

# Cancer Incidence After Retinoblastoma

## Radiation Dose and Sarcoma Risk

F. Lennie Wong, PhD; John D. Boice, Jr, ScD; David H. Abramson, MD; Robert E. Tarone, PhD; Ruth A. Kleinerman, MPH; Marilyn Stovall, PhD; Marlene B. Goldman, ScD; Johanna M. Seddon, MD; Nancy Tarbell, MD; Joseph F. Fraumeni, Jr, MD; Frederick P. Li, MD

**Context.**—There is a substantial risk of a second cancer for persons with hereditary retinoblastoma, which is enhanced by radiotherapy.

**Objective.**—To examine long-term risk of new primary cancers in survivors of childhood retinoblastoma and quantify the role of radiotherapy in sarcoma development.

**Design.**—Cohort incidence study of patients with retinoblastoma followed for a median of 20 years, and nested case-control study of a radiation dose-response relationship for bone and soft tissue sarcomas.

**Setting/Participants.**—A total of 1604 patients with retinoblastoma who survived at least 1 year after diagnosis, identified from hospital records in Massachusetts and New York during 1914 to 1984.

**Results.**—Incidence of subsequent cancers was statistically significantly elevated only in the 961 patients with hereditary retinoblastoma, in whom 190 cancers were diagnosed, vs 6.3 expected in the general population (relative risk [RR], 30 [95% confidence interval, 26-47]). Cumulative incidence ( $\pm$ SE) of a second cancer at 50 years after diagnosis was 51.0% ( $\pm$ 6.2%) for hereditary retinoblastoma, and 5.0% ( $\pm$ 3.0%) for nonhereditary retinoblastoma. All 114 sarcomas of diverse histologic types occurred in patients with hereditary retinoblastoma. For soft tissue sarcomas, the RRs showed a stepwise increase at all dose categories, and were statistically significant at 10 to 29.9 Gy and 30 to 59.9 Gy. A radiation risk for all sarcomas combined was evident at doses above 5 Gy, rising to 10.7-fold at doses of 60 Gy or greater ( $P < .05$ ).

**Conclusions.**—Genetic predisposition has a substantial impact on risk of subsequent cancers in retinoblastoma patients, which is further increased by radiation treatment. A radiation dose-response relationship is demonstrated for all sarcomas and, for the first time in humans, for soft tissue sarcomas. Retinoblastoma patients should be examined for new cancers and followed into later life to determine whether their extraordinary cancer risk extends to common cancers of adulthood.

JAMA. 1997;278:1262-1267

From the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Md (Drs Wong, Boice, Tarone, and Fraumeni and Ms Kleinerman); The University of Texas M.D. Anderson Cancer Center, Houston (Dr Stovall); New York Hospital-Cornell Medical Center, New York, NY (Dr Abramson); and Department of Ophthalmology, Harvard Medical School (Dr Seddon), Dana-Farber Cancer Institute (Dr Li), Harvard School of Public Health (Drs Goldman, Seddon, and Li), Boston Children's Hospital (Dr Tarbell), Boston, Mass. Dr Boice is currently with the International Epidemiology Institute, Rockville, Md. Dr Wong is currently a private statistical consultant, Burbank, Calif.

Reprints: Joseph F. Fraumeni, Jr, MD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6130 Executive Blvd, EPN - Room 543, Rockville, MD 20892.

RETINOBLASTOMA is the prototypic hereditary cancer in humans.<sup>1</sup> Children who survive hereditary retinoblastoma are at exceptionally high risk of developing and dying prematurely from subsequent primary tumors,<sup>2-5</sup> particularly, osteosarcomas and soft tissue sarcomas. However, children with nonhereditary retinoblastoma appear not to be at increased risk for second cancers. The high rate of subsequent cancers in hereditary retinoblastoma patients is attributable primarily to germline mutations in the retinoblastoma tumor suppressor gene,

*RB1*, the first inherited cancer susceptibility gene identified in humans.<sup>6</sup> Also, radiotherapy for retinoblastoma can produce somatic mutations and lead to cancer.<sup>2,5,7</sup> A radiation dose-response relationship for bone sarcoma has been

For editorial comment see p 1284.

demonstrated in 2 populations of childhood cancer survivors that include retinoblastoma patients.<sup>7,8</sup> To quantify risk of subsequent primary cancers in long-term survivors of retinoblastoma, we evaluated cancer incidence in the largest cohort of retinoblastoma patients yet assembled. Dosimetric studies were conducted to quantify effects of radiation dose on development of sarcoma.

## METHODS

### Cohort Analyses

A cohort of 1729 retinoblastoma patients was identified from medical records at hospitals and medical centers in Boston, Mass (1937-1984), and New York, NY (1914-1984).<sup>2</sup> Information on laterality of retinoblastoma, treatment, family history of retinoblastoma, and other neoplasms was obtained from medical records and patient interviews. This study is based on 1604 patients who survived 1 year or more after retinoblastoma diagnosis, resided or died in the United States, and were known to be alive in 1925 or later. Telephone interviews were conducted on 2 occasions, during 1987-1988, and 1993, to collect information on new cancers, retinoblastoma treatments, family history of retinoblastoma and other cancers, and recent deaths. Patients with bilateral tumors or unilateral tumor with a family history of retinoblastoma were classified as hereditary.<sup>2</sup> Patients with a unilateral tumor and no family history of retinoblastoma were classified as nonhereditary, although a

