ARTICLES

Lifetime Risks of Common Cancers Among Retinoblastoma Survivors

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Background: **Compared with the general population, carriers of germline mutations in RB1 who survive retinoblastoma (i.e., hereditary retinoblastoma survivors) are at increased risk of early-onset second cancers, particularly sarcomas, brain tumors, and melanoma. However, their risks for the epithelial cancers that commonly occur after age 50 years are not known.** ***Methods:*** **We used hospital records to identify British retinoblastoma survivors born between 1873 and 1950, a period when few British retinoblastoma patients received high-dose radiotherapy. Cancers and deaths were identified by linkage with national registration records. All statistical tests were two-sided.** ***Results:*** **We could trace the cancer histories of 144 survivors of hereditary retinoblastoma. From age 25 to age 84, there were 58 subsequent cancers, for a cumulative cancer incidence of 68.8% (95% confidence interval [CI] = 48.0% to 87.4%) and a cumulative cancer mortality of 56.3% (95% CI = 40.5% to 73.3%). Only eight of the 58 cancers were of bone or soft tissue, in marked contrast to findings from contemporary studies of American patients treated with external beam radiotherapy, among whom most second tumors are sarcomas. Compared with the general population, hereditary retinoblastoma survivors had higher mortality from lung cancer (standardized mortality ratio [SMR] = 7.01, 95% CI = 3.83 to 11.76), bladder cancer (SMR = 26.31, 95% CI = 8.54 to 61.41), and all other epithelial cancers combined (SMR = 3.29, 95% CI = 1.64 to 5.89). The overall standardized mortality ratio for epithelial cancer was inversely proportional to the approximate square of age (exponent of age = –2.1, 95% CI = –3.6 to –0.7), declining from 11.32 (95% CI = 4.15 to 24.64) at age 25– 44 to 2.83 (95% CI = 1.04 to 6.16) at age 65–84.** ***Conclusions:*** **Survivors of hereditary retinoblastoma who are not exposed to high-dose radiotherapy have a high lifetime risk of developing a late-onset epithelial cancer. Most of the excess cancer risks in hereditary retinoblastoma survivors might be preventable by limiting exposures to DNA damaging agents (radiotherapy, tobacco, and UV light). [J Natl Cancer Inst 2004;96:357–63]**

Retinoblastoma is a rare childhood tumor that arises in the retina of one (unilateral) or both (bilateral) eyes and can occur with (i.e., familial retinoblastoma) or without (i.e., sporadic retinoblastoma) a family history of the disease. Inactivating mutations in the RB1 gene are critical for the development of these tumors *(1)*. Bilateral retinoblastoma arises when a germline mutation in one copy of RB1 is followed by the somatic loss of, or a mutation in, the remaining wild-type copy. Although most patients with unilateral sporadic disease acquire somatic mutations in both copies of RB1, some patients carry a new germline mutation in one copy and acquire a somatic mutation in the other copy.

The protein encoded by RB1, p105 Rb, functions in multiple cellular processes, including proliferation, DNA replication, DNA repair, and cell-cycle checkpoint control *(2)*. The mouse homolog of human RB1 is highly expressed during embryogenesis in the lens of the eye, the developing nervous system, blood cells, and skeletal muscle *(3,4)*, and is ubiquitously expressed in adult animals. During the cell cycle, p105 Rb is phosphorylated by the cyclin D–cyclin-dependent kinase (CDK)4 and cyclin D–CDK6 complexes, whose activities are themselves regulated by a family of polypeptide inhibitors, which includes p16^{INK4a} *(5)*.

p105 Rb and the proteins that interact with it appear to play roles in many other cancers. Mutations in RB1 or altered expression of p105 Rb have been found in many sarcomas *(6–8)*, small-cell lung and bladder cancer cell lines *(9)*, primary breast tumors *(10)*, glioblastomas *(11)* and, less frequently, in various other cancers. Overexpression of cyclin D1 or CDK4 and loss of function of p16^{INK4a} have been found in a range of human tumors *(12–14)*, and truncating mutations in RB1CC1, the gene encoding a putative transcription factor that induces expression of RB1, have been reported in breast cancer *(15)*. The transforming proteins adenovirus E1A, simian virus 40 (SV40) T antigen, and human papillomavirus (HPV) E7 all bind to and inactivate p105 Rb *(2)*.

The combined results of previous cohort studies suggest that hereditary retinoblastoma survivors have increased risks of various soft-tissue sarcomas, osteosarcoma, melanoma, and brain cancer *(16)* and, possibly, an excess of lung cancers *(17–19)*, compared with the general population. However, there have been no reports of a general excess of epithelial cancers among hereditary retinoblastoma survivors, leading Ponten *(20)* to suggest that most stem cells use alternative mechanisms to compensate for the loss of p105 Rb function. However, there is little information available about the overall cancer rates among RB1

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carriers who are older than 50 years because of limited follow-up in the existing cohorts of hereditary retinoblastoma survivors beyond this age. We have followed a cohort of British retinoblastoma survivors who were born between 1873 and 1950, a period when few British patients received high-dose radiotherapy, to determine their lifelong cancer incidence and mortality.

