Original Article

Chronic Medical Conditions in Adult Survivors of Retinoblastoma: Results of the Retinoblastoma Survivor Study

Danielle Novetsky Friedman, MD[1]; Joanne F. Chou, MPH[2]; Kevin C. Oeffinger, MD[1,3]; Ruth A. Kleinerman, MPH[4]; Jennifer S. Ford, PhD[5]; Charles A. Sklar, MD[1]; Yuelin Li, PhD[2]; Mary S. McCabe, RN, MA[6]; Leslie L. Robison, PhD[7]; Brian P. Marr, MD[8]; David H. Abramson, MD[8]; and Ira J. Dunkel, MD[1]

BACKGROUND: Limited data are available regarding long-term morbidity in adult survivors of retinoblastoma (Rb). **METHODS:** The Retinoblastoma Survivor Study is a retrospective cohort of adult survivors of Rb diagnosed between 1932 and 1994. Participants completed a comprehensive questionnaire adapted from the Childhood Cancer Survivor Study surveys. Chronic conditions were classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03). Multivariate Poisson regression was used to compare survivors of Rb with 2377 non-Rb controls, consisting of the Childhood Cancer Survivor Study sibling cohort and survivors with bilateral versus unilateral disease. **RESULTS:** Survivors of Rb (53.6% with bilateral disease) and non-Rb controls had a mean age of 43.3 years (standard deviation, 11 years) and 37.6 years (SD, 8.6 years), respectively, at the time of study enrollment. At a median follow-up of 42 years (range, 15-75 years), 86.6% of survivors of Rb had at least 1 condition and 71.1% had a severe/life-threatening (grade 3-4) condition. The adjusted relative risk (RR) of a chronic condition in survivors compared with non-Rb controls was 1.4 (95% confidence interval [95% CI], 1.3-1.4; $P<.01$); for a grade 3 to 4 condition, the RR was 7.6 (95% CI, 6.4-8.9; $P<.01$). Survivors were at an excess risk regardless of laterality. After stratifying by laterality and excluding ocular conditions and second malignant neoplasms (SMNs), only those with bilateral disease were found to be at an increased risk of any nonocular, non-SMN condition (RR, 1.2; 95% CI, 1.1-1.2) and for grade 3 to 4 nonocular, non-SMN conditions (RR, 1.7; 95% CI, 1.2-2.5). **CONCLUSIONS:** Survivors of Rb have an increased risk of chronic conditions compared with non-Rb controls. After excluding ocular conditions and SMNs, this excess risk was found to persist only for those with bilateral disease. ***Cancer*** **2016;122:773-81**. © *2016 American Cancer Society.*

KEYWORDS: follow-up studies, questionnaires, retinoblastoma, risk, survivors.

INTRODUCTION

Retinoblastoma (Rb) is the most common intraocular tumor of childhood. Due to therapeutic advances, survival rates in higher-income countries now exceed 95%.[1] Although much is known concerning the oculovisual problems of survivors of Rb, as well as the increased risk of second malignant neoplasms (SMNs) in those with hereditary disease,[2-6] to our knowledge little is known regarding the long-term health of these individuals.

The current study was designed to fill this gap by characterizing long-term medical outcomes among adult survivors of Rb. The objectives of this study were to: 1) determine the prevalence and excess risk of any chronic medical condition in adult survivors of Rb when compared with unaffected individuals of similar age, sex, and race/ethnicity; 2) delineate the prevalence and excess risk of nonocular, non-SMN chronic conditions in adult survivors of Rb when compared with a non-Rb cohort; 3) identify factors associated with inferior long-term medical outcomes; and 4) report on the general health of survivors of Rb.

MATERIALS AND METHODS

The current study was modeled after the Childhood Cancer Survivor Study (CCSS), a questionnaire-based, retrospective cohort study investigating the long-term health of >14,000 survivors of childhood cancer diagnosed from 1970 through

Corresponding author: Danielle Novetsky Friedman, MD, Department of Pediatrics, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; Fax: (212) 717-3239; friedmad@mskcc.org

[1]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York; [2]Department of Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; [3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland; [5]Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, New York; [6]Clinical Director, Survivorship Center, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York; [7]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee; [8]Ophthalmic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, New York.

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1986.[7,8] The CCSS has shown that when compared with a sibling comparison group, survivors of childhood cancer exhibit excess premature treatment-related morbidity and mortality.[9-11] Although the CCSS includes survivors of a wide range of pediatric cancers, survivors of Rb are not included in the cohort. We performed a descriptive, cross-sectional, self-report study of health among adult survivors of Rb.

Study Population

Eligible participants were defined as living survivors of Rb who were treated in New York, were at least 18 years of age at the time of study enrollment, and were able to provide informed consent. Survivors were identified via the Memorial Sloan Kettering Cancer Center (MSKCC) and National Cancer Institute (NCI) databases (987 survivors). The study was approved by the MSKCC and NCI Institutional Review Boards/Privacy Boards.