few might have new germline mutations of low penetrance.<sup>1</sup>

A trained nosologist classified subsequent cancers according to topography (primary anatomic site) and morphology (histology) codes of the *International Classification of Diseases for Oncology*.<sup>3</sup> Medical data were obtained from pathology reports, radiotherapy files, clinical records, questionnaire responses, tumor registries, and death certificates. Unconfirmed cancers, benign tumors, and all primary cancers of skin other than malignant melanoma were excluded from the analysis. Over 60% of cancers were classified histologically based on pathology reports. Follow-up began 1 year after diagnosis of retinoblastoma and ended at date of loss to follow-up ( $n=112$ , median duration of follow-up=4.2 years), the date of death ( $n=330$ ), or December 1993 ( $n=1162$ ). Observed numbers of cancers were compared with corresponding expected numbers estimated by multiplying appropriate person-years at risk by sex-, age-, and calendar year-specific cancer rates from the Connecticut Tumor Registry, the first population-based cancer registry in the United States with continuous incidence data since 1935.<sup>10-12</sup> Ratio of observed to expected cancers is denoted by O/E. Tests of significance and confidence intervals (CIs) for O/E ratios and ratios of O/E ratios were calculated using exact Poisson probabilities. Excess risk was calculated as observed minus expected number of cancers, divided by number of person-years at risk. The Kaplan-Meier method was used to estimate cumulative incidence of second cancers and corresponding SEs.<sup>13</sup>

### Case-Control Analyses

A case-control radiation dosimetry study was performed with data from the first follow-up interview (1987-1988). Cases were patients with sarcoma, the most common cancer following retinoblastoma. Sarcomas of diverse anatomic sites were identified by morphology codes. Because sarcoma developed only in bilateral retinoblastoma patients, 100 bilateral patients in the cohort free of second cancers were randomly selected as controls. Radiation doses were estimated for each sarcoma case at the site of the sarcoma and for each control at every anatomic site at which a sarcoma developed in cases.

Except as described, cases and controls were not matched, thus controls lacked a uniquely designated anatomic site at which to estimate radiation dose. Accordingly, anatomic sites of sarcoma were randomly assigned to control subjects according to the frequency distribution of sites of sarcoma in cases. For example, since bone sarcoma occurred in

the right maxilla in 13% of cases, 13% of controls were randomly chosen to be assessed on the basis of estimated radiation doses to the right maxilla as designated "site-matched doses."

Risk of sarcoma for radiation dose absorbed at sites of sarcoma was assessed by the case-control method, conditioning on anatomic sites of sarcomas, and controlling for the effects of age at retinoblastoma diagnosis and duration of follow-up. Dose categories were 0 to 4.9 Gy, 5.0 to 9.9 Gy, 10.0 to 29.9 Gy, 30.0 to 59.9 Gy, and  $\geq 60.0$  Gy. Risk at each dose category relative to the lowest category, approximated by the odds ratio (OR), was modeled as 1 plus the excess relative risk (RR). Maximum likelihood estimates of risk were obtained using the PECAN program.<sup>14</sup> Random assignment of "site-matched doses" in controls introduced variability in resulting risk estimates. Thus, the scheme of randomly assigning "sarcoma site" doses to controls and estimating risks by maximum likelihood estimation was repeated 201 times, producing 201 estimates of RR for each dose category. The median of these estimates is the reported summary RR estimate.

We assessed statistical variability of reported risk estimates with CIs constructed using the bootstrap resampling method.<sup>15</sup> This computer-based approach permits inferences based on statistics for which distributions are not easily derived. Bootstrap samples of cases and controls of the same size as the original case-control study sample were generated using random sampling with replacement (ie, each case or control can be chosen more than once). The estimation procedure described above (201 repeats of random site-matched dose assignment followed by maximum likelihood estimation) was then applied to each bootstrap sample to yield estimates of risk at each dose level. The bootstrap procedure was repeated 1000 times, and from the distribution of the resulting 1000 estimates, 95% bias-corrected bootstrap CIs were constructed.<sup>15</sup>

Estimated bone dose to legs and trunk were less than 5 Gy (ie, in the lowest dose category) for all subjects, so leg and trunk bone sarcomas were eliminated from analysis. There were too few absorbed bone doses less than 5 Gy at sarcoma sites receiving highest exposures (ie, orbit, maxilla, and nasal) to permit stable estimation of RR for osteosarcoma. Thus, dose-response analyses were performed only for soft tissue sarcomas alone and for all sarcomas combined.

### Radiation Dosimetry

Detailed information on radiation treatment of retinoblastoma was abstracted from radiotherapy records for cases and controls, and absorbed dose to

bone or soft tissue at each sarcoma site was estimated by measurements and computer simulations.<sup>7,8,16</sup> Dose reconstruction accounted for age at treatment, height, differential bone absorption, and body-surface area irradiated. Actual conditions of exposure were simulated based on machine characteristics, field configurations, and treatment conditions. Uncertainties regarding exact radiation treatment fields for retinoblastoma and the precise location of subsequent tumors made dose estimation problematic for some subjects. The average of the minimum and maximum calculated doses was used in such cases. Orthovoltage radiation was used for 230 of 238 treatments given before 1960. Thereafter, nearly all radiotherapy was administered with cobalt-60 teletherapy, or betatron (22 megavolts [MV]) or other megavoltage (mostly 6 MV) machines. Since 1980, 21 patients were treated with electron beam therapy.

