Tobacco Use in Adult Long-term Survivors of Retinoblastoma

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Abstract

A significant risk of lung cancer was identified among hereditary, but not nonhereditary, retinoblastoma (Rb) patients. Tobacco use was investigated to determine whether differences in smoking prevalence might explain the lung cancer excess and to characterize smoking patterns in adult survivors of Rb. Subjects were 441 hereditary and 395 nonhereditary 1-year survivors of Rb, age ≥18 years, who responded to a telephone survey about current health behavior, including tobacco use. Response rates were 76% for hereditary and 73% for nonhereditary survivors. We compared patterns and predictors of current tobacco use among hereditary and nonhereditary survivors with other childhood cancer survivor studies and the U.S. population. Hereditary Rb survivors currently smoke cigarettes significantly less frequently than nonhereditary survivors (16. 8% versus 24.3%), although among current smokers, age at smoking initiation (17 years old) and average cigarettes (1.5 packs) smoked daily are similar. Predictors of current and ever cigarette smoking include nonhereditary Rb, older age, being female, less education, and use of other tobacco products. Rb survivors smoke cigarettes significantly less than the U.S. population (rate ratio, 0.63; 95% confidence interval, 0.5-0.8 for males; rate ratio, 0.75; 95% confidence interval, 0.6-0.9 for females), but Rb survivors have comparable smoking rates with other childhood cancer survivors. Smoking did not account for the increased risk of lung cancer among hereditary Rb patients, and this may point to an enhanced sensitivity to the carcinogenic effects of tobacco. Adult survivors of Rb should be encouraged to stop smoking. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1464–8)

Introduction

Retinoblastoma (Rb) is a rare childhood cancer of the eye with a very high survival rate. Rb exists in two forms: hereditary and nonhereditary. Hereditary Rb patients have a germ line mutation in their *RB-1* gene that has been identified as a tumor suppressor gene and regulates cell cycle progression (1). In contrast, nonhereditary Rb patients have acquired somatic mutations in their *RB-1* gene. We previously reported an excess of early-onset lung cancer in hereditary Rb patients that suggested that germ line *RB-1* mutations likely confer an increased risk of lung cancer (2), because alterations in the *RB-1* gene are known to contribute to the development of lung cancer, in particular small-cell lung cancer (3). All five lung cancer deaths in this cohort were diagnosed in female hereditary patients, and all were exposed to cigarette smoke (four smokers and one environmental tobacco smoke). In addition, three of the five lung cancer cases were small cell. We had concluded that carriers of the *RB-1* germ line mutation may be highly susceptible to smoking-induced lung cancers. Since reporting a lung cancer excess, we have completed a telephone survey of Rb survivors and have obtained comprehensive data on tobacco use in this large cohort of Rb survivors.

The number of adult survivors of childhood cancer has been steadily growing over the past few decades with improved treatment, but some survivors face a number of health challenges with their longer survival (4). There has been increasing interest in the lifestyle and risk-taking behaviors of cancer survivors and how these choices may affect their health (5). Tobacco use has been documented in several studies of adult survivors of childhood cancer (6-13). Most of these studies report that survivors are less likely to smoke than the general population; however, the survivors seem less likely to quit in some (9, 11), but not all, studies (7). However, none of these childhood cancer studies included survivors treated for Rb.

This is the first study to evaluate patterns and characteristics of tobacco use in a large cohort of Rb survivors. In addition, we have compared smoking rates in this cohort with other childhood cancer survivor cohorts as well as the general population.

Materials and Methods

Study Population. Survey respondents were selected from a cohort of 1,601 1-year survivors of Rb diagnosed between 1914 and 1984 (median year of diagnosis, 1966) at two medical centers in Boston and New York City (14-16). The cohort was originally identified by a review of medical records at these two institutions. Hereditary subjects had either both eyes affected by Rb (bilateral) or one eye affected (unilateral) with an established family history of Rb. Nonhereditary subjects had Rb diagnosed in one eye (unilateral) with no family history of Rb. Hereditary patients are typically diagnosed and treated at <1 year of age, whereas, those with nonhereditary Rb are usually diagnosed between 1 and 2 years of age.