Eligible participants were sent an introductory mailing that included an invitation to participation; an informed consent form; a survey packet; and a self-addressed, prestamped envelope by mail. Participants were contacted by telephone 2 weeks after the mailing to ascertain interest in participation and were given the option of completing the survey by telephone or by mail, depending on participant preference. In total, 366 surveys (77.9%) were completed by mail. Enrollment occurred from March 2008 through February 2011.

Despite the repeated use of advanced tracing methods among 987 identified survivors of Rb, we were unable to locate or contact 290 survivors (29.3%). An additional 46 patients were found to be ineligible for reasons including never having been diagnosed with Rb (15 patients); death (11 patients); and inability to provide consent due to significant cognitive impairment (8 patients), language barrier (5 patients), or miscellaneous reasons such as incarceration or emotional difficulties (5 patients). Among the remaining 651 subjects, 470 consented and completed the questionnaire; 72.2% of those who were contacted and found to be eligible participated (Fig. 1).

To provide a comparison population that had not been treated for cancer, responses were compared with those obtained from the CCSS sibling cohort,[7] a random sample of CCSS participants' living siblings who were nearest in age and who also completed CCSS questionnaires. None of these individuals were siblings of survivors of Rb. Rather, CCSS siblings who completed the CCSS Follow-Up 4 questionnaire (administered from July 2007-November 2009) were included as a control group

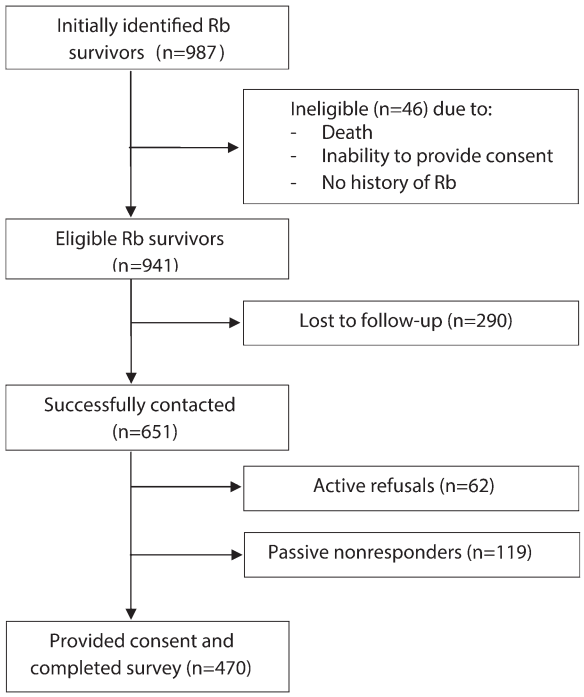

Figure 1. Participation and contact in the Retinoblastoma (Rb) Survivor Study.

(ie, "non-Rb controls"). Self-reported data from 2377 comparison individuals were included.

Outcome Measure

Survivors of Rb completed a comprehensive survey that was adapted from CCSS questionnaires[8,12] and supplemented with questions of specific interest to survivors of Rb (ie, a validated instrument that measures vision-related health status in those with chronic eye diseases[13]). A copy of the survey is available upon request. The survey included items that assessed sociodemographic factors, chronic medical conditions,[9] health status,[14] and visual impairment.[13] The responses of survivors of Rb were compared with previously collected CCSS sibling data, which did not include supplementary visual information. Data regarding survivors' health status, particularly in relation to visual functioning, will be reported elsewhere.

The severity of chronic conditions was coded using the NCI's Common Terminology Criteria for Adverse Events (CTCAE; version 4.03),[15] a scoring system used to grade acute and chronic conditions in patients with cancer and cancer survivors as mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or fatal (grade 5). There were no reported grade 5 conditions because all participants and controls were

alive at the time of study entry. If adequate information to distinguish between grades was unavailable, the lower score was used.

Treatment History

Treatment history was abstracted from the NCI and MSKCC databases. Chemotherapy exposure was recorded as a yes/no/unknown variable; for those treated with chemotherapy, the names of specific agents were abstracted. Treatment with radiotherapy was categorized as a binary yes/no variable; details regarding the type of radiotherapy (brachytherapy, external-beam radiotherapy, or both) were abstracted. All treatment data refer to therapy administered for the treatment of primary or metastatic Rb; details regarding SMN-directed therapy were not available.

