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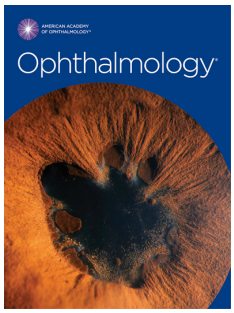

Incidence of retinoblastoma has increased: results from 40 European countries

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Incidence of retinoblastoma has increased: results from 40 European countries

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Report

Retinoblastoma is the most common intraocular malignancy. Its incidence has been reported between 1 case in 15,000 – 18,000 live births, or about 12, 6, or 4 cases per 1 million children under the age of 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 one-year time frame. Data were collected through an international, multicenter, one-year cross-sectional analysis that has been previously described in detail.[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 who described their data as "likely complete".

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

$$Incidence\ (livebirth) = \frac{\#\ Retinoblastoma\ cases\ in\ 2017}{Population\ in\ 2017\ \times Crude\ Birth\ Rate\ in\ 2017}$$

The formula used to calculate the age-cohort incidence rate (per 1 million children aged <5 years) is shown below:

$$Incidence\ (agecohort)\ = \frac{\#\ Retinoblastoma\ cases\ in\ 2017}{Population\ Estimate\ age\ < 5\ years\ in\ 2017} \times 1\ Million$$

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 male, and per capita gross domestic product (GDP) for the year 2017 (World Bank database). Summary data were calculated for each country and European region (North, South, East, West). An alpha 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 (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, map in **Figure 1, available at www.aaojournal.org**).

The combined age-cohort incidence rate was 14.1 per million children <5 years old (CI: 12.9 - 15.9), and 4.6 per million children <15 years old (CI: 4.1 – 5.2, **Table 1**). The age-cohort results were used in a linear regression analysis (full details in **Table 2, available at www.aaojournal.org**). There was no significant relationship between incidence rate and country GDP. 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 presenting and the incidence rate within that country. A similar trend was present for the countries grouped by region (scatter plots demonstrated in **Figure 2, 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 under age 5 and 15 years, respectively – are higher than those previously reported. While some studies have suggested stable incidence rates over many years through the early 2000s, [1,2,4] recent national data from Finland documented an increase from approximately 1 in 16,700 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, even wider in Europe, the incidence of retinoblastoma has increased in recent decades 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 two large countries included in the study whose completeness could not be verified: Italy and Germany. These countries reported high 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 two largest countries with potential missing data were included in the study, they would further support the higher than previously reported incidence rate estimate, even though their results may be underestimates of their true incidence rates. In this study, Russia was the country with the largest number of patients (84) that was not included in the main analysis, but those data are known to be incomplete due to non-participation 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]

Conclusion:

Current data from European countries demonstrate a higher estimate of the incidence of retinoblastoma than what has been reported for previous time periods. The incidence of retinoblastoma has likely 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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Table 1: European Countries included in the analysis with the corresponding number of new patients and calculated incidence rates. The 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)