METHODS

We abstracted information about 726 British retinoblastoma survivors who were born between 1873 and 1950 from records held at Moorfields Eye Hospital (n = 686; London, U.K.), Birmingham Eye Hospital (n = 36; Birmingham, U.K.), and the Royal Victoria Infirmary (n = 4; Newcastle, U.K.). British retinoblastoma survivors who were born after 1950 have been studied separately *(21)*. Retinoblastoma survivors were classified on the basis of their clinical records as either unilateral or bilateral, and as either familial (any recorded family history of retinoblastoma) or apparently sporadic (no known family history). Although the majority of patients with bilateral retinoblastoma carry a germline RB1 mutation, many have no family history because they have acquired new germline mutations in RB1. For the purposes of this study, we classified all survivors of bilateral retinoblastoma and survivors of unilateral retinoblastoma with a positive family history as hereditary retinoblastoma survivors.

The cohort was flagged for continuing notification of mortality, cancer incidence, and emigration through the National Health Service Central Register (NHSCR). The NHSCR is a register of everyone in England and Wales who has ever been registered with an NHS general practitioner and includes virtually all residents. The NHSCR routinely traces and records all cancer registrations and deaths among flagged individuals (including those who have moved to Scotland) as well as permanent emigration. Follow-up for mortality in the NHSCR began on January 1, 1940, after the establishment of the national register on which the NHSCR was based. We calculated the expected numbers of deaths from cancer and from other causes by using the quinquennial age and calendar-specific rates for England and Wales, which are published annually by the Office for National Statistics (http://www.statistics.gov.uk). Follow-up for cancer incidence began on January 1, 1971, when national cancer registration was linked to the NHSCR. We used the date of death as the date of diagnosis for nine cancer deaths in 1971 or later that had no corresponding cancer registration. The earliest of these deaths was in 1981; it is unlikely that any of these individuals had been diagnosed with a second cancer before 1971. All individuals were censored at age 85, at emigration, or on December 31, 1999, whichever came first. Subjects who developed two primary cancers were censored after their first cancer registration. Subjects with *in situ* carcinomas and benign tumors, including one bladder tumor of uncertain behavior and one of unspecified nature, were excluded from the analysis. Mortality and cancer incidence were analyzed only from age 25. Most of the subjects in our cohort were born before 1946 and, hence, had no systematic follow-up for cancer registration before age 25.

Statistical Analysis

We used Poisson regression to model the dependence of cancer rates on age. Standardized mortality ratios (SMRs) are given with exact Poisson 95% confidence intervals (CIs). Cumulative risks for cancer incidence and mortality in the absence of other causes of death were calculated by the Kaplan–Meier method *(22)* with confidence intervals that were based on the modification of Greenwood's formula described by Kalbfleisch and Prentice *(23)*. All statistical significance tests were two-sided. All analyses were carried out using Stata statistical software (version 7.0; Stata Corporation, College Station, TX).

RESULTS

Table 1 summarizes characteristics of the cohort. We excluded 225 of the 726 subjects because they could not be traced in the NHSCR either because of an incomplete name or date of birth or because the subject had died in 1939 or earlier (i.e., before the NHSCR was established). We also excluded 37 subjects who had died in 1940 or later but before reaching the age of 25 years, including 31 subjects who died of retinoblastoma, and 13 subjects who were removed from the NHSCR before age 25, while still alive, usually at emigration. All of our analyses were based on follow-up of the remaining 451 individuals from age 25; 82 (18.2%) subjects were born from 1873 through 1919, 158 (35.0%) subjects were born from 1920 through 1939, and 211 (46.8%) subjects were born from 1940 through 1950. The median age at end of follow-up (i.e., December 31, 1999 or age 85) was 60 years (range = 49–85 years) for the hereditary retinoblastoma survivors and 61 years (range = 49–85 years) for the unilateral sporadic retinoblastoma survivors. There were in total 144 hereditary retinoblastoma survivors and 307 sporadic retinoblastoma survivors.

Mortality from cancer and other causes is shown in Table 2. Survivors of hereditary retinoblastoma had a greater than five-fold excess in overall cancer mortality compared with that in the general population (SMR = 5.41, 95% CI = 3.88 to 7.34).

