Retinoblastoma Incidence Trends in Canada: A National Comprehensive Population-Based Study

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ABSTRACT

Purpose: To determine the incidence rates and geographic distribution of retinoblastoma in Canada to aid cancer control programs.

Methods: Patients with retinoblastoma whose data were available from the Canadian Cancer Registry (CCR) and Le Registre Québécois du Cancer (LRQC) were studied. Using third edition International Classification of Diseases for Oncology (ICD-O) codes, the authors examined the incidence rates and geographic distribution of patients with retinoblastoma between 1992 and 2010. Patient data including sex, age, and laterality of the retinoblastoma were analyzed.

Results: Between 1992 and 2010 in Canada, the average annual incidence rate of retinoblastoma was 11.58 cases per 1 million children younger than 5 years (95% CI [confidence interval]: 10.48 to 12.76). The incidence rate was stable over time, with an average age at diagnosis of 2.30 ± 6.85 years and no gender predilection. The laterality of the reported cases was 81.48% for unilateral cases and 18.52% for bilateral cases. Provincially, Nova Scotia had twice the national average and the highest incidence rates of retinoblastoma across the Canadian provinces.

Conclusions: This is the first study to define the disease burden of retinoblastoma and to highlight important longitudinal, geographic, and spatial differences in the distribution of retinoblastoma in Canada between 1992 and 2010. The results of this study indicate continuity of clinical trends between Canada, the United States, and other developed countries.

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INTRODUCTION

Retinoblastoma is the most common childhood intraocular cancer, and it accounts for 6.1% of cancer in children younger than 5 years.[1] The incidence of retinoblastoma is estimated between 1 in 14,000 and 1 in 34,000 live births, with approximately 8,000 children diagnosed each year worldwide.[2] Retinoblastoma is caused by the biallelic loss of function mutation in the retinoblastoma susceptibility gene *RB1*. *RB1* is the first described tumor-suppressor gene and was used to describe the "two-hit hypothesis" model of cancer initiation.[3] This genetic mutation deregulates the cell cycle in retinoblasts, causing the cells to undergo uncontrollable proliferation and fail to terminally differentiate intraretinal photoreceptor and

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nerve cells. Most patients with retinoblastoma are born with a congenital loss of one *RB1* allele and then lose the other copy several years after birth.[4]

Clinically, although not specific to retinoblastoma, leukocoria is the most common initial sign of retinoblastoma, where the white tumor reflects light and prevents the visualization of the retinal red reflex.[4] Children with retinoblastoma may also present with strabismus, deteriorating vision, or red and irritated eye(s). In advanced stages, usually observed in developing countries, eye enlargement is a common finding. Retinoblastoma presents as two clinical ocular forms: bilateral or unilateral. Although bilateral (multifocal) cases are heritable due to germ line mutations of the *RB1* gene, unilateral (unifocal) disease is mostly sporadic and non-heritable.[5] If detected early, both forms of retinoblastoma have excellent prognoses.[6] Thus, early diagnosis and management is critical to the successful treatment of retinoblastoma.

Because the epidemiology and geographic distribution of retinoblastoma are largely unknown in Canada, the precise risk factors are poorly understood. This study aimed to evaluate the incidence rates and geographic distribution of retinoblastoma in Canada between 1992 and 2010.

PATIENTS AND METHODS

This study was conducted in accordance with the CISS-RDC-668035 and 13-SSH-MCG-3749-S001 protocols approved by the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Québec Inter-University Centre for Social Statistics (QICSS), respectively. In accordance with the institutional policy, this study received an exemption from the McGill University Research Ethics Board review.