A quality score was assigned to individuals' dose estimates, according to completeness of radiotherapy information. Scores ranged from very good, good, fair, to inadequate. A score of very good indicated that radiotherapy records were complete and sufficient for reproducible estimates of dose to tumor sites. Radiotherapy information was fair or better for 83% of cases and 89% of controls. It was not possible to evaluate carcinogenic effects of chemotherapy for retinoblastoma; chemotherapy was rarely given before 1960, and thereafter, drug and dosage data were often unavailable or incomplete.

## RESULTS

### Cohort Study of Subsequent Cancer Risks

Of the 1604 cohort members, 848 (53%) were males, 961 (60%) had hereditary retinoblastoma, and 1150 (72%) were diagnosed as having retinoblastoma before 2 years of age. In those with hereditary disease, 917 (95%) had bilateral retinoblastoma, and 44 had unilateral retinoblastoma with a family history of the tumor. Median calendar year of retinoblastoma diagnosis was 1966. Median age at last follow-up was 22 years, and median follow-up duration was 20 years. Patients with hereditary retinoblastoma were younger at diagnosis (median age, 10 months) than those with nonhereditary retinoblastoma (median, 23 months). Radiotherapy for retinoblastoma was recorded for 848 hereditary patients (88%) and 114 nonhereditary patients (18%). Extensive inquiries failed to uncover any history of radiotherapy for 10 patients, who were included in the nonirradiated group in the analysis.

Table 1.—Risk of Second Primary Cancers (Including 70 Osteosarcomas and 44 Soft Tissue Sarcomas) in 1-Year Survivors of Retinoblastoma

Cancer Site (ICD-O Classification)	Observed (O) and Expected (E) No. of Cancers								
	Hereditary			Nonhereditary			Total		
	O	E*	O/E* (95% CI)†	O	E	O/E (95% CI)	O	E	O/E (95% CI)†
Bone (170)	65‡	0.15	446 (346-573)	0	0.11	0 (0-27)	65	0.26	255 (198-328)
Connective and soft tissue (171)	19§	0.19	103 (62-161)	0	0.13	0 (0-23)	19	0.32	59 (36-93)
Cutaneous melanoma (173 and M872-878)	22	0.43	51 (32-77)	0	0.38	0 (0-7.9)	22	0.81	27 (17-41)
Brain, central nervous system (191-2)	7	0.50	14 (6-29)	1	0.37	2.7 (0.1-15)	8	0.87	9.2 (4.0-18)
Nasal cavities (160)	26‡§	<0.10	>100 (>65)	0	<0.10	0 (0-300)	26	<0.10	>100 (>65)
Female breast (174)	2	0.85	2.4 (0.3-8.5)	4	0.80	5.0 (1.4-13)	6	1.66	3.6 (1.3-7.9)
Hodgkin disease (M9650-67)	3	0.56	5.4 (1.1-16)	1	0.44	2.3 (0.1-13)	4	0.99	4.0 (1.1-10)
Eye and orbit (190)	12§	<0.10	>100 (>52)	0	<0.10	0 (0-100)	12	<0.10	>100 (>52)
Pineoblastoma (194.4)	5	<0.05	>100 (>32)	0	<0.05	0 (0-300)	5	<0.05	>100 (>32)
Others/unknown (199)	29‡§¶#	3.39	8.6 (5.7-12)	3**	3.26	0.9 (0.1-2.7)	32	6.66	4.8 (3.3-6.8)
All sites	190	6.28	30 (26-47)	9	5.59	1.6 (0.7-3.1)	199	11.87	17 (15-19)

\*When O/E ratios or 95% confidence intervals (95% CIs) are  $\geq 10$ , the numbers are rounded to integers.

†Only 1 value is provided for some 95% CIs; this value constitutes the lower bound, based on a small expected value.

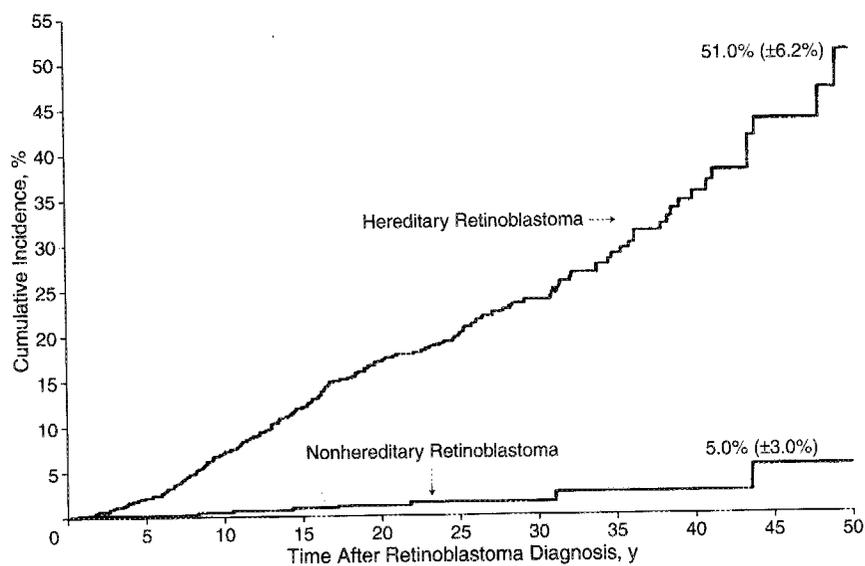
‡By International Classification of Diseases for Oncology (ICD-O) criteria, primary sites of 70 osteosarcomas were bone (65 cases), nasal cavities (4), and nasopharynx (1). §By ICD-O criteria, primary sites of 44 soft tissue sarcomas were connective and soft tissue (15 cases), nasal cavities (13), orbit (11), and others or unknown sites (5). The 4 remaining connective and soft tissue tumors were neuroblastoma (3) and neurilemmoma (1). One additional neuroblastoma and an esthesioneuroblastoma were assigned by topography to cancers of unknown site and nasal cavities, respectively.