Table 1. Characteristics of the cohort

| Characteristic | Sporadic retinoblastoma survivors | Hereditary retinoblastoma survivors | | | |
	Unilateral sporadic	Unilateral familial	Bilateral sporadic	Bilateral familial	Total
Original cohort, No. (%)	499 (100)	36 (100)	116 (100)	75 (100)	726 (100)
Male	262 (52.5)	23 (63.9)	60 (51.7)	33 (44.0)	378 (52.1)
Female	237 (47.5)	13 (36.1)	56 (48.3)	42 (56.0)	348 (47.9)
Traced cohort*, No. (%)	307 (100)	21 (100)	60 (100)	63 (100)	451 (100)
Male	169 (55.0)	15 (71.4)	29 (48.3)	26 (41.3)	239 (53.0)
Female	138 (45.0)	6 (28.6)	31 (51.7)	37 (58.7)	212 (47.0)

*Subjects alive and registered in the National Health Service Central Register at age 25 or older on or after January 1, 1940.

Table 2. Numbers of observed (O) and expected (E) deaths and standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) for all cancers, epithelial cancers, and other causes among survivors of hereditary and sporadic retinoblastoma, by age and sex

	Unilateral sporadic retinoblastoma survivors			Hereditary retinoblastoma survivors*		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)
All cancers						
Sex						
Male	19	15.79	1.20 (0.77 to 1.89)	22	4.41	4.99 (3.13 to 7.55)
Female	10	7.80	1.28 (0.69 to 2.38)	19	3.17	5.99 (3.61 to 9.36)
Total	29	23.59	1.23 (0.85 to 1.77)	41	7.58	5.41 (3.88 to 7.34)
Other causes						
Male	35	43.50	0.80 (0.58 to 1.12)	11	11.14	0.99 (0.55 to 1.78)
Female	5	14.86	0.34 (0.14 to 0.81)	4	4.87	0.82 (0.31 to 2.19)
Total	40	58.36	0.69 (0.50 to 0.93)	15	16.01	0.94 (0.56 to 1.55)
All cancers						
Age, y						
25–34	0	0.46	0.00 (0.00 to 8.02)	4	0.23	17.64 (4.81 to 45.16)
35–44	6	1.44	4.17 (1.53 to 9.10)	9	0.67	13.45 (6.15 to 25.53)
45–54	7	4.23	1.66 (0.67 to 3.41)	13	1.70	7.67 (4.08 to 13.11)
55–64	4	6.70	0.60 (0.16 to 1.53)	9	2.18	4.13 (1.89 to 7.83)
65–74	6	6.84	0.88 (0.32 to 1.92)	5	1.94	2.58 (0.84 to 6.02)
75–84	6	3.92	1.53 (0.56 to 3.33)	1	0.87	1.15 (0.03 to 6.41)
25–84	29	23.59	1.23 (0.85 to 1.77)	41	7.58	5.41 (3.88 to 7.34)
Epithelial cancers†						
25–34	0	0.18	0.00 (0.00 to 20.49)	1	0.09	10.67 (0.27 to 59.45)
35–44	3	0.93	3.21 (1.04 to 9.95)	5	0.44	11.39 (4.74 to 27.37)
45–54	5	3.07	1.63 (0.53 to 3.80)	11	1.24	8.88 (4.92 to 16.03)
55–64	3	5.06	0.59 (0.19 to 1.84)	7	1.65	4.25 (2.03 to 8.92)
65–74	5	5.27	0.95 (0.40 to 2.28)	5	1.48	3.38 (1.41 to 8.12)
75–84	5	3.02	1.66 (0.54 to 3.87)	1	0.64	1.57 (0.22 to 11.14)
25–84	21	17.53	1.20 (0.74 to 1.83)	30	5.54	5.42 (3.65 to 7.73)

*Includes unilateral familial retinoblastoma, bilateral familial retinoblastoma, and bilateral sporadic retinoblastoma.

†Includes cancer of the tongue and mouth, pharynx, esophagus, stomach, colon, rectum, larynx, lung, breast, ovary, cervix, corpus uteri, bladder, kidney, prostate, and nonmelanoma skin cancer.

Survivors of unilateral sporadic retinoblastoma had a standardized mortality ratio of 1.23 for all cancers (95% CI = 0.85 to 1.77) and fewer than expected deaths from nonmalignant causes (SMR = 0.69, 95% CI = 0.50 to 0.93). Age-specific standardized mortality ratios for all cancers and for the major epithelial cancers combined are shown in Table 2. Poisson regression modeling showed that, among hereditary retinoblastoma survivors, the death rate for epithelial cancers increased approximately as the third power of age (estimated exponent = 3.3, 95% CI = 1.9 to 4.7). By contrast, the mortality rate for epithelial cancers in the general population increases approximately as the fifth power of age *(24)*. Thus, the overall standardized mortality ratio for epithelial cancers among hereditary retinoblastoma survivors was inversely proportional to the approximate square of age (exponent of age = –2.1, 95% CI = –3.6 to –0.7), declining from 11.32 (95% CI = 4.15 to 24.64) at ages 25–44 to 2.83 (95% CI = 1.04 to 6.16) at ages 65–84 (Table 2).