We determined vital status of subjects through the National Death Index, and we attempted to find current addresses and telephone numbers through various sources for all subjects known to be alive as of January 1, 2000. We conducted a telephone survey of the cohort in June 2000 to update medical history and cancer incidence, which were originally obtained from medical records and two previous telephone surveys, and to collect new information on several suspected cancer risk

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factors and current health behaviors. The Institutional Review Board of the NIH approved this study.

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 a computer-aided telephone interview survey and 294 (25%) did not respond. Response rates were similar for hereditary (76%) and nonhereditary survivors (73%). Nonresponders did not differ significantly from responders by year of birth, age at survey, sex, hereditary status, age at Rb diagnosis, or treatment for Rb. We excluded data for all subjects under age 18 years ($n = 39$) to minimize misclassification of smoking status, because parents had been interviewed for survivors under age 18 years, and they may have underreported their child's smoking habits. In addition, this age restriction facilitated comparison with the U.S. smoking rates for adults (ages 18-64 years).

Survey. The computer-aided telephone interview survey was administered by highly trained telephone interviewers. Questions included demographics, medical history including hospitalizations and medications, family history of cancer, tobacco and alcohol use, and sun exposure. Smoking status was determined using the screening question: ''Have you smoked at least 100 cigarettes in your entire life?'' Subjects who provided an age when they ''first started smoking fairly regularly'' and were smoking at the time of the interview were considered current smokers. Subjects who smoked at least 100 cigarettes but did not currently smoke cigarettes were designated former smokers. Current and former smokers were asked questions about average number of cigarettes smoked daily and the total number of years they smoked. Former smokers were also asked about the age when they last smoked. Pack years were calculated by multiplying the number of years smoked as reported by survivors by the number of packs smoked per day. All subjects were asked about the frequency of use (occasional, regular or former use, and number of years of use) of other tobacco products (chewing tobacco, snuff tobacco, pipes, and cigars). Information on cigarette smoking habits was unknown for 7 (1.6%) hereditary and 8 (2.0%) nonhereditary respondents.

Statistical Methods. We used a χ^2 for two independent samples to test for differences in selected characteristics and smoking habits between hereditary and nonhereditary survivors. We used unconditional logistic regression to explore factors associated with current and ever smoking in the cohort. These factors included age at survey, sex, race (White, non-White), level of education (high school or less, some college, college graduate, or more), hereditary status, and ever hospitalized in the past 5 years for any reason except childbirth. This variable was selected as a surrogate for contact with the medical care system. Maximum likelihood estimates and 95% Wald-type confidence limits were computed. The Mantel-Haenszel method was used to estimate the rate ratio of cigarette smoking prevalence among Rb survivors, adjusted for current age, compared with the U.S. White adult population (ages 18-64 years) with data collected from the National Health Interview Survey in 1999 (17). These national data were the closest available at the time of the Rb survey in 2000.

Results

Baseline Characteristics. Of the 836 respondents to the 2,000 computer-aided telephone interview survey who were older than 18 years of age, 441 (53%) were hereditary survivors and 395 (47%) are nonhereditary survivors of Rb (Table 1). Hereditary and nonhereditary responders did not differ statistically in their year of birth, age at survey, sex, race, or level of education. Respondents ranged from 19 to 73 years old, with a mean age of 35 years. Approximately 70% of respondents were born between 1960 and 1984. The majority of subjects in this cohort were White, and 45.1% of hereditary and 48.2% of nonhereditary survivors graduated from college. Hereditary survivors were more likely to have been hospitalized in the past 5 years (32.9% versus 21.0%, $P < 0.001$).