European Region	Country	New patients reported in 2017	Calculated births (World Bank)	Live births per one new diagnosis (World Bank)	Live birth per one new diagnosis (United Nations)	Incidence per million children age <5 years (United Nations)	Incidence per million children age <15 years (United Nations)	Incidence per million children <15 years (WORLD BANK)
East	Bulgaria	7	63684	9098	9087	22.4	10.7	10.8
	Poland	28	402533	14376	13385	15.5	5.0	5.0
	Armenia	3	42105	14035	13902	14.1	5.0	5.0
	Czech Republic	8	114420	14302	13901	15.0	4.9	4.9
	Ukraine	34	421413	12394	12569	14.7	4.9	4.9
	Belarus	6	102581	17097	18648	10.4	3.8	3.8
	Slovakia	2	58200	29100	28544	7.2	2.4	2.4
	Georgia	2	-	-	-	-	-	-
	Hungary	5	-	-	-	-	-	-
	Moldova	3	-	-	-	-	-	-
	Romania	8	-	-	-	-	-	-
	Russian Federation	84	-	-	-	-	-	-
	TOTAL	**190**	**1204935**	**13692**	**13496**	**14.6**	**5.2**	**5.2**
North	Denmark	10	61109	6111	6120	35.0	10.6	10.5
	Norway	9	56464	6274	6511	29.9	9.6	9.7
	Finland	7	50125	7161	7362	24.4	7.8	7.8
	Estonia	1	13833	13833	13662	14.9	4.7	4.7
	Lithuania	2	28567	14283	14699	13.2	4.8	4.8
	United Kingdom	51	753071	14766	15103	12.7	4.3	4.4
	Sweden	7	115664	16523	16823	12.0	4.0	4.0
	Latvia	1	20782	20782	20988	9.9	3.3	3.3
	Ireland	2	62015	31008	30963	5.9	1.9	1.9
	TOTAL	**90**	**1161628**	**12907**	**13170**	**16.3**	**5.8**	**5.8**
South	Portugal	5	86523	17305	16124	11.9	3.6	3.6
	Spain	23	391383	17017	17272	11.3	3.4	3.4
	Slovenia	1	20251	20251	20185	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	-	-	-	-	-	-
	TOTAL	**84**	**498156**	**17177**	**17174**	**11.3**	**3.9**	**3.9**
West	Austria	9	87976	9775	9736	21.2	7.2	7.2
	Netherlands	16	169600	10600	10725	18.1	5.7	5.7
	Switzerland	7	87054	12436	12466	16.0	5.6	5.6
	France	49	762263	15556	14867	12.9	4.2	4.0
	Belgium	6	119439	19907	20694	9.4	3.1	3.1
	Andorra	1	-	-	-	-	-	-
	Germany	65	-	-	-	-	-	-
	TOTAL	**153**	**1226331**	**14096**	**13783**	**14.1**	**4.8**	**4.7**
OVERALL		517	4091051	7913	13844	14.1	4.6	4.6

215 **Figure Legend**

216 **Figure 1:** Map depiction of retinoblastoma incidence per 1 million children <5 years old from
217 countries that reported “complete” or “likely complete” data.

218 **Figure 2:** Scatterplot of retinoblastoma incidence in 2017 per 1 million children <5 years against
219 percent of new patients with familial retinoblastoma in (A) 24 European countries that reported
220 “likely complete” data and (B) in four main geographic regions of Europe as given in the World
221 Population Prospects.

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Table 1: European Countries included in the analysis with the corresponding number of new patients and calculated incidence rates. The 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)

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	Armenia	3	42105	14035	13902	14.1	5.0	5.0
	Czech Republic	8	114420	14302	13901	15.0	4.9	4.9
	Ukraine	34	421413	12394	12569	14.7	4.9	4.9
	Belarus	6	102581	17097	18648	10.4	3.8	3.8
	Slovakia	2	58200	29100	28544	7.2	2.4	2.4
	Georgia	2	-	-	-	-	-	-
	Hungary	5	-	-	-	-	-	-
	Moldova	3	-	-	-	-	-	-
	Romania	8	-	-	-	-	-	-
	Russian Federation	84	-	-	-	-	-	-
	TOTAL	**190**	**1204935**	**13692**	**13496**	**14.6**	**5.2**	**5.2**
North	Denmark	10	61109	6111	6120	35.0	10.6	10.5
	Norway	9	56464	6274	6511	29.9	9.6	9.7
	Finland	7	50125	7161	7362	24.4	7.8	7.8
	Estonia	1	13833	13833	13662	14.9	4.7	4.7
	Lithuania	2	28567	14283	14699	13.2	4.8	4.8
	United Kingdom	51	753071	14766	15103	12.7	4.3	4.4
	Sweden	7	115664	16523	16823	12.0	4.0	4.0
	Latvia	1	20782	20782	20988	9.9	3.3	3.3
	Ireland	2	62015	31008	30963	5.9	1.9	1.9
	TOTAL	**90**	**1161628**	**12907**	**13170**	**16.3**	**5.8**	**5.8**
South	Portugal	5	86523	17305	16124	11.9	3.6	3.6
	Spain	23	391383	17017	17272	11.3	3.4	3.4
	Slovenia	1	20251	20251	20185	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	-	-	-	-	-	-
	TOTAL	**84**	**498156**	**17177**	**17174**	**11.3**	**3.9**	**3.9**
West	Austria	9	87976	9775	9736	21.2	7.2	7.2
	Netherlands	16	169600	10600	10725	18.1	5.7	5.7
	Switzerland	7	87054	12436	12466	16.0	5.6	5.6
	France	49	762263	15556	14867	12.9	4.2	4.0
	Belgium	6	119439	19907	20694	9.4	3.1	3.1
	Andorra	1	-	-	-	-	-	-
	Germany	65	-	-	-	-	-	-
	TOTAL	**153**	**1226331**	**14096**	**13783**	**14.1**	**4.8**	**4.7**
OVERALL		517	4091051	7913	13844	14.1	4.6	4.6

