Original Investigation

Association of Radiation Dose to the Eyes With the Risk for Cataract After Nonretinoblastoma Solid Cancers in Childhood

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IMPORTANCE Few studies have been published on the association of the radiation dose received to the eyes during radiotherapy (RT) for childhood cancer and the risk for later cataract.

OBJECTIVE To investigate the risk for cataract after treatment of nonretinoblastoma solid cancer in childhood.

DESIGN, SETTING, AND PARTICIPANTS The study used data from the Euro2K cohort that includes 4389 5-year survivors of solid tumors treated from January 1, 1945, to December 31, 1985; of these, 3172 patients were treated in France. A self-reported questionnaire was sent to French survivors from September 1, 2005, to December 31, 2012, when follow-up was considered completed for this study. However, 619 patients died before the beginning of the study and 128 patients treated for a retinoblastoma or who underwent enucleation were excluded. Likewise, 429 patients with unknown addresses or who did not return the consent form and 163 nonresponders did not participate. The remaining 1833 patients who completed the questionnaire underwent analysis for this study from June 1, 2014, to December 7, 2015.

MAIN OUTCOMES AND MEASURES Radiation doses in both eyes for individuals were estimated for all patients who had received RT. The role of the radiation dose in cataract risk was investigated using the Cox proportional hazard regression model and the excess relative or the absolute risk model. The role of ctytotoxic chemotherapy was also investigated.

RESULTS The 1833 patients (961 men [52.4%]; 872 women [47.6%]; mean [SD] age, 37.0 [8.5]) who returned the questionnaire were included in the analysis. After a mean follow-up of 32 years, 33 patients with unilateral or bilateral cataract were identified, for a total of 47 cataract events. The 47 events were validated by medical record review and by contacting the patients and the corresponding medical physician or ophthalmologist to obtain copies of diagnostic examinations or surgical reports. Overall, in a multivariable Cox proportional hazard regression analysis, patients who received RT had a 4.4-fold (95% CI, 1.5- to 13.0-fold) increased risk for cataract compared with patients who did not receive RT. Exposure to radiation doses of at least 10 Gy to the eyes increased the hazard ratio 39-fold (95% CI, 12.0- to 127.9-fold), relative to no radiation exposure. Although based on few patients, a strong increase in cataract risk (hazard ratio, 26.3; 95% CI, 7.1-96.6) was observed in patients treated with melphalan hydrochloride.

CONCLUSIONS AND RELEVANCE This study can inform guideline-based recommendations for long-term follow-up for cataract.

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Survival rates for most pediatric cancers have improved at a remarkable pace during the last 4 decades. In developed countries, cure is now the probable outcome for most children and adolescents who are diagnosed as having cancer; their 5-year survival rate approaches 80%.[1,2] However, the increased number of survivors has shifted attention to the possible long-term adverse effects of cancer treatments. Long-term survivors are at risk for developing a broad spectrum of adverse outcomes, which may include early death, second neoplasms, and damage to the heart.[3-6] Neurosensory complications affecting the auditory, ocular, olfactory, or speech systems are commonly reported by survivors.[7] Although some of these effects have a minor effect on the survivors' quality of life, others, such as blindness and cataract, may have various important consequences.[7]

A fair degree of consistency exists in the radiogenic risks for cataract in different groups exposed to radiation.[8-15] Since the 1950s, the prevailing view has been that only relatively high doses of at least several grays induce vision-impairing cataracts.[10] However, the incidence of cataract induced by radiotherapy (RT) and cytotoxic chemotherapy (CT) among survivors of childhood cancer is often underestimated and underreported. Few previous studies[7,15,16] addressed the question of cataract after childhood RT for cancer. A retrospective study of retinoblastoma survivors[16] showed that eyes exposed to a therapeutic radiation dose of 5 Gy or more (to convert to rad, multiply by 100) had a 6-fold increased risk for cataract extraction compared with eyes exposed to 2.5 Gy or less. The US Childhood Cancer Survivor Study (CCSS) found that the dose of radiation to the eye was significantly associated with the risk for cataract.[7,15] Whelan et al[7] have also shown an increased risk for cataract in survivors who were treated with prednisone. Unfortunately, these studies have not provided findings on the risk for cataract for each of the main alkylating agents. To date, the possibility of interactions between exposure to specific groups of cytotoxic drugs and to ionizing radiation to the eyes also has not been considered.