¶One intraocular melanoma (in addition to 11 orbital soft tissue sarcomas as noted above).

||Others: 20 total including 2 each of colon, nasopharynx (1 osteosarcoma), parotid gland, lymphoid leukemia, uterus not otherwise specified (1 leiomyosarcoma), uteri corpus (1 leiomyosarcoma), and facial area; 1 each of kidney (sarcoma), scrotum (leiomyosarcoma), thyroid, tongue, urinary bladder, and facial lymph nodes.

#Unknown: 9 total including unspecified malignant neoplasms (3), squamous cell carcinoma (2), and 1 each of small cell carcinoma, leiomyosarcoma, carcinosarcoma, and neuroblastoma.

\*\*Cancer of the rectum and of the thyroid, and malignant neoplasm (1 each).



Group	961	715	473	205	62	11
Hereditary	961	715	473	205	62	11
Nonhereditary	643	529	348	168	53	13
No. of Patients at Risk						

Figure 1.—Cumulative incidence (±SE) of second cancers following diagnosis of retinoblastoma in patients with hereditary and nonhereditary disease.

Overall, 188 survivors of retinoblastoma developed 199 additional cancers (11 hereditary patients each had 2 subsequent primary cancers in different organs), compared with 11.9 expected (O/E, 17 [95% CI, 15-19]) (Table 1). Median time interval between retinoblastoma and second cancer diagnosis was 15.0 years (range, 1.6 to 61.2 years). Observed to expected ratios for subsequent cancers exceeded 25 for bone, nasal cavities, connective and soft tissues, eye and orbit, cutaneous melanoma, and pineoblastoma, which has been called "trilateral retinoblastoma" when associated with bilateral retinoblastoma.<sup>4,17</sup> By morphology, there were 70 osteosarcomas and 44 soft tissue sarcomas. Excess risks were also found for brain tumors, breast cancer, and Hodgkin disease. The excess of Hodgkin disease was based on 4 patients (O/E = 4.0 [95% CI, 1.1-10]), 3 of whom had heredi-

tary retinoblastoma. There were 4 neuroblastomas and 1 esthesioneuroblastoma of diverse sites, a high frequency for these rare cancers.<sup>18</sup>

Of the 199 subsequent cancers, 190 were in patients with hereditary retinoblastoma (O/E = 30 [95% CI, 26-35]), including all cancers of bone, connective and soft tissues, nasal cavities, eye and orbit; cutaneous melanoma; and pineoblastoma. Fifty years after retinoblastoma diagnosis, the cumulative incidence (±SE) of second primary cancer was 51.0% (±6.2%) in hereditary cases and 5.0% (±3.0%) in nonhereditary cases (Figure 1). Radiotherapy increased risk of second cancers in those with hereditary retinoblastoma (cumulative incidence [±SE] at 50 years of follow-up, 58.3% [±8.9%]). The corresponding cumulative incidence (±SE) for nonirradiated hereditary patients was 26.5% (±10.7%) (Figure 2).

No statistically significant excess of subsequent cancers was observed in the 643 nonhereditary retinoblastoma patients (O/E, 1.6 [95% CI, 0.7-3.1]). However, the 4 cases of breast cancer in women exceeded expectation (O/E, 5.0 [95% CI, 1.4-13]). These breast cancers were diagnosed in women at ages 34, 35, 53, and 59 years. The 2 older women were among the 114 nonhereditary retinoblastoma patients who received radiation therapy (O/E, 12 [95% CI, 1.3-42]). In hereditary retinoblastoma patients, 2 breast cancers were diagnosed when the women were 25 and 35 years of age, and both had received orbital radiation (O/E, 2.4 [95% CI, 0.3-8.5]).

The O/E ratios for subsequent cancers decreased with age at observation, while excess risk increased (Table 2).

The O/E ratios for subsequent cancers decreased with age at observation, while excess risk increased (Table 2).

These divergent patterns result from increases in expected frequencies of cancer with age in the general population. Both O/E ratio and excess risk were higher for those diagnosed as having retinoblastoma at younger than older ages. Risk of subsequent cancers was significantly higher in nonirradiated hereditary patients than in nonirradiated nonhereditary patients (ratio of O/E ratios, 5.5 [95% CI, 1.8-18]). Subsequent cancer risk was also higher in irradiated hereditary retinoblastoma patients than in nonirradiated hereditary patients (ratio of O/E ratios, 5.0 [95% CI, 2.6-11]). The higher O/E ratios in recent decades reflect low cancer rates expected in children with limited follow-up.