We examined the data on retinoblastoma incidence and geographic distribution in Canada between 1992 and 2010 using two distinct population-based cancer registeries (Canadian Cancer Registry [CCR] and Le Registre Québécois du Cancer [LRQC]), International Classification of Diseases for Oncology (ICD-O-3) codes, and the same methodology detailed in our previous analyses of melanoma, cutaneous lymphoma, and acute myeloid leukemia incidence and distribution in Canada.[7-9] The subtypes of retinoblastoma analyzed and corresponding ICD-O-3 codes are summarized in **Table A** (available in the online version of this article).[8,10]

The CCR is a database of all Canadian residents from 12 Canadian provinces and territories (excluding Québec) who were diagnosed as having primary tumors between 1992 and 2013. Data for patients in Québec were obtained from the LRQC, which belongs to the Ministère de la Santé et des Services Sociaux. Data from the LRQC database were available between 1992 and 2010. Data on new cases of the previously indicated subtypes of retinoblastoma were obtained from the CCR (2014 version). Because data from the LRQC were not available after 2010, we analyzed data from the CCR and LRQC between 1992 and 2010. The geographical and clinical information provided by the CCR and LRQC were patient sex, laterality of the tumor, year of diagnosis, age at the time of diagnosis, province and city of residence, and the ICD-O-3 code of the tumor. The CCR and LRQC do not collect data on clinical disease stage at the time of diagnosis or on demographic characteristics such as race.

Mandatory Data Rounding

Confidentiality rules apply to the data from the CCR and LRQC prior to publication, such as random rounding of variables. With respect to the random rounding of tabular data, the SSHRC/Statistics Canada requires that each cell count be rounded, independently of other cells, to a lower or higher multiple of 5 using a random rounding scheme. Numbers greater than or equal to 1 and less than 5 cases cannot be released as per the SSHRC regulation to protect patient confidentiality.

Statistical and Mapping Analyses

Crude incidence rates and 95% confidence intervals (95% CIs) were calculated and reported overall, by year of diagnosis, and for specific regions (provinces and cities). CIs were based on exact Poisson distributions. Incidence rates were plotted and linear regression models were used to assess trends over time. Data on population counts nationally, per province, and per city were obtained from the Canadian Census of Population Program from Statistics Canada. Due to the low frequency, number per year in specific age groups, and mandatory rounding, the age-standardized incidence rate was calculated between 1992 and 2010 against the world population. **AQ2**

RESULTS

Four hundred forty-five patients were diagnosed as having retinoblastoma in Canada between 1992

TABLE 1

Clinical Characteristics of Patients With Retinoblastoma[a]

Characteristic	No. of Cases[b]	Cases (%)[c]	Average Age at Diagnosis[c] (y)
ICD-O-3 Code			
9,510 Retinoblastoma, NOS	385	86.52	2.43 ± 7.27
9,511 Retinoblastoma, differentiated	30	6.74	1.60 ± 1.89
9,512 Retinoblastoma, undifferentiated	20	4.49	1.91 ± 2.2
Retinoblastoma, other subtypes	10	2.25	
Total	445	100	2.35 ± 6.85
Laterality			
Right eye	55	12.36	
Left eye	55	12.36	
Unilateral	110	24.72	
Bilateral	25	5.62	
Unknown	305	68.54	
Age at diagnosis (years)			
< 1	150	33.71	
1	120	26.97	
2	80	17.98	
3	40	8.99	
4	25	5.62	
5	5	1.12	
> 5	25	5.62	
Sex			
Male	220	49.44	
Female	225	50.56	

ICD-O = International Classification of Diseases for Oncology
[a]Data represent all cases of retinoblastoma in Canada between 1992 and 2010 regardless of patient age.
[b]Case numbers are rounded to the nearest 5.
[c]Values are represented as percent of retinoblastoma cases.
[d]Values (years) are represented as mean ± standard deviation.

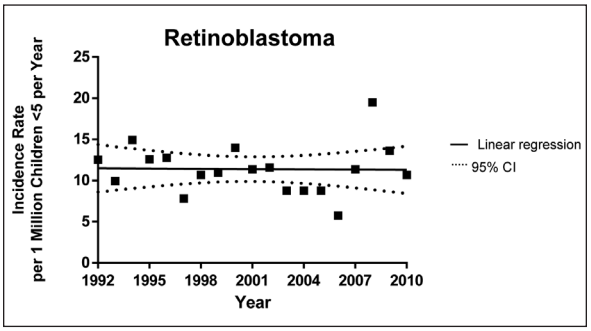

Figure 1. Showing incidence rates of retinoblastoma between 1992 and 2010 in Canada, with the line of best fit and linear regression analysis of the incidence rate over time. The slope of the line = 0.08 ± 0.16 and the average annual incidence rate was 11.58 cases per 1 million children younger than 5 years. Coefficient of determination $R^2 = 0.016$; $P = .60$; CI = confidence interval