The present study reports the incidence of cataract in a cohort of survivors of childhood cancer treated from 1945 to 1985 and followed up for a mean of 32 years. The main purpose of our investigation was to explore the relationship between the radiation dose received to the eyes during RT for childhood cancer and the risk for later cataract, with adjustment for other treatment-related factors, such as the use of glucocorticoids or CT.

Key Points

Question: What is the risk for cataract in long-term survivors of childhood cancer for whom data on radiation doses to both eyes and cytotoxic chemotherapy drugs were estimated and data for known risk factors (alcohol consumption, smoking, and diabetes mellitus) were collected?

Findings: With a mean follow-up of 32 years from cancer diagnosis, the radiation dose received to eyes was associated with cataract and a risk for later cataract after melphalan hydrochloride treatment.

Meaning: This study provides risk estimates for the occurrence of cataract in survivors of childhood cancer.

Methods

Patients and Collection Data

The Euro2K cohort, established from 1985 to 1995 in France and the United Kingdom, consists of patients treated from January 1, 1945, to December 31, 1985, for a solid cancer during childhood. The constitution of the cohort was first described in 1995.[17] In that initial publication, the cohort included 4567 patients. From 1995 to 2009, some French patients were excluded because of diagnostic errors and duplicate records, whereas others were added whose medical records were not available at the time of initial cohort constitution but were discovered during a systematic investigation performed afterward in the Gustave Roussy Institute archives. The final database includes 4389 5-year survivors, of whom 3172 were treated in France and are a part of the French Childhood Cancer Survivor Study that was approved by the Commission Nationale de l'Informatique des Libertés and was obtained with approval of the institutional review board of the Institut National de la Santé et de la Recherche Medicale. All participants provided written informed consent.

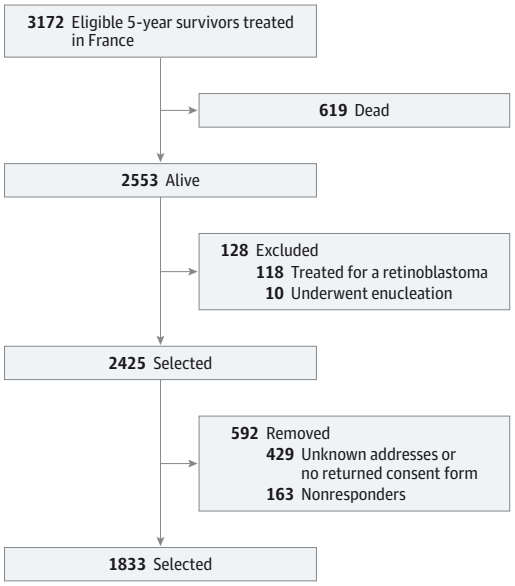
Follow-up of the 3172 French patients initially used the medical records of the cancer centers, and a self-reported questionnaire was sent to the patients beginning on September 1, 2005. Six hundred and nineteen individuals who had died before the beginning of the study, 118 patients treated for a retinoblastoma, and 10 patients who underwent enucleation were excluded. We obtained the most recent address of patients treated in France who were still alive according to the National Health Insurance System. Four hundred and twenty-nine individuals with an unknown address or who did not return the consent form and 163 nonresponders did not participate in this study (**Figure 1**). The questionnaire, based on that used by the British Childhood Cancer Survivor Study, addressed various health, social, and psychological outcomes.[18] The contact letter included a participation agreement to be signed and an authorization to contact the physician and medical facilities. The present study focused on the 1833 patients treated in France for nonretinoblastoma solid cancers in childhood (75.6% of the 2425 patients contacted) who sent back the questionnaire by December 31, 2012 (Figure 1). Nonresponse was significantly related to sex and cancer treatment (**Table 1**).

