Risk of Cataract Extraction Among Adult Retinoblastoma Survivors

Gabriel Chodick, PhD; Ruth A. Kleinerman, MPH; Marilyn Stovall, MPH, PhD; David H. Abramson, MD; Johanna M. Seddon, MD; Susan A. Smith, MPH; Margaret A. Tucker, MD

Objective: To investigate the risk of cataract extraction among adult retinoblastoma survivors.

Design: A retrospective cohort study was performed on retinoblastoma survivors who received the diagnosis from 1914 to 1984 and were interviewed in 2000. Lens doses were estimated from radiotherapy records. The cumulative time interval to cataract extraction between dose groups was compared using the log-rank test and Cox regression.

Results: Seven hundred fifty-three subjects (828 eyes) were available for analysis for an average of 32 years of follow-up. During this period, 51 cataract extractions were reported. One extraction was reported in an eye with no radiation. The average time interval to cataract extraction in irradiated eyes was 51 years (95% confidence interval [CI], 48-54) following 1 treatment and 32 years (95% CI, 27-37) after 2 or 3 treatments. Eyes exposed to a therapeutic radiation dose of 5 Gy or more had a 6-fold increased risk (95% CI, 1.3-27.2) of cataract extraction compared with eyes exposed to 2.5 Gy or less.

Conclusions: The results emphasize the importance of ophthalmologic examination of retinoblastoma survivors who have undergone radiotherapy. The risk of cataract extraction in untreated eyes with retinoblastoma is comparable with the risk of the general population.


Retinoblastoma is a malignant tumor of the retina that predominantly affects young children. Every year, approximately 300 children and adolescents aged 15 years or younger receive the diagnosis of retinoblastoma in the United States, with an annual incidence of 3.1 per million.1 Approximately 10% to 25% of patients have a family history of retinoblastoma.2 The genetic cause of retinoblastoma is a mutation or a deletion in the RB1 gene on chromosome 13q14,3 which is detectable in approximately 89% of patients with hereditary retinoblastoma.4

For more than 100 years, external beam radiotherapy has been used to treat retinoblastoma, because it is useful in achieving tumor control and allows the retention of vision. One of the most common adverse effects of external beam radiotherapy to the orbit has been the induction of cataracts.5 Ionizing radiation has been associated with the formation of posterior subcapsular cataract (PSC) through protein superficial lens opacification6; time to development of a PSC has been inversely related to radiation dose.7 Other risk factors for PSC include aging, corticosteroid use, sex, ultraviolet radiation, metabolic disorders, diabetes, and hypertension and possibly education, cigarette smoking, increased alcohol consumption, and increased body mass.8,9 Cataract in infancy and early childhood may result in stimulus deprivation, as the cataract prevents normal retinal images from forming and being transmitted to the visual cortex, causing amblyopia, strabismus, and nystagmus if the cataracts are bilateral.3 Therefore, the early detection and treatment of cataracts in high-risk patients, such as young retinoblastoma survivors, is of a particular importance.

Most previous investigations of cataracts after external beam radiotherapy for retinoblastoma had relatively small sample sizes, short follow-up periods of less than 15 years, and no information on other potential risk factors resulting in large variability in risk estimates.6,7,10-14 This article presents long-term follow-up of one of the largest cohorts of adult retinoblastoma survivors studied to investigate the risk for cataract extraction associated with therapeutic exposure of ionizing radiation to the lens of the eye.
The methods for this study of retinoblastoma survivors have been previously described in detail. Briefly, we identified a total of 1729 patients with retinoblastoma diagnosed from 1914 to 1984 at 2 medical centers in New York and Boston. We excluded 128 patients who died within 12 months of diagnosis, died outside of the United States, or had uncertain history of retinoblastoma or birth year, which left 1601 (92.7%) eligible patients (Figure 1). Data on medical history, family history of retinoblastoma, treatment for retinoblastoma, reports of additional cancers, and cause of death were collected from medical records and radiotherapy records. In 2000, we used various sources including the National Death Index to determine vital status and locate the cohort participants to conduct a telephone interview. Patients or their families (for patients ≤18 years of age) were interviewed to update their medical history—including age at last cataract extraction, medications, and chronic health conditions—and to collect basic cancer risk factor information, including cigarette smoking, alcohol intake, height and weight to calculate body mass index, and highest level of formal education. Survivors with both eyes affected with retinoblastoma or only 1 eye affected and retinoblastoma in a family member were classified as having hereditary retinoblastoma. All other survivors were classified as having nonhereditary retinoblastoma.