### Case-Control Study of Radiation Effects

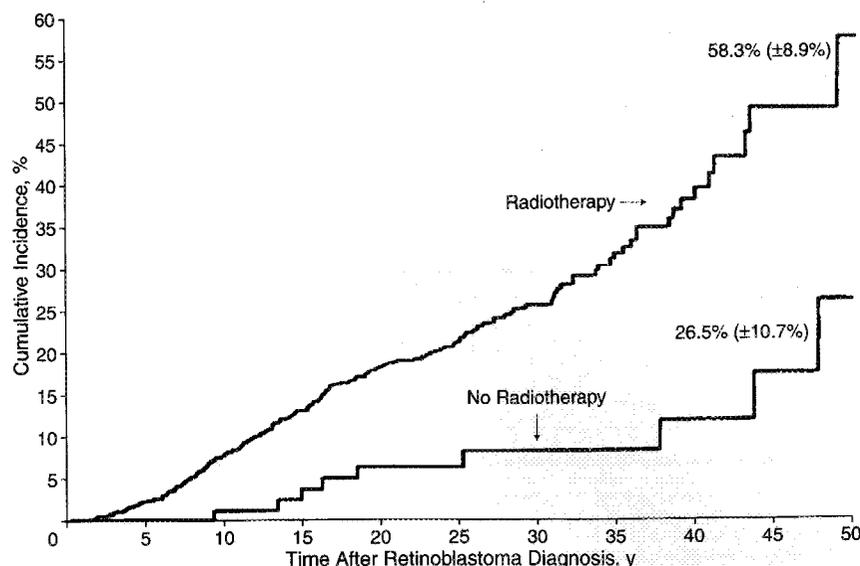
Dosimetry data were collected for 63 patients with bone sarcoma and 37 patients with soft tissue sarcoma. Analysis was restricted to subjects whose dosimetry quality scores were fair or better, leaving a total of 52 cases with bone sarcoma and 31 with soft tissue sarcoma, plus 89 controls. Elimination of 16 leg or trunk bone sarcoma cases resulted in 36 bone sarcoma cases in the final analysis.

Most sarcomas were in the head (Table 3). All but 2 of the 83 sarcoma patients (1 each with bone sarcoma and soft tissue sarcoma) received radiotherapy for retinoblastoma, as did 81 of the 89 controls. The mean dose to the bone tumor site was 32.8 Gy (range, 0-193 Gy), and mean dose for controls at the equivalent anatomic site was 20.0 Gy (range, 0-212 Gy). For soft tissue sarcoma the mean dose was 20.4 Gy (range, 0-82.1 Gy), and for controls, 10.6 Gy (range, 0-112 Gy).

Compared with the referent group of 0 to 4.9 Gy for soft tissue sarcoma, RR increased to over 11-fold for soft tissue sarcoma at doses of 60 Gy or greater (Table 4). The RRs showed a stepwise increase at all dose categories, and were statistically significant at 10 to 29.9 Gy and 30 to 59.9 Gy. For all sarcomas combined, risk was statistically significantly elevated at all dose levels, even at 5.0 to 9.9 Gy. Estimated increase in RR per gray of radiation exposure was 16.6% for soft tissue sarcoma (95% CI, 2.5%-1630%) and 19.1% for all sarcomas combined (95% CI, 13.6%-31.5%). For all sarcomas combined, excess RR per gray did not differ by age at retinoblastoma diagnosis (younger than 1 year compared with older).

### COMMENT

Probability of developing a second cancer in our hereditary retinoblastoma patients had, by 40 years of age, sur-



Radiotherapy	848	619	407	165	42	5
No Radiotherapy	113	96	66	40	20	6
			No. of Patients at Risk			

Figure 2.—Cumulative incidence (±SE) of second cancers following diagnosis of retinoblastoma in patients with hereditary disease, by radiation treatment.

Table 2.—Risk of Developing Second Primary Cancers in 1-Year Survivors of Retinoblastoma According to Selected Characteristics

Characteristic	Observed (O)	Expected (E)	O/E	95% Confidence Interval	Excess Risk*
Time after retinoblastoma diagnosis, y					
1-9	56	1.64	34.1	(25.9-44.8)	4.3
10-19	75	1.88	39.9	(31.6-50.3)	7.0
20-39	55	5.19	10.6	(8.0-13.9)	5.9
≥40	13	3.16	4.1	(2.2-7.0)	12.5
Sex					
Male	95	5.47	17.4	(14.1-21.4)	5.2
Female	104	6.40	16.3	(13.3-19.8)	6.4
Age at retinoblastoma diagnosis, y					
<1	120	3.82	31.4	(26.2-37.7)	8.6
1	57	4.12	13.8	(10.5-18.1)	5.4
2-17	22	3.93	5.6	(3.5-8.5)	2.0
Radiotherapy					
Hereditary retinoblastoma					
Irradiated	180	4.91	36.7	(31.6-42.5)	10.9
Nonirradiated	10†	1.37	7.3	(3.5-13.4)	3.1
Nonhereditary retinoblastoma					
Irradiated	3	1.11	2.7	(0.6-7.9)	1.1
Nonirradiated	6	4.48	1.3	(0.5-2.9)	0.1
Calendar year of retinoblastoma treatment					
1914-1949	44	4.60	9.6	(6.9-12.9)	8.4
1950-1959	57	3.18	17.9	(13.7-23.4)	6.8
1960-1969	54	2.73	19.8	(14.9-26.0)	4.5
1970-1979	35	1.14	30.7	(21.4-42.7)	5.0
1980-1984	9	0.23	39.4	(18.0-74.9)	5.7

\*Excess risk per 1000 persons per year: (O-E)/(person-years at risk)×1000.