Table 3 presents the cancer site–specific mortality data for survivors of sporadic and hereditary retinoblastoma. Compared with the general population, survivors of hereditary retinoblastoma had, as expected, higher mortality from cancers of the bone (SMR = 32.36, 95% CI = 0.82 to 180.31) and soft tissue (SMR = 109.95, 95% CI = 29.94 to 281.37), melanoma (SMR = 23.29, 95% CI = 2.82 to 84.11), and cancers of the brain and central nervous system (SMR = 6.60, 95% CI = 0.80 to 23.84). They also had higher mortality from lung cancer (SMR = 7.01, 95% CI = 3.83 to 11.76), bladder cancer (SMR = 26.31, 95% CI = 8.54 to 61.41), and all other epithelial cancers combined (11 deaths, SMR = 3.29, 95% CI = 1.64 to 5.89), including a possible excess of breast cancer (SMR = 3.65, 95% CI = 0.75 to 10.66; P = .10). Compared with the general population, survivors of unilateral sporadic retinoblastoma had statistically significantly higher mortality from cancers of soft tissue (SMR = 30.79, 95% CI = 6.12 to 86.72) and the testis (SMR = 27.87, 95% CI = 3.33 to 99.24) but similar overall cancer mortality (SMR = 1.23, 95% CI = 0.85 to 1.77) (Table 3). Their cancer mortality prior to age 45 (six deaths, versus 1.90 expected) consisted of three sarcomas and three lung cancers.

Fig. 1 and Table 4 show the cumulative incidence and mortality for the 43 second cancers diagnosed in 1971 or later among survivors of hereditary retinoblastoma and unilateral sporadic retinoblastoma. Survivors of hereditary retinoblastoma had cumulative risks from age 25 to 84 of 56.3% (95% CI = 40.5% to 73.3%) for cancer mortality and 68.8% (95% CI = 48.0% to 87.4%) for cancer incidence. Details of all 58 cancers diagnosed among the hereditary retinoblastoma survivors at age 25 years or older are listed in the footnote to Table 4. These 58 cancers included nine in patients who died before 1971 and six that were third incident cancers. The primary cancer sites or types were lung (14 cancers), bladder (five cancers), breast (seven cancers), sarcoma (six cancers), nonmelanoma skin (four cancers), melanoma (three cancers), brain (three cancers), bone (two cancers), uterus (two cancers), ovary (two cancers), prostate (two cancers), unspecified (two cancers), and one cancer each of the esophagus, colon, rectum, nasal cavities, testis, and cervix. The overall cumulative cancer rate among hereditary retinoblastoma

Table 3. Site- or type-specific cancer mortality of sporadic and hereditary retinoblastoma survivors*