At the time of the survey, we found that 1169 (73%) subjects were alive, 385 (24%) were deceased, and 47 (2.9%) were lost to follow-up. Of the 1169 eligible subjects, 875 (75%) responded to the telephone survey (Figure 1). Response rates were similar for hereditary (76%) and nonhereditary (73%) survivors. Nonresponders did not differ significantly from responders by year of birth, age at survey, sex, hereditary status, or age at retinoblastoma diagnosis. After excluding all 122 survivors with 2 enucleated eyes (117 subjects with hereditary retinoblastoma and 5 subjects with nonhereditary retinoblastoma), 753 subjects (828 eyes) were available for further analysis with a total of 26,328 years of follow-up (an average of 32 years [standard deviation (SD), 10.8 years] per eye). The institutional review board of the National Institutes of Health approved this study.

RADIOThERAPY FOR PATIENTS WITH RETINOBLASTOMA

In this cohort, patients who underwent irradiation (n=350) were treated with external beam radiotherapy (87%), brachytherapy (3%), or a combination of both techniques (10%). The most common external beam treatments in this cohort were a 2-field technique with nasal and lateral fields or a single-field technique, either lateral or anterior. Before 1960, external beam treatments were performed using orthovoltage x-rays. After 1960, treatments were given with 22 to 23 MV of photons (betatrons), 2 to 18 MV of photons (linear accelerators), or cobalt-60 gamma rays. Doses to the affected eyes ranged from 15 to 115 Gy (average, 48 Gy), with the highest doses delivered from orthovoltage external beam radiation machines. Brachytherapy before 1960 was delivered by plaques containing radon 222 seeds (average, 200; range, 160-400 mg/hour of radium equivalents), whereas in the later period, cobalt-60 plaques were used (average, 400; range, 150-800 mg/hour of radium equivalents).

LENS DOSE ESTIMATES

Absorbed doses to the lens from external beam therapy to the lens depend on several factors, including dose delivered, field configuration (anterior, lateral, and nasal) and the position of the fields relative to the lens, use of bolus, use of lens blocking, and use of wedges. When all factors are known, lens dose can be estimated using standard radiotherapy techniques. However, records of earlier periods may be limited. Records for patients in this study generally included field configuration, dose delivered, and use of lens blocking. We used literature sources to determine the position of the lateral fields, which was critical in determining the dose to the lens. For patients treated with anterior and lateral beams, the lateral field was assumed to be placed at the bony canthus. For patients treated with lateral fields alone, the position of the lateral field varied from the bony canthus to the back of the lens, depending on the extent of the disease, resulting in a 2% to 20% variation in lens dose for high-energy beams. We therefore based our doses for lateral fields on the average of the 2 positions, reporting minimum and maximum doses based on the variation in the positions. Lens blocking was taken into account if available. Because little information was found in the records regarding the use of a bolus, doses for anterior fields were the average of the dose with a 1-cm bolus and without a bolus. Wedge correction factors were not taken into account for dosimetry because less than 3% of the patients had any information on wedges. Lens dose was not reported if the field configuration, dose delivered, or laterality was unknown (n=81 eyes). If both eyes were irradiated, the dose to each lens was reported separately.

Brachytherapy consisted of cobalt-60 plaques or radon seeds. From the available records, it was not possible to know the position of the plaque relative to the lens. Therefore, we positioned the implant at 3 locations, delivering a range of dose to the lens from minimum to maximum and calculated lens dose using standard radiotherapy data. Lens doses were based on the tumor dose delivered and treating distance for each implant, known for approximately 50% of the implants. When unknown, tumor dose was assumed to be a typical 40-Gy tumor dose at 6 mm of treating distance.

