AMERICAN ACADEMY OF OPHTHALMOLOGY®

Reports

Incidence of Retinoblastoma Has Increased: Results from 40 European Countries

Retinoblastoma is the most common intraocular malignancy. Its incidence has been reported to be 1 case in from 15 000 to 18 000 live births, or approximately 12, 6, or 4 cases per 1 million children younger than 5, 10, or 15 years, respectively.[1,2] The aim of this study was to estimate the incidence of retinoblastoma across European countries within a 1-year time frame. Data were collected through an international, multicenter, 1-year cross-sectional analysis that has been described in detail previously.[3] Briefly, retinoblastoma treatment centers reported all new cases of retinoblastoma that were diagnosed between January 2017 and December 2017. The final analysis involved only those countries that described their data as being likely complete. The human ethics committees of the London School of Hygiene and Tropical Medicine as well as the ethics committees of all local hospitals approved the study. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Two methods were used to estimate the incidence rate of retinoblastoma: the live birth method and the age cohort method.

$$\text{Incidence (live birth)} = \frac{\text{No. of Retinoblastoma Cases in 2017}}{\text{Population in 2017} \times \text{Crude Birth Rate in 2017}}$$

Country population estimates and birth rates were retrieved from the World Bank Population Prospects and the United Nations database for 2017. The formula used to calculate the live-birth incidence rate in each country is:

The formula used to calculate the age cohort incidence rate (per 1 million children younger than 5 years) is:

$$\text{Incidence (age cohort)} = \frac{\text{No. of Retinoblastoma Cases in 2017}}{\text{Population Estimate Age} < 5 \textit{ Years in } 2017} \times 1 \text{ Million}$$

Bootstrap sampling was used to estimate the distribution of each incidence rate. Linear regression analysis was conducted to identify factors that may affect the country-level incidence rate, including the following variables: age at diagnosis, proportion of bilateral cases, proportion of familial cases, proportion of male births, and per capita gross domestic product for the year 2017 (World Bank database). Summary data were calculated for each country and European region (north, south, east, west). An α level of 0.05 was used.

From the original 40 countries (with 517 retinoblastoma patients), 24 countries were identified as representing likely-complete national-level data, and all 294 patients from these 24 countries were included in the analysis (Table 1). The number of live births for the year 2017 was calculated for each country and region (Table 1). The combined data resulted in a live birth incidence rate of 1 in 13 915 (confidence interval [CI], 12 315−15 150), or 7.2 per 100 000, live births in Europe. The analysis was repeated with the United Nations population data and similar outcomes were seen for each country and overall (1 in 13 844 live births; CI, 12 309−15 083). The highest live birth incidence was seen in northern Europe (1 in 12 907 live births), whereas the lowest incidence rate was seen in southern Europe (1 in 17 177 live births; Fig S1, available at www.aaojournal.org).

The combined age cohort incidence rate was 14.1 per 1 million children younger than 5 years (CI, 12.9−15.9 per 1 million children younger than 5 years) and 4.6 per 1 million children younger than 15 years (CI, 4.1−5.2 children younger than 15 years; Table 1). The age cohort results were used in a linear regression analysis (Table S2, available at www.aaojournal.org). No significant relationship was found between incidence rate and country gross domestic product. The only variable that resulted in a significant association with incidence rate was the proportion of familial cases ($P = 0.002$), which showed an increasing relationship between the proportion of familial cases and the incidence rate within that country. A similar trend was present for the countries grouped by region (Fig S2, available at www.aaojournal.org).

The incidence rates calculated in this study—1 in 13 844 live births or 14.1 and 4.6 per 1 million children younger than 5 and 15 years, respectively—are higher than those reported previously. Although some studies have suggested stable incidence rates over many years through the early 2000s,[1,2,4] recent national data from Finland document an increase from approximately 1 in 16 700 live births to 1 in 12 500 live births from 1990 to 2014.[5] The increase in Finland was not evident when familial retinoblastoma was excluded. Our study supports the conclusion that the incidence of retinoblastoma has increased in recent decades even more widely in Europe because of an increasing number of familial patients.

Improvements in treatments in higher-income countries are leading to less visual impairment,[6] better eye preservation, and better survival. This has led to a reduction in the coefficient of selection, increased fitness, and an increased percentage of familial retinoblastoma in high-income countries.[3] As the percentage of familial cases increases, the overall incidence of retinoblastoma should increase. The results of this study document this increase throughout Europe.