Self-questionnaire items included cataract (yes or no), cataract laterality, age at occurrence, and surgery (yes or no). Cataract was self-reported initially and then confirmed by medical record review or by contacting relevant hospital physicians, private physicians' offices that were identified from the patient record, or ophthalmologists who had made the diagnosis of cataract. For more reliability, only medically confirmed or surgically treated cataracts were considered.

Estimation of the Radiation Dose

Radiation dose was estimated for the right and left eyes of each patient who received external RT. The doses given to most of the other organs of the body and at 188 anatomic sites were

Figure 1. Study Flow Diagram



Patients were treated for cancer from January 1, 1945, to December 31, 1985; questionnaires were sent to adult survivors from September 1, 2005, to December 31, 2012.

also estimated. A computer program called Dos_EG was developed for these calculations.[19-21] To calculate the dose given to anatomic sites, beams were positioned on the individual patient-adjusted phantom (a mathematical representation of the human body, including organs) according to details from the patient's medical record and information about equipment, treatment techniques, and guidelines used at the time of treatment. The RT variables included beam size, shape, inclination, and location, radiation energy, and delivered treatment dose. More details on the dose reconstruction reliability can be found in previous publications.[19-22]

CT and Glucocorticoid Quantification

Drugs were grouped into 7 classes according to their known mechanisms of action in cells: alkylating agents, vinca alkaloids, antimetabolites, epipodophyllotoxins, anthracyclines, antibiotics, and other drugs. The cumulative dose in milligrams per square meter was calculated for CT agents and glucocorticoids for each participant.[7] A detailed description of the CT received by the cohort has been published elsewhere.[22] We performed an analysis of the potential role of each drug.

Statistical Analysis

Data were analyzed from June 1, 2014, to December 7, 2015. Patients and treatment characteristics of all survivors in this cohort were described. Cumulative incidence curves of cataract were constructed using attained age as the timescale. First, the cohort analysis was performed using the Cox proportional hazards regression model with the maximal radiation dose to the right or left eye instead of the mean dose, because the maximal dose provides information on the actual level of radiation dose received by one of the eyes during RT. The Cox proportional hazards regression model for aggregate data was performed using both eyes of the same participant.[23] To take into account the within-participant correlation, we used the proportional marginal means model with the sandwich variance estimate proposed by Wei et al,[24] which provides the robust sandwich variance estimators for the SEs of coefficients.

Table 1. Patient Characteristics of the 2425 5-Year French Survivors in the Euro2K Cohort[a]

Patient Characteristics	Total No.	Nonresponders, No. (%)[b]	Responders						
			No. (%)[b]	Age at Self-administered Questionnaire, Mean (SD), y	Radiation Dose to Eyes, Mean (SD), Gy		No. With Cataract	No. of Cataracts	Cumulative Cataract Incidence, % (95% CI)[c]
					Right	Left			
Sex									
Men	1333	372 (27.9)	961 (72.1)	37.3 (8.2)	2.8 (6.0)	2.8 (5.9)	18	25	3.1 (1.7-5.4)
Women	1092	220 (20.1)	872 (79.8)	36.7 (7.8)	2.5 (5.7)	2.6 (5.6)	15	22	1.5 (0.8-2.8)
Age at first cancer, y									
0-1	712	172 (24.2)	540 (75.8)	33.4 (7.4)	1.0 (3.2)	1.0 (3.2)	7	12	2.2 (0.9-5.2)
2-4	540	121 (22.4)	419 (77.6)	34.8 (7.5)	2.4 (6.1)	2.1 (5.0)	5	7	1.2 (0.5-3.0)
5-9	586	143 (24.4)	443 (75.6)	37.9 (7.0)	3.5 (6.7)	4.1 (7.5)	12	16	2.7 (1.4-5.1)
≥10	587	156 (26.6)	431 (73.4)	42.6 (6.9)	3.5 (6.0)	3.4 (5.7)	9	12	2.1 (0.9-5.0)
Treatment									
No RT/no CT	208	62 (29.8)	146 (70.2)	38.8 (10.1)	0	0	0	0	0
RT/no CT	396	114 (28.8)	282 (71.2)	42.8 (9.3)	3.3 (6.8)	3.4 (6.9)	6	10	1.1 (0.3-4.4)
No RT/CT	669	157 (23.5)	512 (76.5)	32.7 (6.2)	0	0	4	6	1.5 (0.5-4.4)
CT/RT	1152	259 (22.5)	893 (77.5)	37.3 (6.7)	2.4 (5.5)	2.5 (5.4)	23	31	3.5 (2.1-5.7)