Cancer site or type	Unilateral sporadic retinoblastoma survivors			Hereditary retinoblastoma survivors		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Tongue and mouth†	0	0.15	0.00 (0.00 to 24.59)	0	0.04	0.00 (0.00 to 92.20)
Pharynx†	1	0.13	7.65 (0.19 to 42.86)	0	0.04	0.00 (0.00 to 92.20)
Esophagus†	1	0.77	1.30 (0.03 to 7.24)	1	0.23	4.32 (0.11 to 24.05)
Stomach†	1	1.86	0.54 (0.01 to 3.00)	0	0.50	0.00 (0.00 to 7.36)
Colon†	1	1.68	0.60 (0.02 to 3.32)	1	0.51	1.97 (0.05 to 10.97)
Rectum†	0	0.99	0.00 (0.00 to 3.73)	1	0.28	3.55 (0.09 to 19.76)
Larynx†	1	0.19	5.30 (0.13 to 29.32)	0	0.05	0.00 (0.00 to 73.76)
Lung†	10	6.54	1.53 (0.73 to 2.81)	14	2.00	7.01 (3.83 to 11.76)
Breast†	2	1.94	1.03 (0.13 to 3.72)	3	0.82	3.65 (0.75 to 10.66)
Ovary†	1	0.61	1.65 (0.04 to 9.13)	1	0.26	3.88 (0.10 to 21.63)
Cervix†	1	0.34	2.93 (0.07 to 16.39)	1	0.16	6.43 (0.16 to 35.83)
Corpus uteri†	0	0.12	0.00 (0.00 to 30.73)	1	0.05	20.78 (0.53 to 115.83)
Bladder†	0	0.70	0.00 (0.00 to 5.27)	5	0.19	26.31 (8.54 to 61.41)
Kidney†	1	0.43	2.35 (0.06 to 12.96)	0	0.14	0.00 (0.00 to 26.34)
Prostate†	0	1.00	0.00 (0.00 to 3.69)	1	0.24	4.09 (0.10 to 22.81)
Testis	2	0.07	27.87 (3.33 to 99.24)	0	0.03	0.00 (0.00 to 122.93)
Brain and central nervous system	1	0.81	1.24 (0.03 to 6.83)	2	0.30	6.60 (0.80 to 23.84)
Hematologic	0	1.62	0.00 (0.00 to 2.27)	0	0.57	0.00 (0.00 to 6.47)
Bone	0	0.09	0.00 (0.00 to 40.98)	1	0.03	32.36 (0.82 to 180.31)
Soft tissue	3	0.10	30.79 (6.12 to 86.72)	4	0.04	109.95 (29.94 to 281.37)
Melanoma	1	0.23	4.50 (0.11 to 24.36)	2	0.09	23.29 (2.82 to 84.11)
Nonmelanoma skin†	1	0.06	15.54 (0.42 to 92.86)	1	0.02	58.49 (1.48 to 325.83)
Primary site unspecified	1	1.36	0.74 (0.02 to 4.10)	2	0.45	4.46 (0.54 to 16.12)
Other cancers	0	1.80	0.00 (0.00 to 2.05)	0	0.62	0.00 (0.00 to 5.95)
All neoplasms	29	23.59	1.23 (0.85 to 1.77)	41	7.58	5.41 (3.88 to 7.34)
Other causes	40	58.36	0.69 (0.50 to 0.93)	15	16.01	0.94 (0.56 to 1.55)
All causes	69	81.95	0.84 (0.67 to 1.07)	56	23.59	2.37 (1.83 to 3.09)

*O = observed; E = expected; SMR = standardized mortality ratio; CI = confidence interval.

†Epithelial cancers considered in Table 2. Histologic details of the 30 epithelial cancer deaths among hereditary retinoblastoma survivors are as follows: lung (n = 14): carcinoma not otherwise specified (5), oat cell carcinoma (2), small-cell carcinoma (1), alveolar adenocarcinoma (1), no histology (5); bladder (n = 5): carcinoma not otherwise specified (2), urothelial carcinoma (1), well-differentiated squamous cell carcinoma (1), no histology (1); esophagus (n = 1): carcinoma not otherwise specified; colon (n = 1): neoplasm, malignant; rectum (n = 1): adenocarcinoma carcinoma not otherwise specified; breast (n = 3): carcinoma not otherwise specified (1), lobular carcinoma not otherwise specified (1), spheroidal cell carcinoma (1); ovary (n = 1): no histology; cervix (n = 1): no histology; uterus (n = 1): adenocarcinoma not otherwise specified; prostate (n = 1): adenocarcinoma not otherwise specified; nonmelanoma skin cancer (n = 1): squamous cell carcinoma.

survivors included three diagnoses of nonfatal nonmelanoma skin cancers. Exclusion of these three cancers would have had only a small effect on the overall rate, because two of the three patients developed a third primary cancer (one bone cancer and one bladder cancer).

DISCUSSION

The aim of our study was to examine adult cancer risks among survivors of hereditary retinoblastoma. In childhood and early adulthood, these individuals have a high incidence of radiogenic sarcomas of bone and soft tissue (16,25). The incidence of these cancers is strongly associated with the dose of radiotherapy used to treat their retinoblastoma and therefore varies by almost an order of magnitude both between (21) and within (26) different patient cohorts, depending on the radiation dose and the proportion exposed. The high incidence of cancers at nonirradiated sites (i.e., sites distant from the head) in our cohort suggests that survivors of hereditary retinoblastoma also have a high lifetime risk of cancer in adulthood, irrespective of whether the individual was treated with radiotherapy. Although results of several studies and case reports (17–19,27) have suggested that RB1 mutation carriers may have an increased risk of lung cancer compared with the general population, this study is the first cohort study with long enough follow-up to quantify the lifetime risks of epithelial cancers among retinoblastoma survivors.

The radiotherapy methods and doses used to treat retinoblastoma patients have differed widely between the United Kingdom and the United States. Although individual treatment details were not available for our cohort, most retinoblastoma patients in the United Kingdom did not receive radiotherapy during the 1930s and 1940s (28), and those who did were usually treated with implanted radon seeds or, after 1948, with radioactive scleral plaques that were placed next to the tumor (29). The short- and long-term side effects of external irradiation, including case reports of sarcomas of irradiated bone or muscle, led Stallard (29) to conclude in 1952 that radioactive scleral plaques were the best treatment for tumors covering less than one-third of the retina, and this treatment has remained the primary treatment for most localized retinoblastomas (30). By contrast, almost 90% of retinoblastoma patients in the large U.S. cohort studied by Wong et al. (26) were treated with external radiotherapy, and many of those patients received very high doses of radiation, particularly between 1937 and 1965, when the mean orbital dose among patients who later developed osteosarcoma was 111 Gy (26).