and 2010. The characteristics of the reported cases are summarized in **Table 1**. At the time of diagnosis, the mean age was 2.35 ± 6.85 years, and the male-to-female incidence rate was 1:1.02 (M:F:220:225). The laterality of reported retinoblastoma cases was 81.48% for unilateral cases and 18.52% for bilateral cases. Laterality was reported in 32% of all patients in the studied databases.

The overall incidence rate of retinoblastoma for children younger than 5 years between 1992 and 2010 is listed in **Table B** (available in the online version of this article). The average annual incidence rate was 11.58 cases per 1 million children younger than 5 years (95% CI: 10.48 to 12.76), and ranged from 7.83 (1997) to 19.48 (2008) cases per 1 mil-

TABLE 2

Average Annual Incidence Rate of Retinoblastoma[a]

Geographic Distribution	No. of Cases[b]	Population < 5 Years[c]	Incidence Rate[d]	95% CI
Provinces				
Nova Scotia	20	43,985	23.93	14.62 to 36.96
New Brunswick	10	36,525	14.41	6.91 to 26.50
Quebec	110	440,840	13.13	10.79 to 15.83
Alberta	55	244,880	11.82	8.91 to 15.39
Ontario	150	704,260	11.21	9.49 to 13.15
British Columbia	45	219,665	10.78	7.86 to 14.43
Saskatchewan	10	68,760	7.65	3.67 to 14.08
Manitoba	5	77,185	3.41	1.11 to 7.96
Newfoundland and Labrador	< 5			
Prince Edward Island	< 5			
Northern territories	< 5			
Cities				
Brampton	10	37,380	14.08	6.75 to 25.89
Mississauga	10	39,170	13.44	6.44 to 24.71
Halifax	5	19,965	13.18	4.28 to 30.76
Calgary	15	72,010	10.96	6.14 to 18.08
Ottawa	10	49,140	10.71	5.14 to 19.70
Vancouver	5	24,770	10.62	3.45 to 24.79
Montreal	20	106,425	9.89	6.04 to 15.28
Toronto	20	140,510	7.49	4.58 to 11.57
Canada (total)	405	1,840,846	11.58	10.48 to 12.76

CI = confidence interval

[a]Incidence rate of retinoblastoma in patients younger than 5 years in Canadian providences, territories, and major cities between 1992 and 2010.

[b]Case numbers are rounded to the nearest 5

[c]Values are represented as the average population younger than 5 years.

[d]Annual incidence rate is per 1 million children younger than 5 years.

lion children younger than 5 years. Linear regression analyses of the retinoblastoma incidence rates per 1 million children younger than 5 years old revealed no statistically significant changes in incidence during the study period (coefficient of determination [R^2] = 0.08; P = .60) (**Figure 1**).

The incidence rates of retinoblastoma were also investigated for Canadian cities and provinces **(Table 2, Figures 2-3**). Only Nova Scotia had significantly higher incidence rates than the national average (**Table 2**, **Figure 2)**. Conversely, Manitoba had the lowest incidence rate of retinoblastoma in Canada. Incidence rates of retinoblastoma across Canadian cities were comparable to the national average. As expected, the total number of cases was higher in larger cities (including Toronto, Montréal, and Calgary), but the incidence rate in those cities was comparable with the Canadian national average (**Table 2, Figure 3**).