One important finding from these data comes from 2 large countries included in the study whose completeness could not be verified: Italy and Germany. These countries reported high

Table 1. European Countries Included in the Analysis with the Corresponding Number of New Patients and Calculated Incidence Rates

European Region	Country	New Patients Reported in 2017	Calculated Births (World Bank)	Live Births per 1 New Diagnosis (World Bank)	Live Births per 1 New Diagnosis (United Nations)	Incidence per 1 Million Children Younger than 5 Yrs (United Nations)	Incidence per 1 Million Children Younger than 15 Yrs (United Nations)	Incidence per 1 Million Children Younger than 15 Yrs (World Bank)
East	Bulgaria	7	63 684	9098	9087	22.4	10.7	10.8
	Poland	28	402 533	14 376	13 385	15.5	5.0	5.0
	Armenia	3	42 105	14 035	13 902	14.1	5.0	5.0
	Czech Republic	8	114 420	14 302	13 901	15.0	4.9	4.9
	Ukraine	34	421 413	12 394	12 569	14.7	4.9	4.9
	Belarus	6	102 581	17 097	18 648	10.4	3.8	3.8
	Slovakia	2	58 200	29 100	28 544	7.2	2.4	2.4
	Georgia	2	—	—	—	—	—	—
	Hungary	5	—	—	—	—	—	—
	Moldova	3	—	—	—	—	—	—
	Romania	8	—	—	—	—	—	—
	Russian Federation	84	—	—	—	—	—	—
Subtotal		190	1 204 935	13 692	13 496	14.6	5.2	5.2
North	Denmark	10	61 109	6111	6120	35.0	10.6	10.5
	Norway	9	56 464	6274	6511	29.9	9.6	9.7
	Finland	7	50 125	7161	7362	24.4	7.8	7.8
	Estonia	1	13 833	13 833	13 662	14.9	4.7	4.7
	Lithuania	2	28 567	14 283	14 699	13.2	4.8	4.8
	United Kingdom	51	753 071	14 766	15 103	12.7	4.3	4.4
	Sweden	7	115 664	16 523	16 823	12.0	4.0	4.0
	Latvia	1	20 782	20 782	20 988	9.9	3.3	3.3
	Ireland	2	62 015	31 008	30 963	5.9	1.9	1.9
Subtotal		90	1 161 628	12 907	13 170	16.3	5.8	5.8
South	Portugal	5	86 523	17 305	16 124	11.9	3.6	3.6
	Spain	23	391 383	17 017	17 272	11.3	3.4	3.4
	Slovenia	1	20 251	20 251	20 185	9.5	3.2	3.2
	Albania	3	—	—	—	—	—	—
	Bosnia and Herzegovina	3	—	—	—	—	—	—
	Croatia	1	—	—	—	—	—	—
	Greece	4	—	—	—	—	—	—
	Italy	31	—	—	—	—	—	—
	Kosovo	2	—	—	—	—	—	—
	Malta	1	—	—	—	—	—	—
	North Macedonia	1	—	—	—	—	—	—
	Serbia	9	—	—	—	—	—	—
Subtotal		84	498 156	17 177	17 174	11.3	3.9	3.9
West	Austria	9	87 976	9775	9736	21.2	7.2	7.2
	The Netherlands	16	169 600	10 600	10 725	18.1	5.7	5.7
	Switzerland	7	87 054	12 436	12 466	16.0	5.6	5.6
	France	49	762 263	15 556	14 867	12.9	4.2	4.0
	Belgium	6	119 439	19 907	20 694	9.4	3.1	3.1
	Andorra	1	—	—	—	—	—	—
	Germany	65	—	—	—	—	—	—
Subtotal		153	1 226 331	14 096	13 783	14.1	4.8	4.7
Overall		517	4 091 051	7913	13 844	14.1	4.6	4.6

— = In countries without complete data, no calculation of incidence was completed.
Data are grouped by region and completeness (countries with incomplete data are listed in their region, but no calculations were made with their incomplete data).

numbers of cases, with the combined incidence for Italy (31 cases) and Germany (65 cases) corresponding to 1 in 12 900 live births. If the data from the 2 largest countries with potentially missing data were included in the study, they would support further the higher than previously reported incidence rate estimate, although their results may be underestimates of their true incidence rates. In this study, Russia was the country with the largest number of patients (n = 84) that was not included in the main analysis, but those data are known to be incomplete because of nonparticipation of some centers outside the capital, Moscow.

Limitations of this study include its method of data collection and its short duration. The latter limitation introduces bias and

variability into the results because the incidence rate of this rare cancer is not constant from one year to the next. However, the number of new cases used for this analysis (294 patients from 24 countries) is robust and larger than the number used for the recent 50-year-long analysis of incidence in Finland (213 patients) and 40-year-long analysis in Sweden (291 patients).[2,5]

Current data from European countries demonstrate a higher estimate of the incidence of retinoblastoma than what has been reported for previous periods. The incidence of retinoblastoma likely has increased because of improved survival, reproductive capabilities, and confidence of survivors of heritable retinoblastoma. To the best of our knowledge, the increased frequency of carriers of germline *RB1* pathogenic variants in Europe illustrates for the first time the selection relaxation effect of therapeutic intervention for a lethal disorder after only a few generations.

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No animal subjects were included in this study.

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