Abbreviations: CT, chemotherapy; RT, radiotherapy.

SI conversion factor: To convert radiation dose to rad, multiply gray by 100.

[a] Includes patients treated for nonretinoblastoma cancer who did not undergo enucleation from January 1, 1945, to December 31, 1985.

[b] Includes patients who did not return a consent form or whose address was unknown.

[c] Computed as the occurrence of at least 1 cataract at 45 years of age.

Table 2. Characteristics of the 1833 Responding Survivors of Nonretinoblastoma Childhood Cancer

	First Cancer						Cataract		
				Radiation Dose to the Eyes, Mean (SD), Gy					
Childhood Cancer Type	No. of Patients	Age, Mean (Range), y	RT, No. (%)	Left	Right	CT, No. (%)	No. of Patients	No. of Cataracts	Cumulative Incidence, % (95% CI)[a]
Kidney tumor	463	2.8 (0-16)	327 (70.6)	0.2 (0.2)	0.2 (0.2)	424 (91.6)	3	6	0.9 (0.3-3.2)
Neuroblastoma	284	1.3 (0-14)	165 (58.1)	1.2 (3.9)	1 (2.8)	218 (76.8)	4	7	2.3 (0.7-7.2)
Lymphoma	335	8.3 (0-17)	217 (64.8)	3.6 (4.7)	3.3 (3.6)	301 (89.9)	4	6	1.4 (0.4-4.4)
Soft-tissue sarcoma	223	5.9 (0-15)	116 (52.0)	5.0 (10.8)	5.3 (12.1)	171 (76.7)	14	15	6.5 (3.9-10.7)
Bone sarcoma	140	10.3 (0-16)	93 (66.4)	0.4 (1.5)	0.3 (1.0)	108 (77.1)	2	3	3.7 (0.8-15.2)
CNS tumor	192	7 (0-16)	188 (97.9)	7.2 (7.4)	7.3 (7.5)	82 (42.7)	5	8	2.3 (0.5-9.9)
Gonadal tumor	122	5.9 (0-16)	40 (32.8)	1.7 (3.2)	1.5 (2.8)	74 (60.7)	0	0	0
Thyroid tumor	25	10.3 (2-15)	6 (24.0)	0.8 (0.7)	0.7 (0.7)	0	1	2	0
Other	49	7.2 (0-16)	23 (46.9)	4.3 (5.8)	3.7 (5.8)	27 (55.1)	0	0	0
All	1833	5.4 (0-17)	1175 (64.1)	2.6 (5.7)	2.5 (5.7)	1405 (76.7)	33	47	2.3 (1.5-3.5)

Abbreviations: CNS, central nervous system; CT, chemotherapy; RT, radiotherapy.

[a] Computed as the occurrence of at least 1 cataract at 45 years of age.

SI conversion factor: To convert radiation dose to rad, multiply gray by 100.

We also assessed proportional hazards assumptions for the Cox models. Attained age was used as the timescale in these models.