Table 1. Selected characteristics of 836 Rb survey respondents

Characteristic	Hereditary ($n = 441$), n (%)	Nonhereditary ($n = 395$), n (%)	P
Year of birth			
<1960	114 (25.9)	121 (30.6)	
1960-1969	177 (40.1)	130 (32.9)	
1970-1984	150 (34.0)	144 (36.5)	0.082
Age at last follow-up (y)*			
<25	70 (15.9)	72 (18.2)	
25-34	166 (37.6)	119 (30.1)	
35-44	137 (31.1)	135 (34.2)	
45+	68 (15.4)	69 (17.5)	0.152
Sex			
Male	240 (54.4)	198 (50.4)	
Female	201 (45.6)	196 (49.6)	0.243
Race			
White †	402 (91.6)	357 (90.8)	
Black	18 (4.1)	19 (4.8)	
Other	19 (4.3)	17 (4.3)	0.877
Education			
1-12 y	34 (7.9)	22 (5.7)	
Completed high school	88 (20.5)	78 (20.3)	
Some college	114 (26.5)	99 (25.8)	
College graduate	123 (28.6)	113 (29.4)	
Post graduate	71 (16.5)	72 (18.8)	0.723
Hospitalized in the past 5 y ‡			
No	294 (67.1)	309 (79.0)	
Yes	144 (32.9)	82 (21.0)	0.0001

NOTE: Totals differ due to missing data.
*All survivors under age 18 years are excluded.
†Three percent hereditary and 4.6% nonhereditary survivors are White Hispanic.
‡Hospitalized for any reason except childbirth.

Patterns of Tobacco Use. Hereditary survivors smoked significantly less than nonhereditary survivors, with 16.8% of hereditary survivors reported as current smokers compared with 24.3% of nonhereditary survivors ($P = 0.004$; Table 2). There were slightly more former smokers among the nonhereditary compared with hereditary survivors. However, there were no statistically significant differences among the hereditary and nonhereditary current or former smokers for age at smoking initiation (average age 17.2 years old, range 8-30 years old) and the average number of packs per day.

A very small number of hereditary survivors had unilateral Rb ($n = 24$), and the pattern of cigarette smoking in these unilateral hereditary survivors resembled more closely the pattern of smoking in the nonhereditary survivors than the bilateral hereditary survivors (Table 3).

Occasional or regular use of other tobacco products among all Rb survivors included cigars (11.7%), chewing tobacco (2.9%), pipes (1.8%), and snuff (1.8%). The use of any of these products did not differ by hereditary status (Table 2).

Predictors of Tobacco Use. Table 4 shows that the predictors of cigarette smoking for current or ever smokers are similar, with a stronger association for ever smokers with older current age compared with never smokers. Current cigarette smokers compared with never smokers were more likely to be nonhereditary [odds ratio (OR), 1.70; 95% confidence interval (95% CI), 1.2-2.5], female (OR, 1.62; 95% CI, 1.0-2.5), and have used other tobacco products (OR, 3.39; 95% CI, 2.1-5.5). Survivors with a high school degree or less

Table 2. Tobacco use among Rb survivors

Characteristic	Hereditary, *n* (%)	Nonhereditary, *n* (%)	*P*
Smoking status			
Never smoker	285 (65.7)	212 (54.8)	
Current smoker	73 (16.8)	94 (24.3)	
Former smoker	76 (17.5)	81 (20.9)	0.004
Age started smoking (y)—current smokers			
8-14	8 (11.0)	13 (14.0)	
15-18	44 (60.3)	56 (60.2)	
19-22	16 (21.9)	17 (18.3)	
23-30	5 (6.9)	7 (7.5)	0.898
No. pack-years (y)—current smokers			
0.5-<5	13 (18.1)	15 (17.0)	
5-<9	15 (20.8)	16 (18.2)	
9-<18	25 (34.7)	27 (30.7)	
18+	19 (26.4)	30 (34.1)	0.769
Average packs per day (ppd)—current smokers			
<0.5	34 (47.9)	35 (40.2)	
0.5-1	29 (40.8)	42 (48.3)	
>1-2	8 (11.3)	10 (11.5)	0.604
Age started smoking (y)—former smokers			
8-14	9 (12.0)	11 (13.8)	
15-18	44 (58.7)	48 (60.0)	
19-22	19 (25.3)	16 (20.0)	
23-30	3 (4.0)	5 (6.2)	0.808
No. pack-years (y)—former smokers*			
0.5-<5	21 (28.8)	26 (34.2)	
5-<9	23 (31.5)	19 (25.0)	
9-<18	18 (24.7)	10 (13.2)	
18+	9 (12.3)	20 (26.3)	0.105
Average packs per day (ppd)—former smokers			
<0.5	41 (55.4)	45 (58.4)	
0.5-1	26 (35.1)	24 (31.1)	
>1-2	7 (9.5)	8 (10.4)	0.872
Other tobacco use †			
No	320 (73.6)	285 (73.6)	
Yes	115 (26.4)	102 (26.4)	0.979