There appears to be a striking difference in the contribution of epithelial cancers at nonirradiated sites between our cohort and those from centers or countries where external beam irradiation was widely used, although the age-specific incidence rates may be similar. Only seven (4%) of the 190 incident tumors diagnosed among hereditary retinoblastoma survivors in the large

Fig. 1. Cumulative incidence of and mortality from second incident cancers among hereditary and sporadic retinoblastoma survivors from age 25 through 84 years. Includes 43 second incident cancers among hereditary retinoblastoma survivors. Excludes six subsequent (i.e., third) cancers and nine cancer deaths before 1971. HRS = hereditary retinoblastoma survivors; SRS = sporadic retinoblastoma survivors.
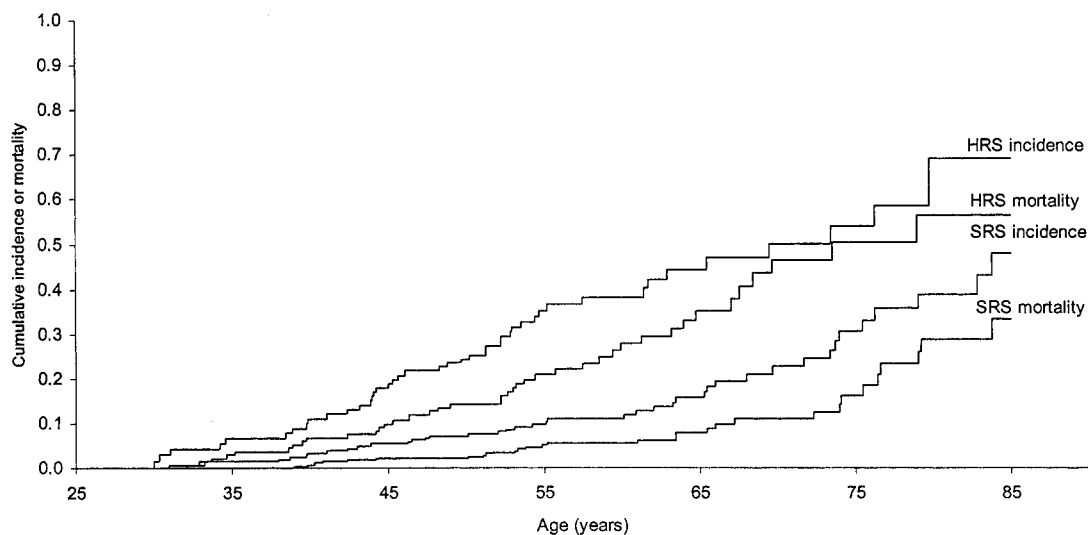
U.S. study reported by Wong et al. *(26)* were carcinomas not originating in the head (two each of breast, colon, and uterine cancer and one bladder cancer), whereas 26 (60%) of the 43 incident tumors (excluding skin cancers) diagnosed among our cohort since 1971 were carcinomas that did not originate in the head. This difference is due largely to the much higher incidence of radiogenic cancers, particularly sarcomas, in the U.S. cohort, but it also reflects the older age range spanned by the follow-up of our cohort. Our cancer incidence data for hereditary retinoblastoma survivors younger than 25 years were too incomplete for useful analysis. However, the 94 hereditary retinoblastoma survivors born in 1940 or later were all followed up for mortality from birth, and there was only one cancer death in an individual younger than 25 years that was not due to retinoblastoma (a peritoneal cancer in an 18-year-old). In our cohort, only three sarcomas were diagnosed among the hereditary retinoblastoma survivors between the ages of 25 and 44 years (including one

sarcoma diagnosed 2 years after an ovarian cancer diagnosis), corresponding to a cumulative risk of sarcoma by age 45 of only 4%. By contrast, the cumulative second cancer incidence among hereditary retinoblastoma survivors in the U.S. cohort was 20% by age 25 and 44% by age 45, and 115 (61%) of the 190 second cancers were sarcomas *(26)*.

