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Risk of cataract extraction among adult retinoblastoma survivors

Gabriel Chodick, PhD¹, Ruth A. Kleinerman, MPH¹, Marilyn Stovall, MPH, PhD², David H. Abramson, MD³, Johanna M. Seddon, MD⁴, Susan A. Smith, MPH², and Margaret A. Tucker, MD¹

¹ Division of Cancer Epidemiology and Genetics, NCI, NIH, DHHS, Rockville, MD 20852

² Department of Radiation Physics, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030

³ Ophthalmic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

⁴ Ophthalmic Genetic Epidemiology Service, Tufts New England Medical Center, Boston, Massachusetts 02111

Abstract

Background and Objectives—For over 100 years, radiotherapy has been widely used to treat retinoblastoma. One of the most common adverse effects of orbital radiotherapy is cataract formation. The objective of this study was to investigate the risk of cataract extraction among adult retinoblastoma survivors.

Methods and Design—A retrospective cohort study was performed on survivors who were diagnosed with retinoblastoma from 1914 to 1984 and responded to a telephone interview in 2000. The interview elicited information about medical outcomes including cataract extraction, demographic and several lifestyle factors. Doses to the lens of each eye for individuals were estimated from available radiotherapy (external beam therapy or brachytherapy) records. The cumulative time interval to cataract extraction between dose groups was compared using the log-rank test, and Cox regression was used to estimate hazard ratios of cataract extraction in multivariate analyses.

Results—753 subjects (828 eyes) were available for analysis for an average of 32 years of follow-up per eye. During this period, 51 cataract extractions were reported. One extraction was reported in an eye with no radiotherapy compared to 36 extractions in 306 eyes with one course of radiotherapy, and 14 among 38 eyes with two or three courses of treatment. The average time interval to cataract extraction in irradiated eyes was 51 years (95% CI: 48–54) following one treatment and 32 years (95% CI: 27–37) for 2 or 3 treatments. Eyes exposed to a therapeutic radiation dose of 5 Gray (Gy) or more (mean exposure of 8.1 Gy) had a six-fold increased risk (95% CI: 1.3–27.2) for cataract extraction compared to eyes exposed to 2.5 Gy or less.

Conclusion—Nearly all cataracts that were extracted within 30 years after diagnosis of retinoblastoma could be associated with radiotherapy and more than 75% of the eyes treated with two or more radiotherapy treatments had a cataract extracted. The results emphasize the importance of ophthalmologic examination throughout adulthood of retinoblastoma survivors who have undergone radiotherapy. In contrast, the annual risk of cataract extraction in non treated eyes is comparable with the risk of the general population.

Introduction

Retinoblastoma (Rb) is a malignant tumor of the retina, predominantly affecting young children. Every year, approximately 300 children and adolescents ≤ 15 years of age are diagnosed with Rb in the US, with an annual incidence of 3.1 per million (1). Approximately 10–25% of patients have a family history of retinoblastoma (2). The genetic cause of Rb is a mutation or a deletion in the RB1 gene on chromosome 13q14 (3), which is detectable in approximately 89% of patients with hereditary disease (4).

For over 100 years, external beam radiotherapy (EBRT) has been used to treat Rb, because it is useful in achieving tumor control and allow the retention of vision. One of the most common adverse effects of EBRT 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 opacification (6), and time to development of a PSC has been inversely related to radiation dose (7). Other risk factors for PSC include aging, corticosteroid use, gender, 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 forming and being transmitted to the visual cortex, causing amblyopia, strabismus, and nystagmus if bilateral (5). Therefore, the early detection and management of cataracts in high risk patients, such as young retinoblastoma survivors, is of a particular importance.

Most previous investigations of cataracts after EBRT for Rb 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 report presents long-term follow-up of one of the largest cohorts of adult Rb survivors to investigate the risk for cataract extraction associated with therapeutic exposure of ionizing radiation to the lens of the eye.