*Missing number of pack-years for 2.7% of hereditary and 1.3% of nonhereditary former smokers.

†Regular or occasional use of other tobacco products (cigars, pipes, chewing tobacco, or snuff).

(3.04; 95% CI, 1.9-4.8) or some college (2.42; 95% CI, 1.5-3.9) were more likely to be current smokers compared with survivors with a college or postgraduate degree. The same trend was observed for ever smokers. Ever being hospitalized in the past 5 years was not related to being a current or ever smoker (OR, = 0.91; 95% CI, 0.6-1.4).

Comparison with U.S. Population Rates and Other Cancer Survivors. Table 5 shows that both male and female Rb survivors smoke significantly less than those in the U.S. population for the same time period, adjusted for age (rate ratio, 0.63; 95% CI, 0.5-0.8 for males and rate ratio, 0.75; 95% CI, 0.6-0.9 for females). When stratified by current age, there were fewer current smokers in the Rb cohort than in the U.S. population in most age groups for both males and females. The percentage of current smokers in the Rb cohort is consistent with the percentage of current smokers ranging from 16.7% to 20% in other recent studies of childhood cancer survivors (8-10), but lower than the 28.6% to 33.3% rates reported in earlier studies of childhood cancer survivors (11-13).

Discussion

Current cigarette smoking information reported by this large cohort of Rb survivors indicated that both hereditary and nonhereditary Rb patients smoked less than the U.S. general population for a similar calendar period. Furthermore, fewer hereditary than nonhereditary survivors currently smoked cigarettes (16.8% and 24.3%), and among the hereditary survivors, those with bilateral disease smoked less than those with unilateral hereditary Rb (16.3% versus 25%). Slightly more nonhereditary than hereditary survivors quit smoking. However, among current smokers, the average number of packs per day and age of smoking initiation did not differ between hereditary and nonhereditary survivors. Thus, neither excess risk of lung cancer observed in hereditary survivors compared with U.S. lung cancer rates, nor the higher lung cancer risk observed in hereditary compared with nonhereditary survivors, is explained by the cigarette smoking habits of hereditary Rb patients. These data provide additional support for the notion that carriers of a germ line mutation in the *RB-1* gene may have increased susceptibility to smoking-induced lung cancer (2), especially in view of the molecular evidence that *RB-1* mutations play a role in the development of lung cancer (1, 3).

Although the years of birth in the original cohort spanned a very wide range of years (1914-1984), and smoking habits varied greatly over these decades, the majority of respondents to the survey were born between 1960 and 1984. Although slightly more hereditary patients were born before 1960, there were still fewer ever smokers among the hereditary patients. This may be attributable in part to their bilateral disease, which led to blindness or impaired vision for survivors.

Self-reports of cigarette smoking data in this Rb survivor cohort are consistent with the more recent reports (1995-2005) from other childhood cancer survivor cohorts from the United States (6, 7, 9, 10) and the United Kingdom (8). In all of these cohorts, survivors smoked less than their siblings or other control groups. However, reports of tobacco use in childhood cancer survivors from earlier years (1979-1992) indicated that a higher proportion of survivors smoked (11-13), which likely reflected the prevailing rate of smoking in the United States at that time. The decline in smoking rates over calendar time in the survivors mirrors the decline in the general population, indicating a growing public health awareness of the carcinogenic effects of tobacco use.