DISCUSSION

Retinoblastoma is mainly a pediatric cancer. In the United States, 66% and 95% of the reported patients were diagnosed at younger than 2 and 5 years, respectively.[11] In the current study, 60% of patients were diagnosed at younger than 2 years and 94% of all patients were diagnosed before 5 years of age. Between 1992 and 2010, there were 445 cases of retinoblastoma and 405 cases occurred in children younger than 5 years. These results correspond to

Figure 2. Geographic map showing the average annual incidence rate of retinoblastoma across Canadian provinces between 1992 and 2010. Annual incidence rates of retinoblastoma are per 1 million children younger than 5 years. **AQ3**

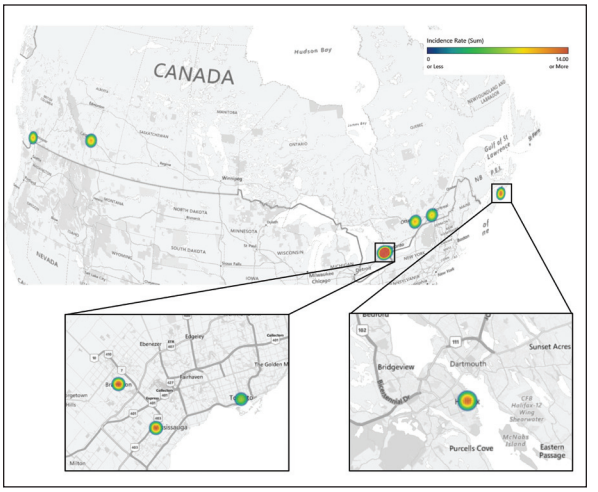

Figure 3. Geographic maps showing the incidence rate of retinoblastoma across Canadian cities between 1992 and 2010. Annual incidence rates of retinoblastoma are per 1 million children younger than 5 years. **AQ3**

an average annual incidence rate of 11.58 (95% CI: 10.48 to 12.76) cases per 1 million children younger than 5 years. The data are within the range of the rates reported by the United States[12] and northern European countries.[13] The mean incidence rate of retinoblastoma in the United States between 1973 and 2012 was 12.14 (95% CI: 11.32 to 12.96) cases per 1 million children younger than 5 years.[12] The incidence rate of retinoblastoma in the United States has remained stable for the past 30 years. Similarly, our study found a stable incidence of retinoblastoma in children younger than 5 years in Canada. In both the United States and Canada, there was no significant sex predilection, nor was there any significant variation of incidence between sexes.[14]

Worldwide, the proportion of bilateral cases of retinoblastoma versus unilateral cases was estimated to be 18% to 37% and 63% to 82%, respectively.[14] The split between bilateral and unilateral cases was 29% and 71%[6] in the United States, 37% and 63% in Sweden and Great Britain, and 18% and 82% in South Africa.[15] Although Canadian data are limited by the 32% rate of laterality reporting, we documented that the Canadian proportion of bilateral versus unilateral retinoblastoma cases among those reported was consistent with the international trends stated previously.

The global incidence rate of retinoblastoma is highly variable, with up to 50-fold differences in geographical regions and individual countries.[16] The annual incidence rate is 6 to 12 cases per 1 million children younger than 5 years in Europe, the United States, and Australia.[12,17] The annual incidence rate was documented in one study[18] as 21.8 cases per 1 million children in Mexico, was in the range of 6 to 20 cases per 1 million children in Asia,[19] and varied between 6 and 60 cases per 1 million children in Africa.[20] Interestingly, there was no significant trend in the age-adjusted incidence rate between races in the United States.[14] However, Parkin et al.[16] reported that the incidence rate of retinoblastoma in the native populations of Hawaii and Alaska is approximately twice the national average in the United States, which suggests variations in environmental exposures or/and genetic susceptibility for this cancer. Racial predilection for retinoblastoma could not be addressed in the Canadian population due to unavailability of such data in the examined databases.

Risk factors that have been associated with retinoblastoma include advanced parental age,[21] use of assisted reproductive technology,[22] human papillomavirus infection,[23] diet,[24] sunlight exposure,[25] direct fetal x-ray exposure,[23] and parental exposure to hazardous occupational substances.[26] Of particular interest, paternal employment as a welder, mechanist, or related metal works have been associated with an increased risk of sporadic retinoblastoma.[26]

Other risk factors are likely to affect disease pathogenesis. Nova Scotia was the only province with a significantly higher incidence of retinoblastoma (twice the national average). Additionally, Nova Scotia has the highest number of individuals employed in the fishing industry.[27] Interestingly, although based on a small sample size, children of Swedish fishermen had a statistically significant increase in the incidence rate of retinoblastoma compared to referent children.[28] In addition to possible environmental and genetic factors, the high inci-

dence rate may be attributed to the fact that Nova Scotia had the highest density of ophthalmologists for the analyzed period, which positively correlates with higher reporting and could introduce a detection bias in this case.[29] Due to the CCR and LRQC rounding limitations and the small population size for children younger than 5 years, we were not able to identify any statistically significant high incidence of retinoblastoma in cities in Canada.