We used Poisson regression based on excess relative or absolute risk models[25] to evaluate the dose-effect relationship between the maximal radiation dose to the right or the left eye and the occurrence of cataract. We have tested linear (Risk = Background [1 + γdose] or Background + αdose), linear quadratic (Risk = Background [1 + $\gamma_1$dose + $\gamma_2$dose^2] or Background + $\alpha_1$dose + $\alpha_2$dose^2), and quadratic (Risk = Background [1 + γ"dose^2] or Background + α"dose^2) models by comparing nested models with excess relative and absolute risk models.[23] Background indicates the model with all the other treatment variables and sex, alcohol use, smoking, age at diagnosis, and calendar year at diagnosis; dose, the maximal radiation dose to the eyes; γ, γ_1, γ_2, and γ", coefficients for the radiation dose or the square of the radiation dose from excess relative risk models; and α, α_1, α_2, and α", coefficients for the radiation dose or the square of the radiation dose from excess absolute risk models. The CIs were estimated for variables using the method of maximum likelihood.[23] All statistical analysis was performed with SAS software (version 9.3; SAS Institute, Inc).[23]

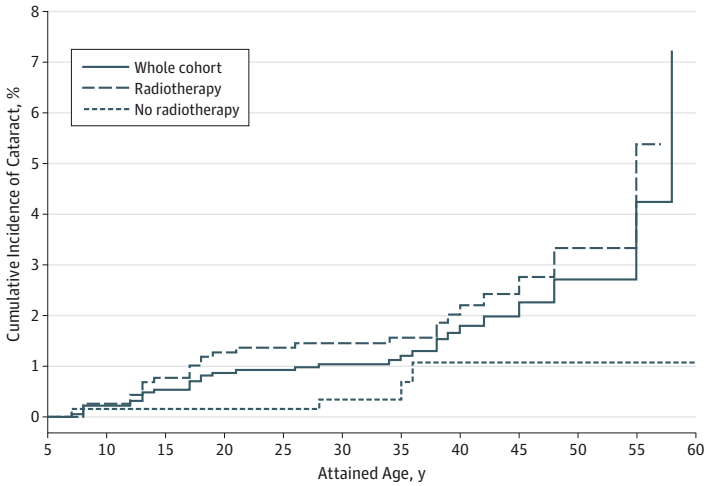
Results

The 1833 patients (961 men [52.4%]; 872 women [47.6%]; mean [SD] age, 37.0 [8.5] years) who returned the questionnaire were included in the study analysis (Figure 1 and Table 1). The median age at the diagnosis of cancer in the cohort study was 4 years (range, <1 to 17 years), and about 1224 patients (66.8%) received a diagnosis from 1948 to 1980. Of 1833 respondents selected for this study, 1175 patients (64.1%) received RT (**Table 2**). Of these 1175 patients, 893 (76.0%) received CT drugs also. The mean radiation dose received to the eyes was 2.6 Gy on the left side and 2.5 Gy on the right side and was higher in patients treated at 5 years or older than in those treated when younger.

A total of 52 cataracts were self-reported by 36 patients; a validation was obtained for 33 patients (19 with unilateral and 14 with bilateral cataracts), with a total of 47 validated cataracts (Table 1). The median time from childhood cancer to cataract diagnosis was 18 (interquartile range, 7-31; range, 2-55) years, and the median age at the diagnosis of cataract was 20 (interquartile range, 12-38; range, 6-62) years. Of the 33 patients, 25 underwent a surgical intervention. Cumulative incidence of cataract across attained age is given in **Figure 2**. The cumulative incidence of cataract at 45 years of age has been found to be approximately 2 times higher in men (3.1%) than in women (1.5%), 2 times higher in patients treated with RT (3.1%) than in patients treated without RT (1.5%) (Table 1 and Figure 2), and 3 times higher in patients treated with CT (2.9%) than in patients treated without CT (0.8%). Patients who received RT and CT had a cumulative incidence of cataract at 45 years of age of 3.5% (95% CI, 2.1%-5.7%) (Table 1). The higher risk for cataract was observed in patients treated for a soft-tissue sarcoma (6.5%) (Table 2), in patients who received a radiation dose to the eye of 10.0 Gy or greater (14.9%), and in patients who received melphalan hydrochloride (33.3%) (**Table 3**).