Both current and ever smokers among Rb survivors were more likely be older, female, be less well educated and have nonhereditary Rb compared with never smokers. These results are consistent with some of the strongest risk factors that have been identified for smoking initiation among young people in general that include lower education and income (18). Other large studies of childhood cancer survivors have also reported that older age at cancer diagnosis, lower household income, and less education predicted current cigarette smoking (7, 9). We found that contact with the medical care system as measured by hospitalization for any reason in the past 5 years was not associated with smoking status in this cohort, although hereditary survivors consistently reported more contacts than nonhereditary survivors.

Some of the difference between lower current smoking rates in the Rb cohort and higher rates in the U.S. population may be due to attained higher education among the Rb survivors. In the United States, age-adjusted current smoking rates for White females over age 25 years declined with increasing level of education from 27.2% for high school graduates to 10% for college graduates and higher, and declined from 30.5% to

Table 3. Smoking status by type of Rb

Smoking status	Hereditary		Nonhereditary
	Bilateral, *n* (%)	Unilateral, *n* (%)	Unilateral, *n* (%)
Current smoker	67 (16.3)	6 (25.0)	94 (24.3)
Former smoker	71 (17.3)	5 (20.8)	81 (20.9)
Never smoker	272 (66.3)	13 (54.2)	212 (54.8)
Total	410 (100.0)	24 (100.0)	387 (100.0)

NOTE: Excludes all Rb survivors <18 years of age.

Table 4. Predictors of current and ever smoking in the Rb cohort

Characteristic	Never smoker (n = 497)	Current smoker		Ever smoker	
		n = 167	OR* (95% CI)	n = 324	OR* (95% CI)
Age at survey (y)					
<25	92	32	1.00 (reference)	47	1.00 (reference)
25-34	189	56	1.06 (0.6-1.8)	92	1.11 (0.7-1.8)
35-44	153	55	1.47 (0.8-2.6)	116	1.94 (1.2-3.1)
45+	63	24	1.82 (0.9-3.6)	69	3.15 (1.8-5.4)
Sex					
Male	255	87	1.00 (reference)	176	1.00 (reference)
Female	242	80	1.62 (1.0-2.5)	148	1.42 (1.0-2.0)
Race					
White	458	143	1.00 (reference)	291	1.00 (reference)
Non-White	39	24	1.76 (0.98-3.2)	33	1.46 (0.9-2.5)
Education					
College graduate	253	50	1.00 (reference)	126	1.00 (reference)
Some college	121	55	2.42 (1.5-3.9)	90	1.74 (1.2-2.5)
≤High school	114	62	3.04 (1.9-4.8)	108	2.31 (1.6-3.4)
Other tobacco use †					
No	401	105	1.00 (reference)	202	1.00 (reference)
Yes	96	61	3.39 (2.1-5.5)	121	3.34 (2.3-4.9)
Hereditary status					
Hereditary	285	73	1.00 (reference)	149	1.00 (reference)
Nonhereditary	212	94	1.70 (1.2-2.5)	175	1.62 (1.2-2.2)
Hospitalized in past 5 y ‡					
No	364	124	1.00 (reference)	232	1.00 (reference)
Yes	132	43	0.91 (0.6-1.4)	92	0.98 (0.7-1.4)

*Risk of ever smokers and current smokers compared with never smokers.
†Ever use of other tobacco products.
‡Hospitalization for any reason except childbirth.

11.8% for White males over age 25 years (17). This decrease in prevalence of current smoking with increasing education level in the U.S. population is similar to our findings for the same time period, with 37.1% of high school graduates currently smoking compared with 13.1% of college graduates.