We also would like to highlight that the CCR is a government-run national registry. Because Canada's health care system is a single tier (payer), which is funded and operated by the provincial governments, the data are collected consistently, where each provincial/territorial cancer registry identifies tumors in its population by combining information from several sources. The CCR performs multiple rigorous processes to ensure comprehensive reporting and accuracy, including an internal record linkage to identify possible duplicate records. Several studies have investigated the detection rates and the accuracy of the diagnostic data in the largest provincial branch of the CCR: the Ontario Cancer Registry. A case ascertainment of close to 100%, a detection rate (detecting and accurately assigning index tumor site) of 81.4% to 96%, and a confirmation rate (correctly assigning tumor site) of 90.9% were shown by these studies,[30-32] which confirm a high quality of data and detection rates in the examined registry.

This study had limitations. There are no available data on the ethnicity and clinical stage at the time of diagnosis for patients with retinoblastoma. To further emphasize the laterality, reporting only 32% of cases and the lack of genetic testing results in the CCR/LRQC databases is an important limitation. Another important limitation is our inability to present all of the data due to federal confidentiality regulations. Although mandatory case rounding does not affect trends in the presented results, suppressed data (due to low numbers) in some cities, provinces, or territories limits our ability to present the detailed picture of retinoblastoma burden in Canada.

Analyzing the epidemiology for retinoblastoma in Canada and around the world will help identify its triggers and improve our understanding of the disease. Furthermore, this study provides a foundation on which to monitor Canadian retinoblastoma incidence patterns and can serve to further stimulate etiologic research.

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TABLE A

ICD-O-3 Codes Used to Recall Retinoblastoma

ICD-O-3 Code	Description
9510/3	Retinoblastoma, NOS
9511/3	Retinoblastoma, differentiated
9512/3	Retinoblastoma, undifferentiated
9513/3	Retinoblastoma, diffuse
9514/1	Retinoblastoma, spontaneously regressed

NOS = **AQ4**

TABLE B

Average Annual Incidence Rate of Retinoblastoma in Canada Between 1992 and 2010[a]

Year	Total Canadian Population[b]	Population > 5 Years[b]	No. of ROP Cases[c]	Incidence Rate[d]
1992	28,371,000	1,993,000	25	12.54
1993	28,685,000	2,014,000	20	9.93
1994	29,001,000	2,010,000	30	14.92
1995	29,302,000	1,985,000	25	12.6
1996	29,610,000	1,961,000	25	12.75
1997	29,906,000	1,917,000	15	7.83
1998	30,155,000	1,872,000	20	10.68
1999	30,401,000	1,828,000	20	10.94
2000	30,686,000	1,791,000	25	13.96
2001	31,021,000	1,758,000	20	11.38
2002	31,358,000	1,726,000	20	11.58
2003	31,642,000	1,708,000	15	8.78
2004	31,938,000	1,707,000	15	8.79
2005	32,242,000	1,709,000	15	8.78
2006	32,571,000	1,733,000	10	5.77
2007	32,888,000	1,758,000	20	11.38
2008	33,246,000	1,797,000	35	19.48
2009	33,629,000	1,834,000	25	13.63
2010	34,005,000	1,873,000	20	10.68

ROP = retinopathy of prematurity

[a]The average annual incidence rate of retinoblastoma in Canada (per 1 million children younger than 5 years) is 11.58 (95% confidence interval: 10.48 to 12.76)

[b]Rounded to the nearest thousand.

[c]Case numbers are rounded to the nearest 5.

[d]Per 1 million children younger than 5 years.