Overall, in a multivariable Cox proportional hazard regression analysis, patients who received RT had a 4.4-fold (95% CI, 1.5- to 13.0-fold) increased risk for cataract compared with patients who did not receive RT. The risk increased with the increasing maximal radiation dose to the eyes (P < .001 for trend), reaching a hazard ratio of 39.1 (95% CI, 12.0-127.9) at 10.0 Gy or more, compared with patients who did not receive RT (Table 3). A strong increase in the risk for cataract after melphalan treatment (P < .001 for trend; hazard ratio, 26.3; 95% CI, 7.1-96.6) was observed, but only a moderate increase in the risk for cataract was observed after other treatment with alkylating agents (P = .04). The analyses were not able to sup-

Figure 2. Cumulative Incidence of Cataract



No. at risk

Whole cohort	1833	1832	1824	1817	1752	1474	1085	661	324	142	57	20
Radiotherapy	1175	1175	1167	1160	1141	1029	811	521	262	111	42	17
No radiotherapy	658	657	657	657	611	445	274	140	62	31	15	3

Incidence is given for the entire cohort and stratified by receipt of radiotherapy.

port that alcohol intake, tobacco smoking, diabetes mellitus, glucocorticoid use, sex, and age at diagnosis modified the risk for cataract. Radiation dose response to the eye and melphalan effects remained significant when considering only the surgically treated cataracts.

Radiation dose in both eyes, accounting for the left and right sides, was associated with a significantly increased risk for cataract ($P < .001$ for trend) (eTable 1 in the Supplement). As described earlier, the radiogenic risk for cataract and the dose-response relationship were very similar when only the radiation dose to the eye that received the highest dose was considered, although the analysis was restricted to patients who did not receive melphalan (eTable 1 in the Supplement).

With use of the linear model, the dose-response relationship yielded an excess relative risk (ERR) per gray of 0.99 (95% CI, 0.06-1.91) (eTable 2 in the Supplement). However, the ERR model with the smallest Akaike information criterion value was the quadratic dose-response relationship. With this model, a dose-response relationship was observed with an increasing square of the radiation dose to the eye ($P = .02$). Whatever the type of analysis used, we observed no significant effect of age at RT on the risk for cataract ($P = .18$).

Discussion

This study is, to our knowledge, one of the largest undertaken to date on the risk for cataract validated in association with the radiation dose to the eye and CT drugs in early childhood, with respect to the size of the baseline cohort and the number of patients with quantitative assessment of the radiation dose. Our study shows that RT in the eye increases the risk for cataract in long-term survivors of childhood cancers. We also observed, for the first time, a higher risk for cataract among patients who had received melphalan compared with those treated without melphalan for their first cancers. We were not able to find evidence of an effect of the age at RT within our cohort.

Recently, Little[8] reported a fair degree of consistency in the radiogenic risks for cataract in several studies when continuous dose-response models were fitted. We estimated the radiation-associated ERR per gray as 0.99 (95% CI, 0.06 to 1.91). This ERR per gray is consistent with that found in some previous cohort studies.[8-14] For instance, a nonsignificant ERR pre gray of 2.00 (95% CI, −0.70 to 4.70) was observed by US radiologic technologists[14] and a significant ERR per gray of 0.32 (95% CI, 0.20-0.50) was observed in atomic bomb survivors.[10] In addition, Whelan et al[7] and Packer et al[15] reported an increased risk for cataract formation with increasing doses of radiation to the eye in the large CCSS cohort. Whelan et al[7] have reported that cancer survivors were at increased risk for cataracts compared with their siblings. This risk for cataracts was associated with exposure to prednisone and to a radiation dose of 30 Gy or greater to the posterior fossa or the temporal lobe. These authors reported that the dose of radiation to the eye also was significantly associated with the risk for cataracts, in a dose-dependent fashion.[7] Our findings are consistent with those of previous studies,[7,15] which relate to patients similar to ours.