Methods

The methods for this study of Rb survivors have been previously described in detail (15). Briefly, we identified a total of 1,729 Rb patients diagnosed from 1914 to 1984 at two medical centers in New York and Boston. We excluded 128 patients who died within 12 months of diagnosis, died outside of the US, or had uncertain history of Rb or birth year, which left 1,601 (92.7%) eligible patients (Figure 1). Data on medical history, family history of Rb, treatment for Rb, reports of additional cancers, and causes of death were collected from medical records and radiotherapy records. In 2000, we used various sources including the National Death Index (NDI) to determine vital status and locate the cohort participants in order 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 (BMI), and highest level of formal education. Survivors with both eyes affected with Rb or only one eye affected and Rb in a family member were classified as hereditary Rb. All other Rb survivors were classified as non-hereditary.

At the time of the survey, we found that 1,169 (73%) subjects were alive, 385 (24%) were deceased, and 47 (2.9%) subjects were lost to follow-up. Of the 1,169 eligible subjects, 875 (75%) responded to the telephone survey (Figure 1). Response rates were similar for hereditary (76%) and non-hereditary survivors (73%). Non-responders did not differ significantly from responders by year of birth, age at survey, sex, hereditary status, or age at Rb diagnosis. After excluding all 122 survivors with two enucleated eyes (117 subjects with hereditary Rb and five

subjects with non-hereditary Rb), 753 subjects (828 eyes) were available for further analysis with a total of 26,328 years of follow-up (an average of 32 years (SD=10.8) per eye). The Institutional Review Board of the National Institutes of Health approved this study.

Radiotherapy for Rb patients

In this cohort, irradiated patients (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 two-field technique with nasal and lateral fields or a single-field technique, either lateral or anterior. Before 1960, external-beam treatments were given with ortho voltage x-rays. After 1960, treatments were given with 22 – 23 MV betatron, 2 – 18 MV photons, or cobalt-60 (^{60}Co) gamma rays. Tumor doses to the affected eyes ranged from 15 to 115 Gy (average, 48 Gy), with the highest doses delivered from ortho voltage external-beam radiation machines. Brachytherapy before 1960 was delivered by plaques containing Rn-222 seeds (average, 200 milligram-hour radium equivalents [mgh Ra eq]; range, 160 to 400 mgh Ra eq), whereas in the later time period, ^{60}Co plaques were used (average, 400 mgh Ra eq; range, 150 to 800 mgh Ra eq).

Lens Dose estimates

Dose from external beam therapy to the lens depends on several factors, including dose delivered, field configuration (anterior, lateral, 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 (16–18). However, records of earlier time 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 (12, 19–22) 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 – 20% variation in lens dose for high-energy beams. We therefore based our doses for lateral fields on the average of the two positions, reporting minimum and maximum doses based on the variation in the positions. Lens blocking was taken into account if available. Since little information was found in the records regarding the use of bolus, doses for anterior fields were the average of the dose with 1-cm bolus and without bolus. Wedge correction factors were not taken into account for dosimetry because fewer than 5% 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 ^{60}Co 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 three locations, delivering a range of dose to the lens from minimum to maximum and calculated lens dose using standard radiotherapy data (23). Lens doses were based on the tumor dose delivered and treating distance for each implant, known for approximately 50% of the implants. Where unknown, tumor dose was assumed to be a typical 40Gy tumor dose at 6 mm treating distance.

In cases (14 eyes) where the range of dose to the lens from minimum to maximum and calculated lens dose were above 15 Gy (range, 15.3–36.8 cGy), they were excluded from further analysis. Overall, we had sufficient information to provide approximate minimal lens dose estimates for 318 eyes, of which 10 were treated with brachytherapy (Figure 1).

Statistical Analysis

Cataract-extraction free time-interval was calculated from the year of Rb 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 (24) was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) 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 Rb, gender (25,26), BMI, education, alcohol consumption, cigarette smoking, and use of medication 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 three radiotherapy dose groups using cut-points of 2.5Gy and 5.0 Gy. We used the cut-point of 2.5 Gy, because this is threshold dose that has been associated with the development of cataracts (27).