Statistical Analysis

Characteristics of survey respondents were described, using summary statistics and frequency counts, between survivors of Rb (stratified by laterality) and the non-Rb controls. Differences between groups were examined by the nonparametric Wilcoxon rank sum test for continuous variables or the Fisher exact test for categorical variables. The prevalence of: 1) any chronic condition and 2) nonocular/non-SMN chronic conditions among survivors of Rb and non-Rb controls was determined. For each analysis, 3 dichotomous outcome variables were assessed: 1) indication of any condition; 2) indication of grade 3 to 4 conditions; and 3) multiple chronic conditions. For participants who had >1 chronic condition, the maximum grade of that condition was used. Tabulation of chronic conditions was censored at the time of SMN diagnosis for survivors of Rb and primary cancer diagnosis for non-Rb controls. All included SMNs were pathologically verified. SMN and oculovisual outcomes such as cataracts, glaucoma, double vision, and blindness were excluded from the second analysis, which focused solely on nonocular, non-SMN chronic conditions.[2,3]

To compare the prevalence of chronic conditions between survivors of Rb and non-Rb controls, Poisson regression analysis with robust variance estimates was used to estimate the relative risk (RR) ratios and their corresponding 95% confidence intervals (95% CIs). Analyses were adjusted for age at study, sex, and race/ethnicity.[16]

Multivariate Poisson regression was used to evaluate differences in severe/disabling or life-threatening conditions and the 2 most common grade 3 to 4 chronic conditions among survivors of Rb according to Rb-directed treatment received.

All statistical analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC) and 2-sided statistical inferences were used throughout the analyses.

RESULTS

Comparisons of Rb Survivor Participants and Nonparticipants

When comparing baseline demographics of eligible survivors of Rb who did or did not participate in the study, participants were more likely to be older at the time of the study (median age, 48 years vs 46 years; $P = .02$), be female (52.1% vs 43.7%; $P<.01$), and have a history of bilateral disease (53.6% vs 46.3%; $P = .02$). There was no difference in age at Rb diagnosis noted among those who participated and those who did not.

Comparisons of Survivors of Rb and the Non-Rb Controls

Characteristics of survivors and non-Rb controls are shown in Table 1. Survivors of Rb were older at the time of the study compared with controls ($P<.001$), were less likely to be white non-Hispanic (<0.001), and were more likely to report a lower household income ($P<.001$). The 2 groups did not differ significantly in terms of sex, health insurance status, or highest level of education attained.

Treatment Characteristics of Survivors of Rb

Among survivors of Rb, 26.0% were treated with any chemotherapy and 56.5% were treated with any radiotherapy (Table 2). Treatment with radiotherapy differed markedly by laterality; radiotherapy was administered to 91.7% of bilateral survivors and 15.7% of unilateral survivors ($P<.01$).

Among survivors of Rb who were treated with systemic chemotherapy, 95.5% had received at least 1 alkylating agent, which included triethylenemelamine (62.2%), cyclophosphamide (27.7%), and/or nitrogen mustard (1.7%) (Table 2). None of the participants had documented exposure to a platinum agent. Survivors of bilateral disease were more likely to have received chemotherapy than survivors of unilateral disease ($P<.01$).

Fifty-eight survivors of Rb had at least 1 pathologically confirmed SMN (grade 3-4), which excluded nonmelanoma skin cancer, at a median age of 40.5 years (range, 5-70 years). Table 3 outlines the distribution of SMN in the 58 affected survivors of Rb.

TABLE 1. Demographic Characteristics of Adult Survivors of Rb and a Non-Rb Control Group

Characteristics	All Rb Survivors n = 470	Unilateral Survivors n = 218	Bilateral Survivors n = 252	Non-Rb Controls n = 2377	*P*[a]
Mean age at study (SD), y	43.3 (11.0)	44.4 (11.0)	42.5 (10.8)	37.6 (8.6)	<.001
Sex, no. (%)					.51
Male	225 (47.9)	98 (44.9)	127 (50.4)	1097 (46.2)	
Female	245 (52.1)	120 (55.1)	125 (49.6)	1280 (53.8)	
Race/ethnicity, no. (%)					<.001
White, non-Hispanic	406 (86.4)	185 (84.9)	221 (87.7)	2117 (89.0)	
Other group	62 (13.2)	32 (14.7)	30 (11.9)	177 (7.5)	
Do not know/missing	2 (0.4)	1 (0.4)	1 (0.4)	83 (3.5)	
Health insurance, no. (%)					.07
Yes or Canadian resident	416 (88.5)	188 (86.2)	228 (90.4)	2163 (91.0)	
No	52 (11.1)	29 (13.3)	23 (9.2)	199 (8.4)	
Do not know/missing	2 (0.4)	1 (0.5)	1 (0.4)	15 (0.6)	
Household income, no. (%)					<.001
<$20,000/y	45 (9.6)	13 (6.5)	32 (13.5)	120 (5.1)	
≥$20,000/y	392 (83.4)	187 (93.5)	205 (86.5)	2095 (88.1)	
Do not know/missing	33 (7.0)	18 (8.3)	15 (5.9)	162 (6.8)	
Education, no. (%)					.16
Complete high school or below	64 (13.8)	28 (13.1)	36 (14.5)	274 (11.5)	
Post-high school graduate or some college training	394 (85.1)	185 (86.5)	209 (83.5)	2100 (88.3)	
Missing	12 (2.6)	5 (2.3)	7 (2.7)	3 (0.1)	

Abbreviations: Rb, retinoblastoma; SD, standard deviation.
[a] Comparisons between all survivors of Rb and the non-Rb control group; responses coded as "do not know/missing" were excluded in the calculations of *P* values.