In addition to cigarette smoking, the use of pipes, cigars, and smokeless tobacco has been linked to cancer of the lung and/or oral cavity (19). The reported current use of snuff and chewing tobacco among Rb survivors was similar to current use of smokeless tobacco in the U.S. population (20) and in another study of cancer survivors (7).

Limitations of this study include two potential sources of bias. It is possible that the subjects who died before the 2000 survey may have smoked more than subjects who participated in the survey, because smoking is associated with poor survival. Many more deaths have occurred among hereditary than nonhereditary subjects. Most of the excess deaths among hereditary subjects were attributable to cancer, but few of these cancers were tobacco-related with the exception of lung cancer. Very few deaths were attributable to heart disease, which has also been linked with tobacco, although the cohort is still relatively young for heart disease. Importantly, the survey of nonrespondents did not differ from respondents by hereditary status.

The younger survivors in our cohort could have been misclassified as nonsmokers by their parents or they may have been too young to start smoking regularly. Therefore, we excluded this age group altogether. Self-report of smoking history and initial age at smoking initiation was found to be reliable, especially for females, in a young adult, noncancer population (21), although another study identified a forward telescoping bias in reported age started smoking for adolescents and young adults (22). Although tobacco use could be underreported in this cohort, smoking rates reported in this study are similar to those found in other childhood cancer survivor studies for the same time period (6-10).

Given the excellent survival for children diagnosed with Rb and the significantly increased risk for lung cancer among patients with the hereditary form of Rb (2), it is important to encourage these survivors to quit smoking. It was surprising to us that despite about one-third of the cohort having some type of regular contact with the medical care system, 20% of survivors over age 18 years currently smoke cigarettes. Unfortunately, this is consistent with reports from other childhood cancer cohorts (6-10). Childhood cancer survivors

Table 5. Percentage of current cigarette smokers in Rb cohort, U.S. population, and other childhood cancer survivor studies

Comparison to U.S. population*

	Percentage of current smokers			
	Males		Females	
Current age (y)	Rb cohort	U.S.	Rb cohort	U.S.
18-24	20.3	30.5	21.6	29.5
25-34	16.4	30.8	21.2	25.5
35-44	21.8	29.5	15.8	27.0
45-64	15.4	24.5	22.6	21.3
Rate ratio † (95% CI)	0.63 (0.5-0.8)		0.75 (0.6-0.9)	

Childhood cancer survivor studies

Cohort study	No. survivors	Age range (y)	Current smokers ‡ (%)
Denmark-Wahnefried (6)	122	≥18	17.0
Emmons et al. (7)	9,709	≥18	17.0
Larcombe et al. (8)	113	≥18	20.0
Tao et al. (9)	592	≥23	16.7
Mulhern et al. (10)	40	≥18	17.5
Haupt et al. (11)	1,289	≥21	28.6
Troyer et al. (12)	263	≥21	33.3
Corkery et al. (13)	425	≥18	30.0

*National Health Interview Survey (1999), ≥18 years, Whites only.
†Adjusted for current age at time of survey.
‡Smoked >100 cigarettes, except for Larcombe (smoked one cigarette per week), Corkery (smoked 21 cigarettes daily), and Troyer, definition of current smoker was not available.

have been identified as a vulnerable group with unique medical needs that are not being well met (4). Development of strategies and recommendations for the long-term follow-up of pediatric cancer survivors has been advocated in both the United States and the United Kingdom (4, 23). This has prompted development of risk-based guidelines for pediatric cancer survivors in the United States (24). Like most smokers in general, childhood cancer survivors started smoking in their teens. Although the average age at smoking initiation among the current smokers in the Rb cohort was 17 years, we found that 11% of hereditary and 14% of nonhereditary survivors had started smoking before age 15 years. This is a time when they are beginning the transition from the pediatric to adult medical care system that may or may not include cancer screening. Cigarettes have a very negative effect on the health of these adult survivors of childhood cancer. Hereditary Rb survivors are at especially high risk of lung cancer. We recommend that physicians treating adult, long-term survivors of Rb encourage these survivors to quit smoking.

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