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

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abstract

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.

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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
or treated for retinoblastoma from 1914 to 2006 at two medical centers in New York, NY, and Boston, MA. 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 family history of retinoblastoma. We restricted the study

tem (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, 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. 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, 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 × 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 × each risk factor). We conducted analyses using SEER*Stat (version 8.3.5), SAS software (version 9.4; SAS Institute, Cary, NC), and Epicure.

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. 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.
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 age.

### 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 $\geq 30 \nu < 15$ years $= 0.39; 95\%$ CI, 0.16 to 0.84; $P_{\text{trend}} = .030$; Table 2). Risk was also higher among patients who were diagnosed with retinoblastoma before 12 months compared with older ages ($P_{\text{trend}} = .033$), 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 ($P_{\text{trend}} = .006$), 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 ($P_{\text{heterogeneity}} = .028$), 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 $\geq 45$ years versus $< 15$ years of age ($P_{\text{trend}} < .001$), whereas there was no association with attained age for head and neck soft tissue sarcomas ($P_{\text{trend}} = .461$; $P_{\text{heterogeneity}} < .001$). The highest risks for head and neck soft-tissue sarcoma were observed for patients who were diagnosed with hereditary retinoblastoma before age 12 months ($P_{\text{trend}} = .028$), whereas age at retinoblastoma diagnosis was not statistically significantly associated with body and extremity soft-tissue sarcoma ($P_{\text{trend}} = .478$; $P_{\text{heterogeneity}} = .061$). 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; $P_{\text{heterogeneity}} = .005$). 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.
| Characteristic                              | Bone Sarcoma | Head and Neck | Soft-Tissue Sarcoma | Body and Extremities | Person-Years* | No. RR† (95% CI) | Person-Years* | No. RR† (95% CI) | Person-Years* | No. RR† (95% CI) | \( P_{\text{het}} \)‡ |
|--------------------------------------------|--------------|---------------|--------------------|----------------------|---------------|-----------------|---------------|-----------------|---------------|-----------------|----------------|
| Age at sarcoma, years                      |              |               |                    |                      |               |                 |               |                 |               |                 |                |
| < 15                                       | 10,139       | 27            | 1.00 REF           |                       |               |                 | 10,171        | 25              | 1.00 REF       |               |                |
| 15-29                                      | 8,382        | 21            | 0.95 (0.53 to 1.69)|                       |               |                 | 8,407         | 16              | 0.80 (0.42 to 1.48)| 5              | 5.85 (0.94 to 11.2) |
| 30-44‡                                     | 7,250        | 8             | 0.39 (0.16 to 0.84)|                       |               |                 | 5,041         | 19              | 1.60 (0.86 to 2.96)| 36             | 28.1 (1.73 to 51.1) |
| ≥ 45                                       |              |               |                    |                      |               |                 | 1,901         | 4               | 0.85 (0.24 to 2.31)| 9              | 35.4 (6.28 to 66.8) |
| \( R_{\text{het}} \)                       |              | .030          |                   |                      |               | .006            | .277          |                 | .461          | <.001           | <.001          |
| Age at retinoblastoma, months              |              |               |                    |                      |               |                 |               |                 |               |                 |                |
| 0-11‡                                      | 14,956       | 41            | 1.00 REF           |                       |               |                 | 14,884        | 43              | 1.00 REF       |               |                |
| 12-23                                      | 7,346        | 10            | 0.49 (0.23 to 0.95)|                       |               |                 | 7,293         | 18              | 0.83 (0.46 to 1.42)| 30             | 1.10 (0.47 to 2.49) |
| 24                                          | 3,468        | 5             | 0.53 (0.18 to 1.23)|                       |               |                 | 3,442         | 3               | 0.29 (0.07 to 0.88)| 7              | 1.43 (0.53 to 3.50) |
| \( R_{\text{het}} \)                       |              | .033          |                   |                      |               | .064            | .348          |                 | .028          | .478            | 0.061          |
| Year of retinoblastoma diagnosis            |              |               |                    |                      |               |                 |               |                 |               |                 |                |
| < 1960                                     | 7,721        | 21            | 1.00 REF           |                       |               |                 | 7,503         | 22              | 1.00 REF       |               |                |
| 1960-69                                    | 9,028        | 18            | 0.68 (0.36 to 1.27)|                       |               |                 | 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)|                       |               |                 | 9,002         | 21              | 0.82 (0.43 to 1.56)| 4              | 0.60 (0.16 to 1.79) |
| \( R_{\text{het}} \)                       |              | .101          |                   |                      |               | .151            | .028          |                 | .523          | .321            | 0.779          |
| Sex                                        |              |               |                    |                      |               |                 |               |                 |               |                 |                |
| Male                                       | 13,312       | 28            | 1.00 REF           |                       |               |                 | 13,154        | 41              | 1.00 REF       |               |                |
| Female                                     | 12,458       | 28            | 1.05 (0.62 to 1.78)|                       |               |                 | 12,366        | 23              | 0.59 (0.35 to 0.97)| 21             | 2.09 (1.00 to 4.66) |
| \( R_{\text{het}} \)                       |              | .851          |                   |                      |               | .498            | .528          | .036            | .050          | .005            |                |
| Family history of retinoblastoma           |              |               |                    |                      |               |                 |               |                 |               |                 |                |
| No/unknown                                 | 20,606       | 47            | 1.00 REF           |                       |               |                 | 20,755        | 53              | 1.00 REF       |               |                |
| Yes                                        | 4,774        | 9             | 0.77 (0.35 to 1.52)|                       |               |                 | 4,765         | 11              | 0.89 (0.44 to 1.60)| 4              | 0.94 (0.27 to 2.45) |
| \( R_{\text{het}} \)                       |              | .473          |                   |                      |               | .544            | .381          | .720            | .907          | 9.21            |                |
| Chemotherapy for retinoblastoma            |              |               |                    |                      |               |                 |               |                 |               |                 |                |
| No                                         | 15,034       | 30            | 1.00 REF           |                       |               |                 | 14,896        | 37              | 1.00 REF       |               |                |
| Yes                                        | 10,735       | 26            | 1.20 (0.69 to 2.06)|                       |               |                 | 10,663        | 27              | 1.06 (0.63 to 1.76)| 39             | 1.82 (0.88 to 3.92) |
| \( R_{\text{het}} \)                       |              | .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) 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). |
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 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 that expected in the general population.

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. 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, although that study lacked information on

Despite the very high risks for bone and soft-tissue sarcomas after retinoblastoma reported in this and other cohorts, 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, despite its use in patients with other inherited cancer predisposition syndromes, such as Li Fraumeni syndrome. 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. 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, although that study lacked information on

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

FIG 2. Cumulative incidence of subsequent sarcomas after retinoblastoma by location (head/neck v body/extremities). (A) Bone and (B) soft tissue.
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\(^{11,12}\) 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 penetration 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.\(^{15}\) 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.\(^{28}\) 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.
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Bone and Soft-Tissue Sarcoma Risk in Long-Term Survivors of Hereditary Retinoblastoma Treated With Radiation

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