†Cancers are as follows: osteosarcoma, melanoma, and Hodgkin disease (2 each); soft tissue sarcoma, lymphoid leukemia, uterine carcinoma, and unspecified malignant neoplasm (1 each).

passed the lifetime risk of cancer for the general population.<sup>19</sup> These patients were at exceptionally high risk for sar-

coma, brain tumor, cutaneous melanoma, and pineoblastoma, as reported in prior studies that included subsets of the

Table 3.—Location of Sarcoma and Mean Dose of Radiation to Site of Sarcoma Occurrence in Cases and to Corresponding Body Areas in Controls\*

Second Cancer Site	Bone Sarcoma			Soft Tissue Sarcoma		
	No. (%)	Case (n=52)	Control† (n=89)	No. (%)	Case (n=31)	Control† (n=89)
		Mean Dose‡	Mean Dose‡		Mean Dose‡	Mean Dose‡
Skull, face	2 (3.8)	41.7	16.0	...	...	...
Orbit	15 (28.8)	56.0	46.0	8 (25.8)	45.2	35.8
Maxilla	11 (21.2)	27.5	14.9	3 (9.7)	24.4	13.2
Nasal region	7 (13.5)	31.7	23.3	7 (22.6)	23.9	12.3
Temporal region	1 (1.9)	6.0	8.5	5 (16.1)	7.9	7.0
Brain, frontal lobe	...	...	...	3 (9.6)	2.3	3.4
Brain, orbitofrontal	...	...	...	1 (3.2)	19.5	8.4
Upper trunk	1 (1.9)	0.3	0.6	1 (3.2)	0.3	0.4
Lower trunk	0	...	...	3 (9.7)	0.1	0.1
Legs	15 (28.8)	0.1	0.1	...	...	...
All sites	52	32.8	20.0	31	20.4	10.6

\*Ellipses indicate no cases and no controls in the category.  
 †Controls were selected randomly from among the bilateral retinoblastoma cohort members who were free of subsequent cancers. The same 89 subjects were used as controls for cases of bone and soft tissue sarcoma.  
 ‡Mean dose (Gy) to the site of tumor in cases and to the equivalent site in controls. For paired anatomic sites such as orbit, mean dose was the average of right- and left-side doses.

Table 4.—Risk of Bone and Soft Tissue Sarcoma by Radiation Dose to the Site of Tumor

Sarcoma Type	Radiation Dose, Gy				
	0-4.9	5.0-9.9	10.0-29.9	30.0-59.9	≥60.0
Soft tissue					
Median control dose, Gy*	1.6	7.2	19.3	39.6	82.8
No. of cases	9	4	10	5	3
No. of controls†	39	17	18	11	4
Odds ratio (95% confidence interval)‡	1.0§	1.6 (0.4-12.4)	4.6 (1.7-24.8)	6.4 (1.1-51.8)	11.7 (0.0-162)
Soft tissue and bone‖					
Median control dose, Gy*	1.7	7.2	19.6	40.1	97.7
No. of cases	12	8	20	13	14
No. of controls†	28	15	22	16	8
Odds ratio (95% confidence interval)‡	1.0§	1.9 (1.4-2.6)	3.7 (2.8-4.5)	4.5 (3.7-5.6)	10.7 (8.6-14.5)

\*Median of median doses in each dose category from 201 replicates of randomized "site-matched dose" assignments in controls.  
 †Median frequency for each dose category based on 201 replicates of randomized "site-matched dose" assignments in controls.  
 ‡Median of odds ratios from 201 replicates of randomized "site-matched dose" assignments in controls. Estimates were adjusted for age at retinoblastoma diagnosis and length of follow-up.  
 §Reference category.  
 ‖Sixteen osteosarcoma cases (1 in the upper trunk and 15 in the legs) were excluded from the dose-response analysis (see "Methods").

present series.<sup>2,5,7,8,20,25</sup> The 400-fold increase in bone cancer risk in the hereditary retinoblastoma patients is virtually identical to that reported for a smaller series of 439 patients with shorter follow-up (mean, 17.6 years).<sup>8</sup> The 22 cutaneous melanomas seen in the 190 subsequent cancers following hereditary retinoblastoma (12%) are within proportional frequencies of melanoma (3%-25%) reported in other follow-up surveys of hereditary retinoblastoma.<sup>4,5,25</sup> No statistically significant overall increase in cancer risk has been found in nonhereditary retinoblastoma cases in any study. These results indicate that germline mutations in the retinoblastoma gene exert a powerful carcinogenic effect on tissues other than the retina.

Previously we reported statistically significant elevated mortality from second cancers in unilateral retinoblastoma

patients in this series.<sup>2</sup> In the current study, however, unilateral patients were further classified as hereditary or nonhereditary by incorporating family history information. Overall cancer incidence was not statistically significantly elevated in nonhereditary patients, although isolated patients in this category might have unilateral retinoblastoma due to a new germline *RB1* mutation.<sup>1</sup> The current incidence study also extends our mortality study by 3 years of follow-up, with more than double the number of cancer cases.