Results

As shown in Table 1, the cohort was predominantly under 40 years of age (76%) and 47% of the study members were females. During the follow-up period, 51 cataracts extractions were reported. One cataract extraction was reported in an eye with no radiation treatment for Rb compared to 36 cataract extractions in 312 eyes with a history of one course of radiotherapy treatment, and 14 among 38 eyes with two or three courses of treatment. Compared to non-irradiated eyes, the HR for cataract in eyes receiving two or more radiation treatments was 284 (95%CI: 37–2170). The significant (log rank $p<0.001$) 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 that 77% of the eyes with 2 or 3 radiotherapy treatments were operated for cataract extraction, compared to 17% in eyes treated once, and less than 1% in non-treated eyes. The estimated average survival time to cataract extraction in non-irradiated eyes was 71.7 years (95%CI: 71.2–72.2) compared to 50.8 years (95%CI: 47.6–54.0) and 31.6 years (95%CI: 26.6–36.7) for eyes treated with one and 2 or 3 radiotherapy treatments, respectively. The number of courses of external radiation treatments were significantly associated with cataract extraction in a multivariate model, with a HR of 57.3 ($p<0.001$) and 332.7 ($p<0.001$) for eyes treated with one and 2 or 3 treatments, respectively (Table 2). During the follow-up period, 30 cataract extractions were reported among the 318 eyes (78% with one treatment, 8% with 2 or 3 treatments) which were available for the dose response analysis. In the multivariate model, children diagnosed with Rb after the first year of life were at higher risk (HR=2.14, 95%CI: 1.06–4.33) of cataract extraction compared to children diagnosed with Rb at a younger age. In the dose-response analysis, eyes that were exposed to a therapeutic radiation dose of 5–22.0 Gy (mean, 8.0 Gy) had a six-fold risk (95% CI: 1.33–27.15) for cataract extraction compared to eyes exposed to 2.5Gy 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.

Discussion

This study was one of the largest undertaken to date on risk of cataract extraction in relation to orbital radiation in early childhood, with respect to size of the baseline cohort and number of patients with quantitative radiation dose assessment. The results indicate that nearly all cataract extractions among adult Rb survivors within 30 years after Rb diagnosis could be associated with radiotherapy and that more than 75% of the eyes treated with two 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, where approximately 10% of study eyes exposed to 12–16 Gy had undergone cataract surgery (28). Our results compare favorably with a previous report on the incidence of clinically significant PSC in 85% of Rb patients treated with anterior fields after a median follow-up of 10 years (11). Egbert et al (10) reported on the diagnosis of PSC 2 to 12 years later in 66% of the eyes treated with radiotherapy for Rb, but cataracts were unrelated to calculated tumor dose or age at treatment. An earlier evaluation of a subset of Rb patients from this cohort compared the rate of cataract formation following two EBRT 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 significance difference in the rate of cataract formation between the two techniques (22).

Numbers of both epithelial cells and fibers in the human lens increase by approximately 45–50% during the first two decades, 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 diagnosed before and after one year of age, according to common treatment protocols (30), Rb patients below one year of age are treated with more fractions over a longer period of time weeks compared to older pediatric patients. Thus, the lower risk of cataract extraction in patients younger than one 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 less than 18 months of age during treatment of skin hemangiomas, which 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 (TBI) and a dose of radiotherapy above 5 Gy (32). Our analysis indicates that patients exposed to doses of 2.5 Gy and 5.0 Gy also have a higher risk of cataract extraction. In a more recent study on 32 neuroblastoma patients treated with Total Body Irradiation, six patients developed cataracts within 3–5 years of treatment (33). The major caveat in interpreting the findings of the present study is that all information concerning cataract surgeries 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. However, cataract surgery is probably a more relevant outcome for PSC than clinical lens changes, because the presence of PSC is the most important lens opacity associated with cataract surgery (34). Additionally, data from the Salisbury Eye Study (SEE) found 94% sensitivity and 100% specificity for self-reported history of cataract surgery, and a positive predictive value of 100% (35). Another limitation related to cataract surgery as an outcome is that many Rb survivors and their physicians may have been more likely to observe rather than extract their cataracts due to uncertainty regarding ocular, visual, and survival outcomes after such surgery, particularly in patients with an enucleated eye (28). 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 an accurate estimation of the dose to the lens weakens our study. However, we observed an exposure-response relationship even when using the categorical exposure variable (i.e., number of courses of ionizing radiation). Although we were unable to evaluate the risk of cataract extraction related to UV 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 Rb patients include recurrence or extraorbital extension of disease and retinal detachment (36). Therefore, the prevention of cataracts should be considered in selecting treatment techniques which lessen the risk of cataract, such as using a modified lateral beam approach for the treatment of intraocular Rb with EBRT (22). The high incidence of cataract surgeries in Rb survivors undergoing radiotherapy necessitates continuing ophthalmologic follow-up of these patients. In contrast,