TABLE 2. Treatment Characteristics of Survivors of Rb by Laterality

Characteristics	All Rb Survivors n = 470	Unilateral Survivors n = 218	Bilateral Survivors n = 252	*P*
RT				<.01
Yes	265 (56.5)	34 (15.6)	231 (91.7)	
No	200 (42.6)	180 (82.6)	20 (7.9)	
Unknown	5 (1.0)	4 (1.8)	1 (0.4)	
Type of RT (n = 265)				<.01
Brachytherapy	8 (3.0)	3 (1.1)	5 (1.9)	
External	224 (84.5)	28 (10.6)	196 (73.9)	
External/brachytherapy	29 (11.0)	1 (0.4)	28 (10.6)	
Unspecified	4 (1.5)	2 (0.8)	2 (0.8)	
Chemotherapy				<.01
Yes	119 (25.3)	25 (11.5)	94 (37.3)	
No	347 (73.8)	190 (87.2)	157 (62.3)	
Unknown	4 (0.9)	3 (1.3)	1 (0.4)	
Type of chemotherapy[a]				
TEM	74 (62.2)	6 (27.3)	68 (76.4)	
Cyclophosphamide	33 (27.7)	16 (72.7)	17 (19.1)	
Nitrogen mustard	2 (1.7)	0 (0.0)	2 (2.2)	
Nonalkylating agent	30 (27.0)	14 (63.6)	16 (17.9)	

Abbreviations: Rb, retinoblastoma; RT, radiotherapy; TEM, triethylenemelamine.
[a] A total of 111 survivors of Rb with complete chemotherapy data (22 with history of unilateral disease and 89 with history of bilateral disease).

General Health of Survivors of Rb

Survivors of Rb were asked to provide self-reported ratings of their general health ("excellent," "very good," "good," "fair," or "poor"). The vast majority of survivors (94.4%) described their health as "good" (24.2%), "very good" (40.0%), or "excellent" (28.9%) versus fair (4.9%) or poor (0.6%). Compared with patients with bilateral disease, a greater percentage of patients with unilateral disease described their health as good to excellent (98.1% among patients with unilateral and 91.2% among patients with bilateral disease; $P<.01$).

TABLE 3. Distribution of Pathologically Verified Subsequent Malignancies in 58 Survivors of Rb[a]

SMN Distribution	No.
Sarcoma, any	24
Leiomyosarcoma	10
Spindle cell sarcoma	2
Osteosarcoma	7
Synovial sarcoma	1
Fibrosarcoma	1
Liposarcoma	2
Malignant fibrous histiocytoma	1
Melanoma	19
Breast cancer	7
Thyroid cancer	6
Adenocarcinoma, nasal cavity	4
Tongue cancer	2
Parotid cancer	1
Bladder cancer	1
Neuroendocrine cancer	1
Malignant meningioma of the sphenoid sinus	1
Chronic lymphocytic leukemia	1
Uterine cancer	1
Endometrial cancer	1
Non-Hodgkin lymphoma	1
Lung cancer	1
Kidney cancer	1
Adenocarcinoma, colon	1
Neuroblastoma	1
Malignant epithelioma	1

Abbreviations: Rb, retinoblastoma; SMN, second malignant neoplasm.
[a] Numbers do not sum to 58 due to history of multiple subsequent malignancies in some survivors.

Overall Risk of Chronic Medical Conditions: Comparison of Survivors of Rb by Laterality and the Non-Rb Controls

Table 4 summarizes the risk of a chronic health condition of any grade among the cohort of survivors of Rb (stratified by laterality) and non-Rb controls.

Risk in the overall cohort of survivors of Rb

With a median follow-up of 42 years (range, 15-75 years), 407 survivors of Rb (86.6%) had a chronic health condition of any grade, and 334 (71.1%) had a severe, disabling, or life-threatening (grade 3-4) condition. Table 5 outlines the distribution of all grade 3-4 chronic conditions in the Rb cohort. Non-Rb controls reported fewer chronic conditions, with 58.1% reporting any chronic condition and 8.2% reporting a grade 3 to 4 condition.

After adjusting for age at study, sex, and race/ethnicity, the RR of a survivor having any chronic condition when compared with non-Rb controls was 1.4 (95% CI, 1.3-1.4; $P<.01$), whereas the RR of a grade 3 to 4 chronic condition was 7.6 (95% CI, 6.4-8.9; $P<.01$). Survivors of Rb were 1.8 times more likely to have ≥ 2 chronic health conditions (95% CI, 1.6-2.0; $P<.01$) when compared with non-Rb controls (Table 4).

Risk by laterality

Within the cohort of survivors of Rb, the percentage of chronic conditions differed significantly by laterality, with 78.4% of patients with unilateral disease and 93.7% of patients with bilateral disease reporting a chronic condition of any grade ($P<.01$), and 61.0% of patients with unilateral disease and 79.8% of patients with bilateral disease reporting a grade 3 to 4 chronic condition ($P<.01$) (Table 4).