Table 2: Linear regression analysis of potential predictors of higher incidence rate of retinoblastoma in 24 European countries that reported "likely complete" data for 2017

European Region	Country	Incidence per million children < 5 years	Mean age of presentation (months)	Proportion with positive family history	Proportion bilateral disease	Proportion males	GDP/Capita 2017 (US$)
East	Bulgaria	22.4	17.4	0	0.36	0.55	8228
	Poland	15.5	20.4	0	0.21	0.71	13863
	Czech Republic	15.0	12.5	0.13	0.13	0.63	20368
	Ukraine	14.7	19.6	0.12	0.24	0.47	2640
	Armenia	14.1	18.6	0	0.00	0.67	3937
	Belarus	10.4	18.2	0	0.00	0.50	5728
	Slovakia	7.2	31.9	0	0.00	0.50	17605
	Total	**14.6**	**19.1**	**0.07**	**0.21**	**0.58**	
North	Denmark	35.0	25.3	0.20	0.40	0.50	56308
	Norway	29.9	33.0	0.22	0.22	0.78	75505
	Finland	24.4	30.2	0	0.14	0.57	45703
	Netherlands	18.1	19.6	0	0.44	0.50	48223
	Estonia	14.9	13.1	0	0.00	1.00	19705
	Lithuania	13.2	17.6	0	0.50	1.00	16681
	United Kingdom	12.7	18.9	0.10	0.37	0.51	39720
	Sweden	12.0	26.5		0.43	0.43	53442
	Latvia	9.9	2.4	0	0.00	0.00	15594
	Ireland	5.9	13.7	0	0.50	0.50	69331
	Total	**16.3**	**22.1**	**0.11**	**0.34**	**0.54**	
South	Portugal	11.9	14.1	0	1.00	0.80	21136
	Spain	11.3	17.6	0.09	0.35	0.30	28157
	Slovenia	9.5	38.9	0	0.00	1.00	23597
	Total	**11.3**	**17.7**	**0.07**	**0.45**	**0.41**	
West	Austria	21.2	16.4	0.11	0.33	0.56	47291
	Switzerland	16.0	11.3	0.14	0.71	0.29	80190
	France	12.9	19.8	0.10	0.35	0.57	38477
	Belgium	9.4	19.3	0	0.50	0.33	43324
	Total	**14.1**	**18.7**	**0.08**	**0.40**	**0.52**	
Overall	p-value		0.11	0.002	0.85	0.58	0.105