One original finding of the present report is that the quadratic model provided an adequate fit to the dose response among survivors of childhood cancer who received moderate or high radiation doses for their treatment. However, among atomic bomb survivors, Neriishi et al[10] reported that no significant dose-response nonlinearity was seen in the incidence of cataract surgery after brief exposures to relatively low doses of radiation (0 to approximately 3.0 Gy). This difference can be explained by the different levels of radiation exposure to the lens in these 2 studies; in our study, 25% of sur-

Table 3. Multivariable Analysis of the Risks for Developing 1 or More Cataracts in a Cohort of 1833 Patients Treated for a Nonretinoblastoma Childhood Cancer

Treatment-Related Factors	Any Cataract				Cataract Surgery			
	No. of Patients With Cataract/Total No.	HR (95% CI)[a]	*P* Value	Cumulative Incidence, % (95% CI)[b]	No. of Patients With Cataract/Total No.	HR (95% CI)[a]	*P* Value	Cumulative Incidence, % (95% CI)[b]
Any alkylating agent treatment except melphalan hydrochloride								
No	13/928	1 [Reference]	.04	1.6 (0.8-3.2)	10/928	1 [Reference]	.07	1.1 (0.5-2.7)
Yes	20/905	2.5 (1.0-6.1)		2.9 (1.7-4.9)	15/905	2.5 (0.9-6.7)		2.0 (1.1-3.4)
Melphalan treatment								
No	29/1815	1 [Reference]	<.001	1.9 (1.2-2.8)	23/1815	1 [Reference]	.002	1.3 (0.8-2.1)
Yes	4/18	26.3 (7.1-96.6)		33.3 (11.6-73.8)	2/18	13.5 (2.5-71.5)		24.3 (5.4-75.5)
Radiation dose to the eyes, range (mean), Gy[c]								
No RT	4/711	1 [Reference]	<.001	1.0 (0.3-2.7)	4/711	1 [Reference]	<.001	1.0 (0.3-2.7)
>0 to 0.49 (0.2)	7/633	2.1 (0.6-7.3)		2.0 (0.9-4.5)	5/633	1.4 (0.4-5.5)		1.5 (0.5-4.0)
0.50 to 4.99 (2.2)	6/277	4.4 (1.2-16.7)		0.6 (0.1-4.4)	6/277	3.5 (0.9-13.6)		0.6 (0.1-4.4)
5.00 to 9.99 (7.1)	3/125	4.1 (0.9-19.3)		4.2 (1.2-14.1)	2/125	2.8 (0.5-15.9)		1.8 (0.5-7.1)
≥10.00 (22.7)	13/87	39.1 (12.0-127.9)		14.9 (9.0-24.3)	8/87	21.7 (6.1-77.4)		9.4 (4.8-17.9)
Glucocorticoid treatment								
No	32/1818	1 [Reference]	.72	2.3 (1.5-3.5)	24/1818	1 [Reference]	.65	1.6 (1.0-2.7)
Yes	1/15	1.4 (0.2-11.6)		0.0 (0.0-0.0)	1/15	1.6 (0.2-14.0)		0.0 (0.0-0.0)
Diabetes mellitus								
No	32/1777	1 [Reference]	.67	2.2 (1.4-3.4)	25/1777	1 [Reference]	.99	1.7 (1.0-2.9)
Yes	1/56	0.6 (0.1-5.0)		2.9 (0.4-19.1)	0/56	NA		0.0 (0-0)
Alcohol use								
No	7/402	1 [Reference]	.35	2.8 (1.0-7.5)	5/402	1 [Reference]	.42	2.3 (0.7-7.4)
Yes	26/1431	1.6 (0.6-4.0)		2.1 (1.3-3.3)	20/1431	1.6 (0.5-4.5)		1.4 (0.9-2.4)
Smoking								
No	18/861	1 [Reference]	.67	2.6 (1.4-4.7)	14/861	1 [Reference]	.98	2.1 (1.0-4.3)
Yes	15/972	1.2 (0.6-2.5)		2.0 (1.1-3.7)	11/972	1.0 (0.4-2.4)		1.2 (0.6-2.4)
Sex								
Women	15/872	1 [Reference]	.52	1.5 (0.8-2.8)	13/872	1 [Reference]	.72	1.2 (0.6-2.4)
Men	18/961	1.3 (0.6-2.7)		3.1 (1.7-5.4)	12/961	1.2 (0.5-2.7)		2.1 (1.0-4.3)
All, age at diagnosis	33/1833	0.9 (0.8-1.0)	.18	NA	25/1833	1.0 (0.9-1.1)	.44	NA

Abbreviations: NA, not applicable; RT, radiotherapy.