The high incidence of cancers at nonirradiated sites that we observed in the older hereditary retinoblastoma survivors in our cohort seems unlikely to be an effect of treatment. They had a low incidence of radiogenic tumors, and they were treated before the introduction of chemotherapy. It was recognized many years ago that retinoblastoma patients who did not receive radiotherapy have increased risks for melanoma and osteogenic sarcoma and that retinoblastoma patients who did receive radiotherapy have increased risks for these cancers at nonirradiated sites *(21)*. Apart from sarcomas, melanoma was the most common type of second primary tumor diagnosed among retinoblastoma survi-

Table 4. Cumulative incidence of and mortality from second cancers among sporadic and hereditary retinoblastoma survivors at ages 25–84 years*

Age group, y	Person-years since January 1, 1940	No. of cancer deaths	Death rate per 1000 person-years	Cumulative cancer mortality at end of interval, % (95% CI)	Person-years since January 1, 1940	Second incident cancers	Incidence rate per 1000 person years	Cumulative cancer incidence at end of interval, % (95% CI)
Hereditary retinoblastoma survivors								
25–34	1312	4	3.0	3.0 (1.1 to 7.8)	633	5	7.9	6.8 (2.9 to 15.5)
35–44	1266	9	7.1	9.7 (5.7 to 16.1)	861	11	12.8	17.9 (11.3 to 27.5)
45–54	1046	13	12.4	20.8 (14.6 to 29.1)	761	17	22.3	35.1 (26.4 to 45.8)
55–64	493	9	18.3	35.2 (25.8 to 46.8)	332	5	15.0	44.2 (33.9 to 56.1)
65–74	192	5	26.0	50.1 (36.9 to 64.9)	155	3	19.4	53.7 (40.8 to 67.7)
75–84	54	1	18.5	56.3 (40.5 to 73.3)	48	2	41.5	68.8 (48.0 to 87.4)
Unilateral sporadic retinoblastoma survivors								
25–34	2635	0	0.0	0.0	1244	2	1.6	1.4 (0.3 to 5.5)
35–44	2780	6	2.2	2.1 (1.0 to 4.7)	1922	8	4.2	5.3 (2.9 to 9.7)
45–54	2593	7	2.7	5.0 (2.9 to 8.5)	1959	9	4.6	9.7 (6.2 to 14.8)
55–64	1466	4	2.7	7.7 (4.8 to 12.5)	1052	7	6.7	15.6 (10.7 to 22.5)
65–74	670	6	9.0	16.1 (10.0 to 25.3)	481	9	18.7	30.4 (21.5 to 42.0)
75–84	240	6	25.0	33.2 (21.2 to 49.4)	186	5	26.9	47.7 (33.3 to 64.4)

*Cancer site or type (number: sex [m = male, f = female], age at diagnosis or at death, in years) for 43 second incident cancers among hereditary retinoblastoma survivors: esophagus (1: m62), colon (1: m43), rectum (1: m65), nasal cavities (1: f51), lung (9: m34, f43, m44, m45, m48, m52, f54, m57, m61), bone (1: m30), sarcoma (3: f39, m45, m48), melanoma (3: f31, f42, m52), nonmelanoma skin (4: m46, m50, m54, f61), breast (6: f≤38, f41, f43, f49, f52, f76), uterus (2: f53, f52), ovary (1: f30), prostate (2: m69, m79), testis (1: m55), bladder (3:f45, m51, m73), brain (3: f39, m34, m44), unspecified primary (1: m38). Six subsequent (i.e., third) cancers were censored in Table 4: sarcoma (2: f32, f59), breast (1: f57), lung (1: f38), bladder (1: f67), bone (1: m59). Nine cancer deaths before 1971 were excluded from incidence rates in Table 4: lung (4: m46, m52, f59, f63), sarcoma (1: f38), cervix (1: f65), ovary (1: f33), bladder (1: m55), unspecified primary (1: f61).

vors in the studies reviewed by Moll et al. *(16).* Various authors *(20,26,31)* have commented that the virtual absence of lung and bladder cancers among previous cohorts of retinoblastoma survivors seems surprising, considering the high rate of somatic RB1 inactivation in these tumor types. However, Wong et al. *(26)* cautioned that few members of their cohort had yet been followed to age 50, and Kleinerman et al. *(19)* subsequently reported five lung cancer deaths among that cohort after a further 7 years of follow-up. The youngest survivors in our cohort were at least 49 years old by the end of follow-up, and 19 (33%) of the 58 incident cancers in the hereditary retinoblastoma survivors originated in the lung (14 cases) or bladder (five cases). We observed a statistically significant increase in mortality from lung cancer (SMR = 7.01), bladder cancer (SMR = 26.31), all other major epithelial cancers combined (SMR = 3.29), and melanoma (SMR = 23.29). The epithelial cancer category included three breast cancer deaths (SMR = 3.65; P = .10). In addition, there were four nonfatal breast cancers, including one that had not been registered in the NHSCR but was mentioned on a death certificate that noted lung cancer as the cause of death and one that was diagnosed 6 years after the diagnosis of a nasal cavity tumor. Horowitz et al. *(9)* found aberrant p105 Rb1 expression in 31 of 32 small-cell lung cancer cell lines, in six of 16 bladder cancer cell lines, and in two of 10 breast cancer cell lines. Thus, in the general population, somatic RB1 mutation is common in the same types of epithelial cancer that show the largest excesses among survivors of hereditary retinoblastoma.