the annual risk of cataract extraction in non treated eyes in cohort was relatively low and comparable with the risk of the general population (37).

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Figure 1.
Inclusions and Exclusions in the analytic cohort for risk of cataracts, retinoblastoma survivors' cohort (1984–2000)

Figure 2.
Kaplan Meier curve for time to cataract extraction among retinoblastoma patients' eyes, according to number of courses of ionizing radiation

Table 1

Selected characteristics of retinoblastoma survivors with at least one non-enucleated eye (n=753)

		n	%
Age	<20	82	10.9%
	20–29	209	27.8%
	30–39	278	36.9%
	>40	184	24.4%
Gender	Male	399	53.0%
	Female	354	47.0%
Highest education	<12 years/unknown	106	14.1%
	High school	331	44.0%
	College or higher	316	42.0%
Race	Non-Hispanic White	647	85.9%
	Other/UNK	106	14.1%
Hereditary Status	hereditary	349	46.3%
	Sporadic	404	53.7%
Diabetes *	No/Unknown	741	98.4%
	yes	12	1.6%
Radiotherapy treatment	ERBT	304	40.4%
	Brachytherapy	11	1.5%
	ERBT and brachytherapy	30	4.0%
	Other/unspecified	5	0.7%
	Missing data	3	0.4%
	None	400	53.1%

* Based on use of medications for diabetes in the past 5 years.

Table 2

Risk of cataract extraction in retinoblastoma survivors according to different risk factors

	Cases	Hazard Ratio [*]	95%CI	P-Value
			low	high
Age at Rb diagnosis				
<1 year	11	1 (ref.)		
≥1 year	40	2.14	1.06	4.33
Sex				
Men	28	1 (ref.)		
Women	23	1.31	0.72	2.39
Hereditary Status				
Hereditary	49	1 (ref.)		
Sporadic	2	0.63	0.11	3.63
Highest education				
<12 years	7	1 (ref.)		
High school	18	0.56	0.19	1.60
College/graduate	26	0.80	0.28	2.29
Smoking				
Never	29	1 (ref.)		
Former	10	0.78	0.35	1.72
Current	10	0.93	0.42	2.08
Unknown	2	1.16	0.21	6.44
Body Mass Index (kg/m²)				
18.5–25	20	1 (ref.)		
<18.5	1	1.63	0.20	13.0
25–30	16	1.04	0.50	2.14
>30	14	1.06	0.49	2.29
Alcohol consumption				
≤1 drinks/day	5	1 (ref.)		
> 1 drinks/day	24	1.75	0.63	4.81
Unknown	22	0.86	0.32	2.35
History of external beam radiotherapy or brachytherapy				
None	1	1 (ref.)		
1 treatment	36	57.27	5.00	656.5
2–3 treatments	14	332.7	26.5	4181.5

* Adjusted for age at RB diagnosis, sex, education level, smoking, BMI, alcohol intake, hereditary RB

Table 3

Age-and-gender adjusted Hazard Ratio (RR) and 95% confidence interval (CI) of cataract extraction, according to ionizing radiation to the lens of the eye from radiotherapy* for retinoblastoma

Dose to the lens of the eye	Eyes	cases	HR	95%CI
0.3–2.5 Gy (mean, 1.0 Gy)	98	2	1	
2.5–5.0 Gy (mean, 3.3 Gy)	153	15	3.31	0.75 14.68
5.0–22.0 Gy (mean, 8.1 Gy)	67	13	6.00	1.33 27.15

* Including brachytherapy and external beam therapy