Figure 1. Study flowchart of the analytic retinoblastoma survivors’ cohort for risk of cataracts (1984-2000).
As shown in Table 1, the cohort was predominantly younger than 40 years (76%), and 47% of the study members were female. During the follow-up period, 51 cataract extractions were reported. One cataract extraction was reported in an eye with no radiation treatment for retinoblastoma compared with 36 cataract extractions in 312 eyes with a history of 1 course of radiotherapy treatment and 14 among 38 eyes with 2 or 3 courses of treatment. Compared with unirradiated eyes, the HR for cataract in eyes receiving 2 or more radiation treatments was 284 (95% CI, 37-2170). The significant (log rank, P < .001) differences in survival to cataract extraction according to number of external radiation treatments are depicted in Figure 2. The Kaplan-Meier curve shows that after 40 years of follow-up, 77% of the eyes with 2 or 3 radiotherapy treatments were operated on for cataract extraction, compared with 17% of eyes treated once and less than 1% of untreated eyes. The estimated average survival time to cataract extraction in unirradiated eyes was 71.7 years (95% CI, 71.2-72.2) compared with 50.8 years (95% CI, 47.6-54.0) and 31.6 years (95% CI, 26.6-36.7) in eyes treated with 1 or 2 to 3 radiotherapy treatments, respectively. The number of courses of external radiation treatments were significantly associated with cataract extraction in a multivariate model, with HRs of 57.3 (95% CI, 47.6-54.0) and 31.6 years (95% CI, 26.6-36.7) in eyes treated with 1 or 2 to 3 radiotherapy treatments, respectively (Table 2). During the follow-up period, 30 cataract extractions were reported among the 318 eyes (78% with 1 treatment, 8% with 2 or 3 treatments) that were available for the dose-response analysis. In the univariate analysis, the multivariate model included the following baseline values of factors primarily related to cataract formation: age at diagnosis of retinoblastoma, sex, highest education, race, diabetes, alcohol consumption, cigarette smoking, and use of medications for diabetes. To examine the dose-response trends, we calculated the HR for therapeutic radiation exposure to the lens of the eye, modeled as a categorical variable with 3 radiotherapy dose groups using cut-off points of 2.5 Gy and 5.0 Gy. We used the cut-off point of 2.5 Gy, because it is the threshold dose that has been associated with the development of cataracts.

Table 1. Characteristics of 753 Retinoblastoma Survivors With at Least 1 Unenucleated Eye

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>82 (10.9)</td>
</tr>
<tr>
<td>20-29</td>
<td>209 (27.8)</td>
</tr>
<tr>
<td>30-39</td>
<td>278 (36.9)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>184 (24.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>399 (53.0)</td>
</tr>
<tr>
<td>F</td>
<td>354 (47.0)</td>
</tr>
<tr>
<td>Highest education</td>
<td></td>
</tr>
<tr>
<td>&lt;12 y/unknown</td>
<td>106 (14.1)</td>
</tr>
<tr>
<td>High school</td>
<td>331 (44.0)</td>
</tr>
<tr>
<td>≥College</td>
<td>316 (42.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>647 (85.9)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>106 (14.1)</td>
</tr>
<tr>
<td>Hereditary status</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>349 (46.3)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>404 (53.7)</td>
</tr>
<tr>
<td>Diabetesa</td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>741 (98.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (1.6)</td>
</tr>
<tr>
<td>Radiotherapy treatment</td>
<td></td>
</tr>
<tr>
<td>External beam radiotherapy</td>
<td>304 (40.4)</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>11 (1.5)</td>
</tr>
<tr>
<td>External beam radiotherapy and brachytherapy</td>
<td>30 (4.0)</td>
</tr>
<tr>
<td>Other/ unspecified</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Missing data</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>None</td>
<td>400 (53.1)</td>
</tr>
</tbody>
</table>