A germline genetic defect that reduces the number of rate-limiting steps in multistage carcinogenesis was proposed by Ashley *(32)* to explain why the incidence of colon cancer increases as the fifth power of age in the general population but only as the third or fourth power of age in polyposis coli patients. Likewise, germline loss or inactivation of one copy of RB1 bypasses one of the critical somatic events in carcinogenesis, so the standardized mortality ratio for cancer among hereditary retinoblastoma survivors might be expected to be inversely proportional to age. Our observation of an approximately quadratic decline in the standardized mortality ratio for epithelial cancers with increasing age may be due, at least in part, to heterogeneity of risk among RB1 mutation carriers resulting in the progressive elimination of those at highest risk from the surviving population. Heterogeneity of risk is likely to arise from differences in the functional consequences of different RB1 mutations as well as from nongenetic influences, particularly cigarette smoking. This apparently quadratic decline in the standardized mortality ratio with increasing age could, however, also be due to chance, because the exponent of age we estimated (i.e., –2.1, 95% CI = –3.6 to –0.7) is statistically consistent with a linear decline in the standardized mortality ratio.

We observed a small excess in overall cancer mortality among unilateral sporadic retinoblastoma survivors younger than age 45 (six deaths observed versus 1.90 deaths expected; three sarcomas and three lung cancers), which presumably reflects the inclusion of some unilaterally affected RB1 mutation carriers among the survivors of apparently sporadic retinoblastoma. Eng et al. *(33)* reported a similar excess in overall cancer mortality among survivors of unilateral retinoblastoma, although this excess mortality was reduced when familial cases were excluded from their cohort *(26).* Unilateral RB1 carriers with no known family history may also account for the unexpected excess of testicular cancer (two deaths observed versus 0.07 deaths expected) in our unilateral sporadic patients, although this could be a chance finding. Testicular cancer was also diagnosed in a 55-year-old patient with hereditary retinoblastoma.

The spectrum of early-onset cancers that are associated with germline p53 mutation, which includes osteosarcoma, soft tissue sarcomas, breast cancer, and brain cancer *(34),* is similar to that seen in RB1 mutation carriers. The only tumor clearly associated with p53 germline mutations that is not also seen among hereditary retinoblastoma survivors is adrenocortical carcinoma. The widely reported association between germline p53 mutation and childhood leukemia is due at least partly to ascertainment bias *(34),* and the relative excess of pancreatic cancer recently reported by Birch et al. *(35)* was not seen in the larger series of Li–Fraumeni families reviewed by Nichols et al. *(34).*

Our results suggest that carriers of mutant or deleted RB1 who did not receive high-dose radiotherapy have a much higher lifetime risk of common epithelial cancers, particularly cancers of the lung, bladder and, probably, breast, than of sarcomas and other early-onset cancers. However, the number of cancers in our cohort is still relatively small, and data from several cohorts with longer follow-up will need to be combined to estimate more precisely the risks for specific cancers. Although ascertainment of mortality in cohorts flagged through the NHSCR is virtually complete, British cancer registration is known to be incomplete, particularly for nonfatal cases *(36).* The adult cancer risk among RB1 mutation carriers may thus be even higher than the cumulative incidence of 68.8% from age 25 to 84 shown in Fig. 1. Their excess risk is concentrated in cancers normally associated with exposure to ionizing radiation or other DNA-damaging agents (i.e., sarcomas, tobacco-related lung and bladder cancers, and UV-related skin melanomas). Most of these cancers could probably have been prevented. The sarcoma risk can be greatly reduced by limiting the use of radiotherapy *(26),* and the very high lung and bladder cancer risk in middle and older age among RB1 mutation carriers could presumably be reduced by avoiding tobacco. No smoking data were available for our cohort. However, four of the five lung cancer deaths reported by Kleinerman et al. *(19)* occurred in smokers. That only 17% of the hereditary retinoblastoma survivors in their cohort were current smokers suggests that smoking increases the lung cancer risk approximately 20-fold among RB1 mutation carriers, similar to the relative risk of lung cancer associated with smoking in the general population. The standardized mortality ratios for lung cancer and bladder cancer (SMRs of 7.01 and 26.31, respectively) that we observed among hereditary retinoblastoma survivors would constitute a virtually penetrant lifetime risk among heavy smokers but a risk of less than one in 10 among non-smokers. Finally, avoiding sunburn would presumably reduce their melanoma hazard.

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