Fraumeni syndrome using whole-body magnetic resonance imaging: A meta-analysis. JAMA Oncol 3:1634-1639, 2017
24. Chauveinc L, Mosseri V, Quintana E, et al: Osteosarcoma following retinoblastoma: Age at onset and latency period. Ophthalmic Genet 22:77-88, 2001
25. MacCarthy A, Bayne AM, Brownbill PA, et al: Second and subsequent tumours among 1927 retinoblastoma patients diagnosed in Britain 1951-2004. Br J Cancer 108:2455-2463, 2013

26. Francis JH, Kleinerman RA, Seddon JM, et al: Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. Gynecol Oncol 124:254-259, 2012
27. Abramson DH, Frank CM: Second nonocular tumors in survivors of bilateral retinoblastoma: A possible age effect on radiation-related risk. Ophthalmology 105: 573-579, discussion 579-580, 1998
28. Moll AC, Imhof SM, Schouten-Van Meeteren AY, et al: Second primary tumors in hereditary retinoblastoma: A register-based study, 1945-1997—Is there an age effect on radiation-related risk? Ophthalmology 108:1109-1114, 2001
29. Kleinerman RA, Tucker MA, Abramson DH, et al. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst 99:24-31, 2007
30. Berrington de Gonzalez A, Kutsenko A, Rajaraman P: Sarcoma risk after radiation exposure. Clin Sarcoma Res 2:18, 2012
31. Schwartz B, Benadjaoud MA, Cléro E, et al: Risk of second bone sarcoma following childhood cancer: Role of radiation therapy treatment. Radiat Environ Biophys 53:381-390, 2014
32. Henderson TO, Rajaraman P, Stovall M, et al: Risk factors associated with secondary sarcomas in childhood cancer survivors: A report from the Childhood Cancer Survivor study. Int J Radiat Oncol Biol Phys 84:224-230, 2012
33. Gianferante DM, Mirabello L, Savage SA: Germline and somatic genetics of osteosarcoma: Connecting aetiology, biology and therapy. Nat Rev Endocrinol 13: 480-491, 2017
34. Cancer Genome Atlas Research Network: Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. Cell 171:950-965.e28, 2017
35. Dommering CJ, Mol BM, Moll AC, et al: RB1 mutation spectrum in a comprehensive nationwide cohort of retinoblastoma patients. J Med Genet 51:366-374, 2014
36. Chaussade A, Millot G, Wells C, et al: Correlation between RB1germline mutations and second primary malignancies in hereditary retinoblastoma patients treated with external beam radiotherapy. Eur J Med Genet 62:217-223, 2019
37. Abramson DH, Daniels AB, Marr BP, et al: Intra-arterial chemotherapy (ophthalmic artery chemosurgery) for group D retinoblastoma. PLoS One 11:e0146582, 2016
38. Abramson DH, Shields CL, Munier FL, et al: Treatment of retinoblastoma in 2015: Agreement and disagreement. JAMA Ophthalmol 133:1341-1347, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Bone and Soft-Tissue Sarcoma Risk in Long-Term Survivors of Hereditary Retinoblastoma Treated With Radiation

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Johanna M. Seddon
Consulting or Advisory Role: Gemini Therapeutics
Travel, Accomodations, or Expenses: Gemini Therapeutics

No potential conflicts of interest were reported.