< 10 per million

> 20 per million

Between 14-20 per million

Between 10-14 per million

Incomplete Data

Figure 2a

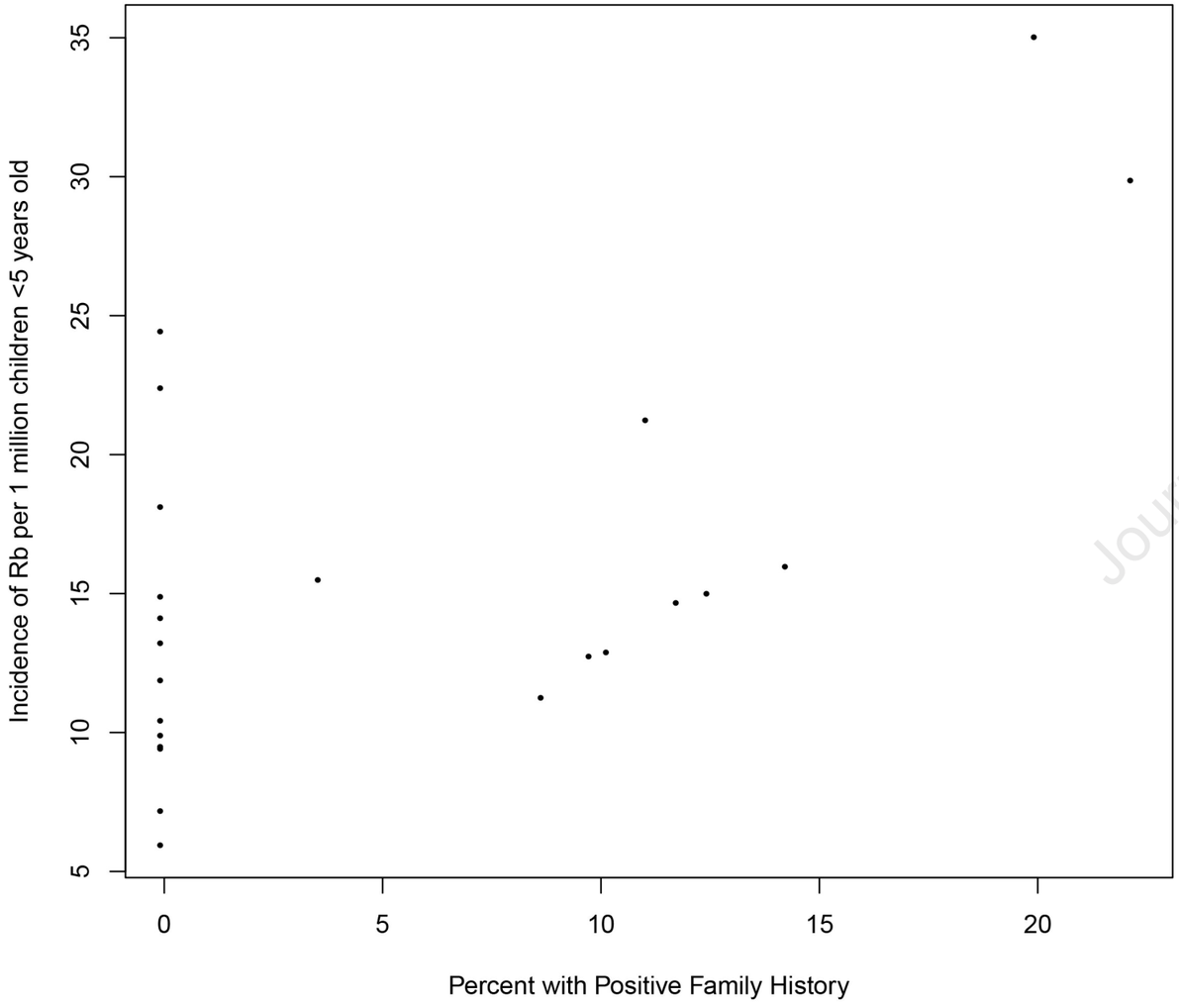
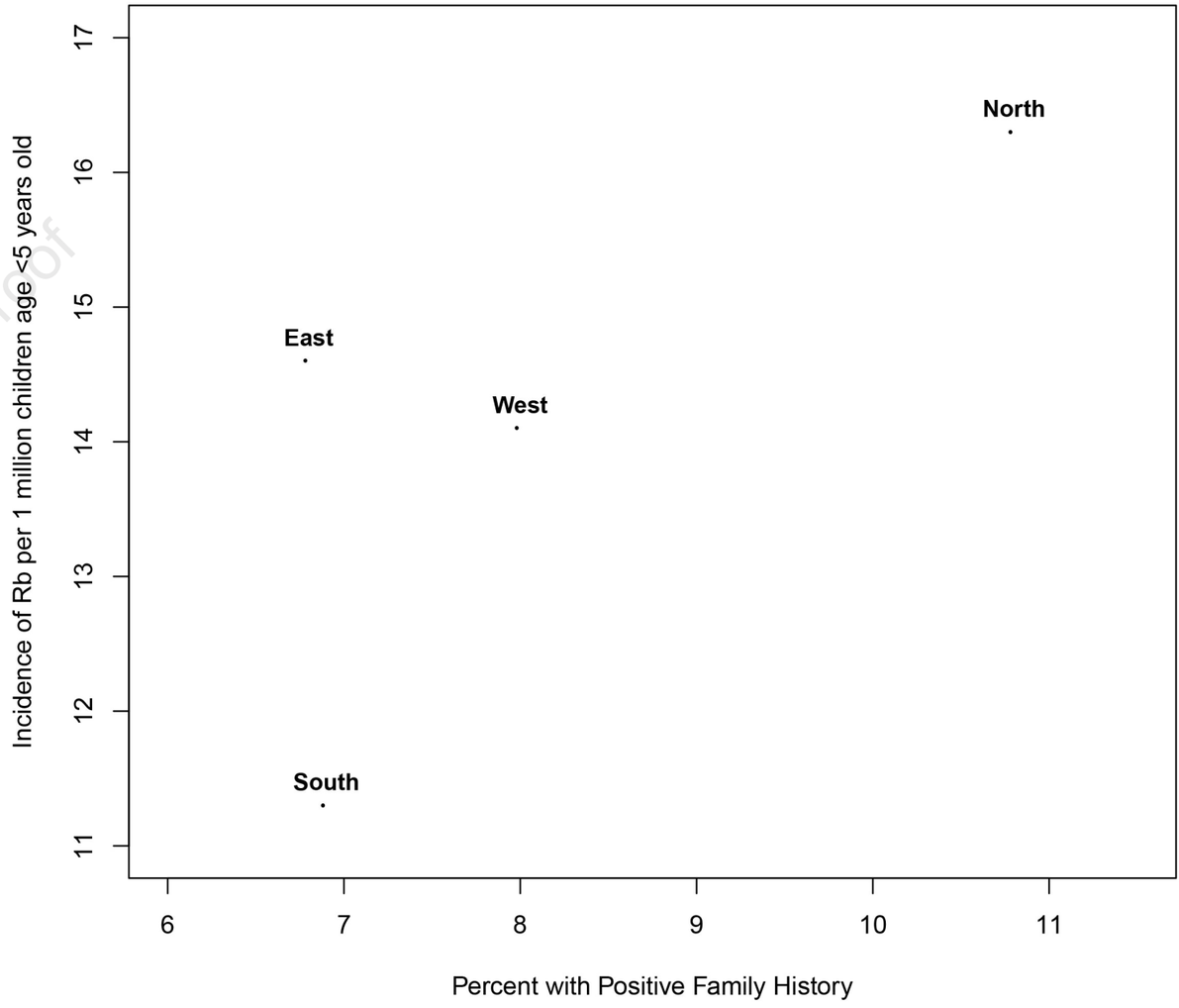


Figure 2b



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