When compared with non-Rb controls of similar age, sex, and race/ethnicity, survivors of Rb were at an increased risk of developing any chronic condition regardless of laterality (RR, 1.2; 95% CI, 1.1-1.3 [$P<.01$] for survivors of unilateral disease and RR, 1.5; 95% CI, 1.4-1.6 [$P<.01$] for survivors of bilateral disease). Similarly, survivors of Rb with a history of unilateral disease (RR, 5.7; 95% CI, 4.6-7.1 [$P<.01$]) and bilateral disease (RR, 8.3; 95% CI, 7.0-9.7 [$P<.01$]) were both at an increased risk of developing a grade 3 to 4 chronic condition, in comparison with non-Rb controls.

Risk of Nonocular, Non-SMN Chronic Medical Conditions: Comparison of Survivors of Rb by Laterality and Non-Rb Controls

Risk in the overall cohort of survivors of Rb

Given the paucity of data regarding long-term medical outcomes other than SMN and oculovisual conditions in adult survivors of Rb, a separate analysis focusing only on nonocular, non-SMN conditions was performed. Among 470 adult survivors of Rb, 68.1% reported at least 1 nonocular, non-SMN chronic condition of any grade and 11.7% reported a grade 3 to 4 nonocular, non-SMN condition (Table 6). In contrast, 55.3% of non-Rb controls reported a nonocular, non-SMN condition of any grade, and 6.0% reported a grade 3 to 4 nonocular, non-SMN condition.

The adjusted RR of a nonocular, non-SMN condition of any grade in a survivor of Rb when compared with non-Rb controls was 1.1 (95% CI, 1.02-1.2; $P<.01$); the risk of multiple nonocular, non-SMN conditions was 1.3 (95% CI, 1.1-1.5; $P<.01$). However, there was no excess risk of a grade 3 to 4 nonocular, non-SMN chronic condition noted among survivors of Rb (RR, 1.3; 95% CI, 0.9-1.8 [$P = .19$]) when compared with non-Rb controls.

Risk by laterality

After stratifying survivors of Rb by laterality, we found that survivors of bilateral disease were more likely to report a nonocular, non-SMN chronic condition of any grade (RR, 1.2; 95% CI, 1.1-1.3 [$P<.01$]); a grade 3 to 4 nonocular, non-SMN chronic condition (RR, 1.7; 95% CI, 1.2-2.5 [$P<.01$]); and multiple nonocular, non-SMN

TABLE 4. Any Chronic Health Condition (Including Ocular Outcomes and SMN) in Adult Survivors of Rb[a]

Health Condition[b]	All Survivors of Rb n = 470	Unilateral Survivors n = 218	Bilateral Survivors n = 252	Non-Rb Controls n = 2377	All Survivors of Rb Versus Non-Rb Controls RR (95% CI)[c]	Unilateral Survivors Versus Non-Rb Controls RR (95% CI)[c]	Bilateral Survivors Versus Non-Rb Controls RR (95% CI)[c]
Any condition							
Grades 1-4	407 (86.6)	171 (78.4)	236 (93.7)	1381 (58.1)	1.4 (1.3-1.4)	1.2 (1.1-1.3)	1.5 (1.4-1.6)
Grades 3-4	334 (71.1)	133 (61.0)	201 (79.8)	195 (8.2)	7.6 (6.4-8.9)	5.7 (4.6-7.1)	8.3 (7.0-9.7)
Multiple health conditions (grades 1-4)							
≥2	297 (63.2)	113 (51.8)	184 (73.0)	714 (30.0)	1.8 (1.6-2.0)	1.3 (1.1-1.6)	2.1 (1.9-2.4)

Abbreviations: 95% CI, 95% confidence interval; Rb, retinoblastoma; RR, relative risk; SMN, second malignant neoplasm.
[a] The severity of health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 4.03).
[b] All survivors and members of the non-Rb control group were alive at the time of study entry, and therefore no grade 5 or fatal conditions existed at the time of the study.
[c] Comparisons between survivors and non-Rb controls were adjusted for age at enrollment, sex, and race/ethnicity.

TABLE 5. Distribution of All Grade 3 to 4 Chronic Health Conditions in 470 Adult Survivors of Rb

Chronic Condition	No. of Affected Survivors of Rb
Visual dysfunction	291
Legally blind in 1 eye	190
Legally blind in both eyes or loss of an eye	101
Subsequent malignant neoplasms	58
Cataracts, requiring surgery	51
Severe hearing loss	15
Thyroid nodules requiring surgery	12
Diabetes requiring insulin	7
Stroke/CVA	7
Nerve paralysis	5
Lung fibrosis, requiring oxygen	4
Intestinal obstruction requiring surgery	4
Heart attack, requiring cardiac catheterization, angioplasty, or CABG	3
Congestive heart failure, requiring medication	2
Blood clot in head, lung, arm, leg, or pelvis	2
Heart valve replacement	2
Pulmonary embolism	2
Emphysema, requiring medication	1
Sleep apnea, requiring surgery	1
Arrhythmia, requiring pacemaker	1
Cirrhosis	1
Urinary incontinence	1

Abbreviations: CABG, coronary artery bypass graft surgery; CVA, cardiovascular accident; Rb, retinoblastoma.

conditions of any grade (RR, 1.6; 95% CI, 1.4-1.8 [$P<.01$]) when compared with non-Rb controls. In contrast, survivors of unilateral disease were not found to be at an increased risk of any of these outcomes (Table 6).