SI conversion factor: To convert radiation dose to rad, multiply gray by 100.

[a] Cox proportional hazards regression model was adjusted for administration of melphalan and other alkylating agents, sex, age at diagnosis, calendar year at diagnosis, glucocorticoids, diabetes mellitus, smoking, and alcohol use.

[b] Computed as the occurrence of at least 1 cataract at 45 years of age.

[c] Indicates dose to the eye that received the highest dose.

vivors of childhood cancer who underwent RT had received radiation doses to the eyes of greater than 3.0 Gy.

To our knowledge, the present study elucidated for the first time the risk for cataract after treatment with melphalan and RT among survivors of childhood cancer. Melphalan was significantly associated with the risk for cataract development. This result is consistent with the conclusion of Suesskind et al,[26] who reported that melphalan may induce cataract formation, possibly as a toxic effect of this CT agent to the lens, maybe combined with radiation exposure.

In our analysis, we found no substantially increased risk for cataract owing to alcohol intake. This result is consistent with that from a recently published meta-analysis of 7 prospective cohort studies.[27] A link between tobacco smoking and risk for cataract development was not identified. This result is in contrast with those of most of the studies that have reported a link between tobacco smoking and an increased risk for cataract development in the general population.[28,29] However, the main cause of cataracts that is clinically relevant is aging, and comparison with the general population on an environmental risk factor such as smoking is challenging given the young age at onset of cataract in survivors of childhood cancer (median age, 20 years) and thus their relatively weak exposure to tobacco. The analysis did not show a clear dependency of age at RT on the risk for cataract. In a study population very close to the present work in its range of age at diagnosis,

Alloin et al[30] have also pointed out that age at RT does not appear to affect the risk significantly.

Although we restricted our analysis to confirmed cataract cases or those undergoing surgery, the major caveat in interpreting the findings is that we could not identify patients with a stable cataract with slight or no concerns about visual acuity, the stage of the cataract, or the type of the cataract—namely, cortical, nuclear, and posterior subcapsular. However, cataract surgery is probably a more relevant outcome for posterior subcapsular cataract than clinical lens changes, because the presence of posterior subcapsular cataract is the most important lens opacity associated with cataract surgery.[31] Another limitation of our study is the small number of cataracts—33 patients with unilateral or bilateral cataract, for a total of 47 validated cataracts—which strongly limits the analysis of risk factors. In our study, only 2 patients had received busulfan; therefore, we were unable to investigate its potential role in an increase of cataract risk. The analyses did not support modification of the risk for cataract by administration of glucocorticoids (n=15) or the presence of diabetes mellitus (n=56). In only 1 case did the patient receive glucocorticoids, and in another case, only 1 patient had diabetes mellitus. In addition, consensus lies in the fact that among the main sources of uncertainty in retrospective dose estimates, the completeness of RT records is the most critical point.[32] For all patients included in the present study, the RT records contain the most critical information on sizes and locations of irradiation fields, prescribed dose, and patient clinical characteristics. Last, results of this study are limited to the use of a self-administered questionnaire instead of face-to-face interviews. Patients who had major visual impairments may not have answered the self-administered questionnaire, which may introduce participation bias. This bias could underestimate the risk but has a minimal effect given the satisfactory rate of the responses (75.6%).

Conclusions

The present study, with a mean follow-up of 32 years from cancer diagnosis, adds new information by providing risk estimates for the occurrence of late eye-related effects. The availability of detailed treatment information, including individual radiation dosimetry to the eye, allowed for investigation of treatment-related risk factors, which can inform guideline-based recommendations for long-term follow-up for cataracts.

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