Soft tissue sarcoma following radiotherapy for cancer is a recognized sequelae of exposure to high-dose radiation,<sup>26-29</sup> but a dose-response relationship has not been previously reported. The RRs for soft tissue sarcoma showed a stepwise increase with dose; however, statistically significant increase in risk

was not seen at tumor doses of 5 to 9.9 Gy or at 60 Gy or greater. Risk of all sarcomas combined was statistically significantly elevated at doses between 5 to 9.9 Gy (OR, 1.9) and at all higher dose categories. Notably, sarcomas have not been increased in populations exposed to much lower radiation levels, such as atomic bomb survivors<sup>30</sup> or tuberculosis patients examined repeatedly with x-ray fluoroscopy (dose, <1 Gy).<sup>31</sup> The risk per gray for development of sarcoma (19.1%) is lower than that estimated for most other forms of radiation-induced cancer (eg, risk per gray is >500% for leukemia).<sup>32</sup> No sarcomas occurred in unilateral (mostly nonhereditary) retinoblastoma patients, who had not been irradiated or received lower orbital radiation doses (mean bone dose in those irradiated, 33 Gy, vs 55 Gy in bilateral patients).

Although the dose-response pattern of risk for soft tissue sarcoma is similar to that previously observed for osteogenic sarcoma,<sup>7,8</sup> more bone sarcoma than soft tissue sarcoma was observed. This likely reflects higher absorbed doses in bone than soft tissue, and enhanced susceptibility to bone sarcoma conferred by *RB1* mutations, independent of radiotherapy. More than one fourth of bone sarcoma in retinoblastoma survivors occurred in the legs, where scatter doses were low (<0.5 Gy). No soft tissue sarcoma developed in the legs.

Excess cancer risk due to radiation was primarily limited to patients exposed to high doses administered decades ago. Highest doses to bone were delivered between 1937 and 1965, when average absorbed dose to orbital bone was 111 Gy in osteosarcoma cases. Orbital bone doses for retinoblastoma diagnosed after 1965 have declined to an average of 35 Gy because of use of higher-energy (MV) photon beams. The trend toward lower dose implies lower carcinogenic risk in more recently treated patients, although patients with hereditary retinoblastoma remain highly susceptible.

Sarcomas comprise the majority of subsequent primary cancers in this study, but are uncommon in the general population. Radiation-associated sarcomas are difficult to treat and often lethal.<sup>2,33</sup> The histopathologic classification of sarcoma is complex, and a range of diagnoses, including neuroectodermal tumor, have been assigned to subsequent sarcoma following hereditary retinoblastoma.<sup>3,27,34-36</sup> In the present study, cancers were classified according to data obtained from pathology, medical, and mortality records. An independent pathology review was not conducted since

many tumor specimens from past decades were no longer available and earlier pathology reviews of cancer specimens from our series underscored the difficulties in classification.<sup>3</sup>

Statistically significant elevated risk of Hodgkin disease in hereditary patients, and breast cancer in female patients have not been reported before. Four of the 6 women who developed breast cancer had received radiotherapy, with estimated breast doses ranging between 0.3 and 0.5 Gy. These breast doses resulted from close proximity to orbital radiation fields in small children; treatment with orthovoltage in years past produced much more scatter radiation than MV units in current use. Doses of this magnitude would be anticipated to double risk of breast cancer based on studies of infants given radiotherapy for enlarged thymus and women with tuberculosis monitored repeat-

edly with chest fluoroscopy.<sup>31,32</sup> The excess risk of Hodgkin disease and breast cancer need confirmation in other series of retinoblastoma survivors.<sup>4,5</sup>

Strengths of our study include large size of the cohort, extensive and nearly complete follow-up, including telephone interviews with patients, and verification of over 60% of subsequent cancers with pathology records. A comprehensive dosimetry evaluation program provided accurate and reproducible estimates of radiation dose to sites of subsequent cancers. However, as previously mentioned, difficulties were encountered in the estimation of radiation dose, and in the proper classification of tumors on the basis of topography, particularly for soft tissue sarcomas that can arise in diverse sites.

Inactivation of the *RB1* gene as a somatic (acquired) event is frequent in common cancers of adulthood, including car-

cinomas of the lung and bladder.<sup>37,38</sup> These cancers are not known to occur excessively in hereditary retinoblastoma survivors. However, few of our patients are older than 50 years, when rates for most epithelial cancers increase sharply.<sup>41</sup> Continued long-term follow-up will help elucidate the role of germline *RB1* mutations in cancers that commonly appear later in life, and may provide knowledge about interaction between low-dose scatter radiation and genetic susceptibility in cancer development.

Field work was supported by NCI contracts N01-CP-85604 and N02-CP-33013 to Westat, Inc.

We are indebted to the late Robert M. Ellsworth, MD, of the New York-Cornell Medical Center for his pioneering work in studying the New York cohort; Daniel Wilson and Elena Adrianza of Westat, Inc, for providing essential field and data-management support; David Hacker of Information Management Systems, Inc, for programming support; and Rita Weathers of the University of Texas, M. D. Anderson Cancer Center, for computer modeling of radiation doses.