Most Common Grade 3 to 4 Nonocular, Non-SMN Chronic Conditions Within the Cohort of Survivors of Rb

The 2 most common grade 3 to 4 nonocular, non-SMN conditions among survivors of Rb were loss of hearing and suspicious thyroid nodules requiring partial or total thyroidectomy. Among the 15 survivors of Rb who developed grade 3 to 4 severe hearing loss, 73.3% (11 survivors) received radiotherapy and 20% (3 survivors) received nonplatinum chemotherapy. Among the 12 survivors of Rb who developed grade 3 thyroid nodules, 75% (9 survivors) received radiotherapy and 41.7% (5 survivors) received chemotherapy. Approximately 87% of those who developed severe hearing loss and 83% of those who developed grade 3 thyroid nodules had a history of bilateral disease.

Predictors of Risk of the Development of Grade 3 to 4 Chronic Conditions: Overall and Nonocular, Non-SMN

Impact of treatment exposures and age at enrollment

In multivariate models, exposure to radiotherapy and increasing age at study were found to predict increased risk of the development of any grade 3 to 4 chronic condition (RR, 1.2; 95% CI, 1.01-1.3 [$P = .03$] for radiation exposure and RR, 1.1; 95% CI, 1.01-1.1 [$P = .01$] for older age at study) (Table 7). Exposure to chemotherapy alone was not found to be a predictor of increased risk (RR, 1.1; 95% CI, 0.98-1.3 [$P = .09$]).

When these same factors were examined in relation to the development of a grade 3 to 4 nonocular, non-SMN condition, Rb-directed therapeutic exposures were not found to increase survivors' risk of these outcomes (Table 8). However, there was a trend toward significance for those previously exposed to radiotherapy (RR, 1.7; 95% CI, 0.9-2.8 [$P = .07$]). Patients who were older at the time of study were more likely to report a grade 3 to 4 nonocular, non-SMN chronic condition (RR, 1.5; 95% CI, 1.2-1.9 [$P<.01$]) compared with younger patients.

TABLE 6. Nonocular/Non-SMN Chronic Health Conditions in Adult Survivors of Rb[a]

Health Condition[b]	All Survivors of n = 470	Unilateral Survivors n = 218	Bilateral Survivors n = 252	Non-Rb Controls n = 2377	All Survivors of Rb Versus Non-Rb Controls RR (95% CI)[c]	Unilateral Survivors Versus Non-Rb Controls RR (95% CI)[c]	Bilateral Survivors Versus Non-Rb Controls RR (95% CI)[c]
Any condition							
Grades 1-4	320 (68.1)	132 (60.5)	188 (74.6)	1314 (55.3)	1.1 (1.02-1.2)	0.9 (0.8-1.1)	1.2 (1.1-1.3)
Grades 3-4	55 (11.7)	17 (7.8)	38 (15.1)	142 (6.0)	1.3 (0.9-1.8)	0.7 (0.4-1.2)	1.7 (1.2-2.5)
Multiple health conditions (Grades 1-4)							
≥2	212 (45.1)	74 (33.9)	138 (54.7)	671 (28.2)	1.3 (1.1-1.5)	0.9 (0.7-1.1)	1.6 (1.4-1.8)

Abbreviations: 95% CI, 95% confidence interval; Rb, retinoblastoma; RR, relative risk; SMN, second malignant neoplasm.
[a] The severity of health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 4.03).
[b] All survivors and members of the non-Rb control group were alive at the time of study entry, and therefore no grade 5 or fatal conditions existed at the time of the study.
[c] Comparisons between survivors and non-Rb controls were adjusted for age at enrollment, sex, and race/ethnicity.

TABLE 7. Predictors of Grade 3 to 4 Chronic Health Conditions in Adult Survivors of Rb

	RR (95% CI)	*P*
Radiotherapy		.03
Yes	1.2 (1.01-1.3)	
No (reference)	1.0	
Chemotherapy		.09
Yes	1.1 (0.98-1.3)	
No (reference)	1.0	
Age at study[a]	1.1 (1.01-1.1)	.01

Abbreviations: 95% CI, 95% confidence interval; Rb, retinoblastoma; RR, relative risk.
[a] Estimating 10-year increments of age.

Impact of low visual acuity

The impact of low visual acuity on grade 3 to 4 nonocular, non-SMN chronic condition risk was explored as well. A significantly greater percentage of those with grade 3 to 4 vision loss reported a severe, disabling, or life-threatening nonocular, non-SMN condition when compared with those with grades 0, 1, or 2 vision loss (14.1% vs 7.8%; $P = .04$).