Statistical analysis

The time free of cataract extraction was calculated using the year of retinoblastoma diagnosis (median age at diagnosis was 1 year) and treatment until the date of the telephone interview (2000) or year of last cataract extraction, whichever occurred first, and was analyzed using the Kaplan-Meier method. The log-rank test was used to test for differences in cumulative survival to cataract extraction by number of radiation treatments, and Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of cataract extraction in the univariate analysis. The multivariate model included the following baseline values of factors primarily related to cataract formation: age at diagnosis of retinoblastoma, sex, body mass index, education, alcohol consumption, cigarette smoking, and use of medications for diabetes. To examine the dose-response trends, we calculated the HR for therapeutic radiation exposure to the lens of the eye, modeled as a categorical variable with 3 radiotherapy dose groups using cut-off points of 2.5 Gy and 5.0 Gy. We used the cut-off point of 2.5 Gy, because it is the threshold dose that has been associated with the development of cataracts.

Results

As shown in Table 1, the cohort was predominantly younger than 40 years (76%), and 47% of the study members were female. During the follow-up period, 51 cataract extractions were reported. One cataract extraction was reported in an eye with no radiation treatment for retinoblastoma compared with 36 cataract extractions in 312 eyes with a history of 1 course of radiotherapy treatment and 14 among 38 eyes with 2 or 3 courses of treatment. Compared with unirradiated eyes, the HR for cataract in eyes receiving 2 or more radiation treatments was 284 (95% CI, 37-2170). The significant (log rank, P < .001) differences in survival to cataract extraction according to number of external radiation treatments are depicted in Figure 2. The Kaplan-Meier curve shows that after 40 years of follow-up, 77% of the eyes with 2 or 3 radiotherapy treatments were operated on for cataract extraction, compared with 17% of eyes treated once and less than 1% of untreated eyes. The estimated average survival time to cataract extraction in unirradiated eyes was 71.7 years (95% CI, 71.2-72.2) compared with 50.8 years (95% CI, 47.6-54.0) and 31.6 years (95% CI, 26.6-36.7) in eyes treated with 1 or 2 to 3 radiotherapy treatments, respectively. The number of courses of external radiation treatments were significantly associated with cataract extraction in a multivariate model, with HRs of 57.3 (95% CI, 47.6-54.0) and 31.6 years (95% CI, 26.6-36.7) in eyes treated with 1 or 2 to 3 radiotherapy treatments, respectively (Table 2). During the follow-up period, 30 cataract extractions were reported among the 318 eyes (78% with 1 treatment, 8% with 2 or 3 treatments) that were available for the dose-response analysis. In the multivariate model, children diagnosed with retinoblastoma after the first year of life were at higher risk (HR, 2.14; 95% CI, 1.06-4.33) of cataract extraction compared with children with retinoblastoma diagnosis at a younger age. In the dose-response analysis, eyes that were exposed to a therapeutic radiation dose of 5 to 22.0 Gy (mean, 8.1 Gy) had a 6-fold risk (95% CI, 1.33-27.15) for cataract extraction compared with eyes exposed to 2.5 Gy or less (mean, 1.0 Gy) (Table 3). Similar risk estimates were calculated when patients who were treated with brachytherapy alone were excluded from analysis.

Comment

This study was one of the largest undertaken to date on the risk of cataract extraction in relation to orbital radiation in early childhood, with respect to the size of the
baseline cohort and number of patients with quantitative radiation dose assessment. The results indicate that nearly all cataract extractions among adult retinoblastoma survivors within 30 years after retinoblastoma diagnosis could be associated with radiotherapy and that more than 75% of the eyes treated with 2 or more radiotherapy treatments had a cataract extracted. The rates of cataract surgery in the present study also agree with results from a 66-month follow-up study among patients with choroidal melanoma treated with iodine-125 brachytherapy, in which approximately 10% of study eyes exposed to 12 to 16 Gy had undergone cataract surgery.28 Our results compare favorably with a previous study on the incidence of clinically significant PSC in 85% of patients with retinoblastoma treated with anterior fields after a median follow-up of 10 years.11 Egbert et al29 reported on the diagnosis of PSC in 66% of the eyes 2 to 12 years after treatment with radiotherapy for retinoblastoma, but cataracts were unrelated to calculated tumor dose or age at treatment. An earlier evaluation of a subset of patients with retinoblastoma from this cohort compared the rate of cataract formation following 2 external beam radiotherapy techniques (anterior lens sparing and modified lateral beam) and reported that 22% of patients had developed cataracts up to 159 months after radiotherapy, with no significant difference in the rate of cataract formation between the 2 techniques.22