## References

- Knudson AG Jr. Retinoblastoma: a prototypic hereditary neoplasm. *Semin Oncol.* 1978;5:57-60.
- Eng C, Li FP, Abramson DH, et al. Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst.* 1993;85:1121-1128.
- Roarty JD, McLean IW, Zimmerman LE. Incidence of second neoplasms in patients with bilateral retinoblastoma. *Ophthalmology.* 1988;95:1583-1587.
- Moll AC, Imhof SM, Bouter LM, et al. Second primary tumors in patients with hereditary retinoblastoma: a register-based follow-up study, 1945-1994. *Int J Cancer.* 1996;67:515-519.
- Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. *Br J Cancer.* 1986;53:661-671.
- Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature.* 1986;323:642-646.
- Tucker MA, D'Angio GJ, Boice JD Jr, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med.* 1987;317:588-593.
- Hawkins MM, Wilson LM, Burton HS, et al. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst.* 1996;88:270-278.
- World Health Organization. *ICD-O: International Classification of Diseases for Oncology.* Geneva, Switzerland: World Health Organization; 1976.
- Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res.* 1969;105:529-535.
- Heston JF, Kelly JAB, Meigs JW, Flannery JT, Cusano MM, Young JL Jr. Forty-five years of cancer incidence in Connecticut: 1935-79. *Natl Cancer Inst Monogr.* 1986;70:1-706.
- Boice JD Jr, Storm HH, Curtis RE, et al, eds. Multiple primary cancers in Connecticut and Denmark. *Natl Cancer Inst Monogr.* 1985;68:1-434.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
- Preston DL, Lubin JH, Pierce DA. *Epicure User's Guide.* Seattle, Wash: Hirosoft International; 1991.
- Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci.* 1986;1:54-77.
- Stovall M, Smith SA, Rosenstein M. Tissue doses from radiotherapy of cancer of the uterine cervix. *Med Phys.* 1989;16:726-733.
- Pesin SR, Shields JA. Seven cases of trilateral retinoblastoma. *Am J Ophthalmol.* 1989;107:121-126.
- Young JL, Ries LG, Silverberg E, Horm JW, Miller RW. Cancer incidence, survival, and mortality for children younger than age 15 years. *Cancer.* 1986;58:598-602.
- Young JL, Perry CL, Asine AJ, eds. Surveillance, epidemiology and end results; incidence and mortality data. *Natl Cancer Inst Monogr.* 1981;57:70-73.
- Abramson DH, Ellsworth RM, David F, Tung G. Second non-ocular tumors in retinoblastoma survivors. *Ophthalmology.* 1984;91:1351-1355.
- DerKinderen DJ, Koten JW, Wolterbeek R, Beemer FA, Tan KE, Den Otter W. Non-ocular cancer in hereditary retinoblastoma survivors and relatives. *Ophthalm Paediatr Genet.* 1987;8:23-25.
- Francois J, de Sutter E, Coppieters R, de Bie S. Late extraocular tumours in retinoblastoma survivors. *Ophthalmologica.* 1980;181:93-99.
- Winther J, Olsen JH, de Nully Brown P. Risk of nonocular cancer among retinoblastoma patients and their parents: a population-based study in Denmark, 1943-1984. *Cancer.* 1988;62:1458-1462.
- Bader JL, Meadows AT, Zimmerman LE, et al. Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. *Cancer Genet Cytogenet.* 1982;5:203-213.
- Traboulsi EI, Zimmerman LE, Manz HJ. Cutaneous malignant melanoma in survivors of heritable retinoblastoma. *Arch Ophthalmol.* 1988;106:1059-1061.
- Meadows AT, Baum E, Fossati-Bellani F. Second malignant neoplasms in children: an update from the Late Effects Study Group. *J Clin Oncol.* 1985;3:592-598.
- Laskin WB, Silverman TA, Enzinger FM. Post-radiation soft tissue sarcomas: an analysis of 53 cases. *Cancer.* 1988;62:2330-2340.
- Ruka W, Sikorowa L, Iwanowska J, Romeyko M. Induced soft tissue sarcomas following radiation treatment for uterine carcinomas. *Eur J Surg Oncol.* 1991;17:585-593.
- Kony SJ, de Vathaire F, Chompret A, et al. Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. *Lancet.* 1997;350:91-95.
- Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors, part II: solid tumors, 1958-1987. *Radiat Res.* 1994;137:S17-S67.
- Davis FG, Boice JD Jr, Hrubec Z, Monson RR. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res.* 1989;49:6130-6136.
- United Nations Scientific Committee on the Effects of Atomic Radiation. *UNSCEAR 1994 Report to the General Assembly, With Scientific Annexes: Sources and Effects of Ionizing Radiation.* New York, NY: United Nations; 1994: Vol E.94.IX.11.
- Robinson E, Neugut AI, Wylie P. Clinical aspects of postirradiation sarcomas. *J Natl Cancer Inst.* 1988;80:233-240.
- Klein EA, Anzil AP, Mezzacappa P, Borderon M, Ho V. Sinonasal primitive neuroectodermal tumor arising in a long-term survivor of heritable unilateral retinoblastoma. *Cancer.* 1992;70:423-431.
- Schifter S, Vendelbo L, Jensen OM, Kaae S. Ewing's tumor following bilateral retinoblastoma: a case report. *Cancer.* 1983;51:1746-1749.
- Folberg R, Cleasby G, Flanagan JA, Spencer WH, Zimmerman LE. Orbital leiomyosarcoma after radiation therapy for bilateral retinoblastoma. *Arch Ophthalmol.* 1983;101:1562-1565.
- Horowitz JM, Park SBH, Bogenmann E, et al. Frequent inactivation of the retinoblastoma anti-oncogene is restricted to a subset of human tumor cells. *Proc Natl Acad Sci U S A.* 1990;87:2775-2779.
- Xu HB, Hu SBX, Cagle PT, Moore GE, Benedict WF. Absence of retinoblastoma protein expression in primary non-small cell lung carcinomas. *Cancer Res.* 1991;51:2735-2739.