In multivariate analyses adjusting for age at enrollment, exposure to chemotherapy, and radiotherapy, survivors of Rb with grade 3 to 4 vision loss were no more likely to report a grade 3 to 4 nonocular, non-SMN condition than those with grades 0, 1, or 2 vision loss (RR, 1.6; 95% CI, 0.9-2.6 [$P = .09$]).

DISCUSSION

To the best of our knowledge, the current study is the largest study to date to assess the medical outcomes and general health of adult survivors of Rb. Although extensive data exist regarding the risk of SMN[3-6,17] and oculovisual outcomes[18-22] in survivors of Rb, there is a paucity of information regarding chronic medical conditions in this population. In the current report, we found that adult survivors of Rb were 1.4 times more likely to report any chronic condition, and 7.6 times more likely to have a severe or life-threatening chronic condition, when compared with a similarly aged cohort of individuals without a history of Rb. It is interesting to note that survivors of Rb were also more likely to develop multiple chronic conditions compared with controls. This excess risk was evident for survivors of Rb regardless of laterality, although those with bilateral disease were at greater risk than those with unilateral disease.

Existing data regarding long-term medical outcomes in survivors of Rb are limited. One report on medical outcomes in 21 survivors of Rb found the most frequent late effect to be postradiotherapy orbital deformation.[23] Another study on health-related quality of life in Swiss survivors of childhood cancer noted that a diagnosis of Rb was associated with lower scores in the physical component summary of the Short Form-36 (SF-36).[24] Van Dijk et al[25-28] and others[21,29] have studied psychosocial, behavioral, and functional outcomes in survivors of Rb, but have not described survivors' treatment-related chronic medical conditions.

Other reports have demonstrated similar excess risks of chronic conditions in survivors of non-Rb childhood cancer. In a landmark study of >10,000 adult survivors of childhood cancer from the CCSS, survivors of non-Rb cancer were found to have a 3.3-fold increased risk of developing a chronic condition and an 8.2-fold increased risk of a grade 3 to 4 condition when compared with unaffected siblings (who also comprise the control group in the current

TABLE 8. Predictors of Grade 3 to 4 Nonocular, Non-SMN Chronic Health Conditions in Adult Survivors of Rb

	RR (95% CI)	*P*
Radiotherapy		.07
Yes	1.7 (0.9-2.8)	
No (reference)	1.0	
Chemotherapy		.64
Yes	0.9 (0.5-1.6)	
No (reference)	1.0	
Age at study[a]	1.5 (1.2-1.9)	<.01

Abbreviations: 95% CI, 95% confidence interval; Rb, retinoblastoma; RR, relative risk; SMN, second malignant neoplasm.
[a] Estimating 10-year increments of age.

report).[9] More recently, Armstrong et al reported that the cumulative incidence of a grade 3 to 5 health condition among childhood cancer survivors by age 50 years was 53.6%.[30] Although the risk of serious chronic conditions is modestly higher in the CCSS survivor cohort compared with the Rb cohort reported herein, it is important to note that we censored survivors at the time of SMN diagnosis, whereas the CCSS report did not.

Given that the nonocular, non-SMN medical outcomes of survivors of Rb have been understudied, we conducted a separate analysis of these outcomes. We found that survivors of Rb were more likely to develop a nonocular, non-SMN chronic condition of any grade when compared with non-Rb controls, but were not more likely to develop a grade 3 to 4 nonocular, non-SMN condition. It is important to note that the excess risk of developing nonocular, non-SMN chronic conditions in survivors of Rb was confined to those with a history of bilateral disease.

Encouragingly, despite these excess risks, the vast majority of adult survivors of Rb reported good to excellent health. As expected, significantly fewer patients with a history of bilateral disease reported good to excellent health when compared with subjects with unilateral disease. This self-perceived inferior general health may be attributed to the excess risk of chronic conditions, higher lifelong risk of SMN, and/or morbidities related to additional more intensive therapies among patients with bilateral disease.

The current analysis has some limitations that must be considered when interpreting the results. First, with the exception of SMNs, which were pathologically verified, chronic conditions and ratings of general health were self-reported by survivors and were not externally validated. Second, the cohort included only survivors who were alive at the time of the survey; surrogates for those who had died were not included, which may have led to underreporting of serious medical conditions. Third, we were unable to include radiation or chemotherapy doses in the analysis, which would have allowed us to examine the impact of treatment exposures more closely. In addition, because details of SMN-directed therapies were not available, we could not account for the impact of these therapies and thus censored all survivors of Rb at the time of SMN diagnosis. Last, survivors included in the current study were treated in an era during which radiotherapy was used more frequently.