The number of both epithelial cells and fibers in the human lens increases by approximately 45% to 50% during the first 2 decades of life and particularly before age 4 years,29 raising the possibility of age-related sensitivity to radiation in cataract formation. Although there was no significant difference in the mean dose to the lenses between patients with retinoblastoma diagnosed before and after 1 year of age, according to common treatment protocols,30 patients with retinoblastoma younger than 1 year of age are treated with more fractions over a longer period compared with older pediatric patients. Thus, the lower risk of cataract extraction in patients younger than 1 year at the time of radiation exposure may also relate to their more fractionated radiation exposure. Our data are also consistent with a study of individuals who were exposed to a lenticular dose of 1 Gy at younger than 18 months of age during treatment of skin hemangiomas; that study reported a 50% increased risk (odds ratio, 1.50; 95% CI, 1.1-2.5) of developing a posterior subcapsular opacity associated with radiation exposure.31

It is well known that cataracts are associated with total body irradiation and a dose of radiotherapy above 5 Gy.32 Our analysis indicates that patients exposed to 2.5- and 5.0-Gy doses also have a higher risk of cataract extraction. In a more recent study on 32 patients with neuroblastoma treated with total body irradiation, 6 patients developed cataracts within 3 to 5 years of treatment.33 The major caveat in interpreting the findings of the present study is that all information concerning cataract operations was obtained by self-report without clinical confirmation. Thus, we could not identify patients with a stable cataract with no or only slight complaints or the type of cataract extracted. Additionally, data from the Salisbury Eye Study found 94% sensitivity and 100% specificity for self-reported history of cataract surgery and a positive predictive value of 100%.34 Another limitation related to cataract surgery as an outcome is that many retinoblastoma survivors and their physicians may have been more likely to observe rather than extract their cataracts owing to uncertainty regarding ocular, visual, and survival outcomes after such surgery, particularly in patients with enucleated eyes.35 Such a differential bias could have resulted in an underestimation of the true risk of developing a cataract. Additionally, the large number of patients with insufficient radiotherapy treatment data available for esti-
mation of the dose to the lens weakens our study. Even with the full radiotherapy record, the lens doses are subject to large uncertainty because geometry of the treatment fields and location of the plaques are critical in estimating dose; these are details that may not be included in full treatment records. Nonetheless, the dosimetry assumptions in our study were consistently applied to all patients, and the results were reviewed by the radiation oncologist (D.H.A.), who treated many of the patients. Also, a similar exposure-response relationship was observed even when using the categorical exposure variables (ie, number of courses of ionizing radiation). In addition, because misclassification of dose estimates is non-differential, our calculated risk estimates can only underestimate the true relative risks. Although we were unable to evaluate the risk of cataract extraction related to ultraviolet radiation exposure, we were able to include the contribution of most other known risk factors for cataract development.

The immediate and long-term risks of cataract extraction in patients with retinoblastoma include recurrence or extraorbital extension of disease and retinal detachment.33 Therefore, the prevention of cataracts should be considered in selecting treatment techniques that lessen the risk of cataract, such as using a modified lateral beam approach for the treatment of intraocular retinoblastoma with external beam radiotherapy.22 The high incidence of cataract operations in retinoblastoma survivors undergoing radiotherapy necessitates continuing ophthalmologic follow-up of these patients. In contrast, the annual risk of cataract extraction in untreated eyes in this cohort was relatively low and comparable with the risk of the general population.36

Submitted for Publication: August 19, 2008; final revision received January 28, 2009; accepted February 10, 2009.

Correspondence: Gabriel Chodick, PhD, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Bethesda, MD 20892-7238 (chodik_g@nih.gov).

Author Contributions: Dr Chodick had full access to the data and the integrity of the data and the accuracy of the data analysis. Financial Disclosure: None reported.

Funding/Sponsor: This research was supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, Division of Cancer Epidemiology and Genetics.

REFERENCES