Contemporary patients are less likely to receive radiotherapy and more likely to receive chemotherapy (either intravenous or intra-arterial) with agents different from those used in the current study cohort. It is interesting to note that none of the survivors in this cohort had documented exposure to platinum agents, including those with severe hearing loss. The lack of an association between exposure to chemotherapy and risk of chronic conditions in the current study cohort is likely due to the small number of survivors treated in this manner. Assessment of survivors treated with chemotherapy as it is used in more contemporary protocols will be required to detect its true impact on the risk of chronic conditions. Nonetheless, the cohort in the current study provides important historical data that may be used as a benchmark for future studies on late effects in survivors of Rb.

To the best of our knowledge, the current study is the first to demonstrate that adult survivors of Rb have an increased risk of chronic conditions when compared with non-Rb controls of similar age, sex, and race/ethnicity. This excess risk is largely driven by those with a history of bilateral disease. Information from the current study can be used to inform risk-based screening guidelines for the long-term follow-up of adult survivors of Rb. The data from the current study suggest that health care providers should perform careful skin and thyroid examinations, focus on signs and symptoms related to SMN in patients with hereditary disease, consider audiologic evaluations when indicated, and comanage ocular problems with an experienced ophthalmic oncologist. Special attention should be given to those individuals with a history of bilateral disease. Late effects related to newer treatment modalities will need to be delineated by assessing late outcomes in more contemporarily treated patients.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al, eds. SEER cancer statistics review, 1975–2009 (vintage 2009 populations). Available at: http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed April 23, 2013.
2. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA.* 1997;278: 1262-1267.
3. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol.* 2005;23:2272-2279.
4. Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF Jr. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J Natl Cancer Inst.* 2007;99:24-31.
5. Kleinerman RA, Schonfeld SJ, Tucker MA. Sarcomas in hereditary retinoblastoma. *Clin Sarcoma Res.* 2012;2:15.
6. Francis JH, Kleinerman RA, Seddon JM, Abramson DH. Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. *Gynecol Oncol.* 2012;124:254-259.
7. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol.* 2002;38:229-239.
8. Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27:2319-2327.
9. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006; 355:1572-1582.
10. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2008;100:1368-1379.
11. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27:2328-2338.
12. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol.* 2009;27:2308-2318.
13. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD; National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol.* 2001;119:1050-1058.
14. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA.* 2003;290:1583-1592.
15. National Cancer Institute, National Institutes of Health. Common terminology criteria for adverse events. Version 4.03. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed April 24, 2013.
16. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004;159:702-706.
17. Wong JR, Morton LM, Tucker MA, et al. Risk of subsequent malignant neoplasms in long-term hereditary retinoblastoma survivors after chemotherapy and radiotherapy. *J Clin Oncol.* 2014;32:3284-3290.
18. Peylan-Ramu N, Bin-Nun A, Skleir-Levy M, et al. Orbital growth retardation in retinoblastoma survivors: work in progress. *Med Pediatr Oncol.* 2001;37:465-470.
19. Kaste SC, Chen G, Fontanesi J, Crom DB, Pratt CB. Orbital development in long-term survivors of retinoblastoma. *J Clin Oncol.* 1997;15:1183-1189.
20. Ek U, Seregard S, Jacobson L, Oskar K, Af Trampe E, Kock E. A prospective study of children treated for retinoblastoma: cognitive and visual outcomes in relation to treatment. *Acta Ophthalmol Scand.* 2002;80:294-299.
21. Desjardins L, Chefchaouni MC, Lumbroso L, et al. Functional results after treatment of retinoblastoma. *J AAPOS.* 2002;6:108-111.
22. Abramson DH, Melson MR, Servodidio C. Visual fields in retinoblastoma survivors. *Arch Ophthalmol.* 2004;122:1324-1330.
23. Nahum MP, Gdal-On M, Kuten A, Herzl G, Horovitz Y, Weyl Ben Arush M. Long-term follow-up of children with retinoblastoma. *Pediatr Hematol Oncol.* 2001;18:173-179.
24. Rueegg CS, Gianinazzi ME, Rischewski J, et al. Health-related quality of life in survivors of childhood cancer: the role of chronic health problems. *J Cancer Surviv.* 2013;7:511-522.
25. van Dijk J, Oostrom KJ, Imhof SM, et al. Behavioural functioning of retinoblastoma survivors. *Psychooncology.* 2009;18:87-95.
26. van Dijk J, Oostrom KJ, Huisman J, et al. Restrictions in daily life after retinoblastoma from the perspective of the survivors. *Pediatr Blood Cancer.* 2010;54:110-115.
27. van Dijk J, Imhof SM, Moll AC, et al. Quality of life of adult retinoblastoma survivors in the Netherlands. *Health Qual Life Outcomes.* 2007;5:30.
28. van Dijk J, Grootenhuis MA, Imhof SM, Cohen-Kettenis PT, Moll AC, Huisman J. Coping strategies of retinoblastoma survivors in relation to behavioural problems. *Psychooncology.* 2009;18: 1281-1289.
29. Weintraub N, Rot I, Shoshani N, Pe'er J, Weintraub M. Participation in daily activities and quality of life in survivors of retinoblastoma. *Pediatr Blood Cancer.* 2011;56:590-594.
30. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol.* 2014;32:1218-1227.