

1 **Incidence of retinoblastoma has increased: results from 40 European countries**

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3 Andrew W Stacey, MD<sup>1</sup>, Richard Bowman, FRCOphth<sup>2,3</sup>, Allen Foster, FRCOphth<sup>2</sup>, Tero T. Kivelä,  
4 MD<sup>4</sup>, Francis L Munier, MD<sup>5</sup>, Nathalie Cassoux, MD, PhD<sup>6</sup>, Ido Didi Fabian, MD<sup>2,7</sup> for the Global  
5 Retinoblastoma Study Group

6 Global Retinoblastoma Study Group

7 Lamis Al Harby, MD<sup>8</sup>, Silvia Alarcón Portabella, MD<sup>9</sup>, Donjeta B Alia, MD<sup>10</sup>, Charlotta All-  
8 Eriksson, MD, PhD<sup>11</sup>, Romanzo Antonino, MD<sup>12</sup>, Nicholas J Astbury, FRCS FRCOphth<sup>2</sup>, Julia  
9 Balaguer, MD, PhD<sup>13</sup>, Walentyna Balwierz, MD<sup>14</sup>, Honorio Barranco, MD, PhD<sup>13</sup>, Covadonga  
10 Bascaran, MD MSc<sup>2</sup>, Maja Beck Popovic, MD<sup>15</sup>, Eva M Biewald, MD<sup>16</sup>, Nadia Bobrova, MD<sup>17</sup>,  
11 Norbert Bornfeld, MD<sup>16</sup>, Bénédicte G Brichard, MD, PhD<sup>18</sup>, Sharon Blum, MD<sup>7</sup>, Michael Capra,  
12 FRCPI<sup>19</sup>, Guilherme Castela, MD<sup>20</sup>, Jaume Català-Mora, MD, PhD<sup>21</sup>, Guillermo L Chantada, MD<sup>21</sup>,  
13 Violeta S Chernodrinska, MD, PhD<sup>22</sup>, Krzysztof Cieslik, MD<sup>23</sup>, Codruta Comsa, MD<sup>24</sup>, Maria G  
14 Correa Llano, MD<sup>21</sup>, Monika Csóka, MD, PhD<sup>25</sup>, Patrick De Potter, MD, PhD<sup>18</sup>, Laurence  
15 Desjardins, MD<sup>26</sup>, Monica D Dragomir, MD, PhD<sup>24</sup>, Ana Fernández-Teijeiro, MD, PhD<sup>27</sup>, David  
16 García Aldana, MD<sup>28</sup>, Pernille A Gregersen, MD<sup>29</sup>, Nir Gomel, MD<sup>30</sup>, Theodora Hadjistilianou,  
17 MD<sup>31</sup>, Stanislava Hederova, MD<sup>32</sup>, Marlies Hummlen, MD<sup>33</sup>, Kristina Husakova, MD<sup>32</sup>, Russo  
18 Ida, MD<sup>12</sup>, Vesna R Ilic, MD<sup>34</sup>, Helen Jenkinson, MD, PhD<sup>35</sup>, Noa Kapelushnik, MD<sup>7</sup>, Tamar  
19 Kardava, PhD<sup>36</sup>, Naama Keren-Froim, B.Med.Sc.<sup>37</sup>, Tomas Kepak, MD<sup>38</sup>, Zaza Khotenashvili,  
20 MD<sup>36</sup>, Artur Klett, MD, PhD<sup>39</sup>, Dalia Krivaitiene, MD, PhD<sup>40</sup>, Slobodanka Latinović, MD, PhD<sup>41</sup>,  
21 Livia Lumbroso, MD<sup>26</sup>, Lesia Lysytsia, MD<sup>42</sup>, Erika Maka, MD<sup>25</sup>, Nieves Martín Begue, MD, PhD<sup>9</sup>,  
22 Edoardo Midená, MD, PhD<sup>43</sup>, Annette C Moll, MD, PhD<sup>44</sup>, Gabriela Murgoi, MD<sup>24</sup>, Larisa  
23 Naumenko, , MD, PhD<sup>45</sup>, Vladimir Neroev, MD, PhD<sup>46</sup>, Marina Nikitovic, MD, PhD<sup>34</sup>, Andrzej  
24 Olechowski, MD<sup>23</sup>, Ruzanna Papyan, MD<sup>47</sup>, Raffaele Parrozzani, MD, PhD<sup>43</sup>, Manoj V Parulekar,  
25 MS, FRCOphth<sup>35</sup>, Katarzyna Pawinska-Wasikowska, MD, PhD<sup>14</sup>, Sanja Perić, MD, PhD<sup>48</sup>, Pavel  
26 Pochop, MD, PhD<sup>49</sup>, Vladimir G Polyakov, MD<sup>50</sup>, M. Ashwin Reddy, FRCOphth<sup>51</sup>, Petra Ritter-  
27 Sovinz, MD<sup>52</sup>, Svetlana Saakyan, MD, PhD<sup>46</sup>, Mandeep S Sagoo, FRCS (Ed)<sup>53</sup>, Sonsoles San  
28 Román Pacheco, MD<sup>54</sup>, Stefan Seregard, MD, PhD<sup>11</sup>, Sónia Silva, MD<sup>20</sup>, Tetyana Sorochynska,  
29 MD, PhD<sup>17</sup>, Christina Stathopoulos, MD<sup>6</sup>, Branka Stirn Kranjc, MD, PhD<sup>55</sup>, Karel Svojgr, MD,  
30 PhD<sup>56</sup>, Gevorg Tamamyan, MD, PhD<sup>47</sup>, Alketa Tandili, MD, PhD<sup>10</sup>, Bekim Tateshi, MD, PhD<sup>57</sup>,  
31 Manca Tekavcic Pompe, MD, PhD<sup>55</sup>, Steen F Urbak, MD, PhD<sup>58</sup>, Tatiana L Ushakova, MD<sup>50</sup>,  
32 Sandra Valeina, MD<sup>59</sup>, Milo van Hoefen Wijsard, MD<sup>44</sup>, Nevyana V Veleva-Krasteva, MD, PhD<sup>22</sup>,  
33 Maris Viksnins, MD<sup>59</sup>, Werner Wackernagel, MD<sup>60</sup>, Charlotte Wolley Dod, MD<sup>9</sup>, Vera A  
34 Yarovaya, MD<sup>61</sup>, Andrey A Yarovoy, MD, PhD<sup>61</sup>, Katsiaryna Zhilyaeva, MD<sup>45</sup>, Marcia Zondervan,  
35 MBA<sup>2</sup>

36

37 **Affiliations:**

38 <sup>1</sup>Department of Ophthalmology, University of Washington, Seattle, WA, US, <sup>2</sup>International  
39 Centre for Eye Health, London School of Hygiene & Tropical Medicine, London,  
40 UK, <sup>3</sup>Ophthalmology Department, Great Ormond Street Children's Hospital, London, UK, <sup>4</sup>Ocular  
41 Oncology Service, Department of Ophthalmology, University of Helsinki and Helsinki University  
42 Hospital, Helsinki, Finland, <sup>5</sup>Jules-Gonin Eye Hospital, Fondation Asile de Aveugles, University of  
43 Lausanne, Lausanne, Switzerland, <sup>6</sup>Institut curie, université de Paris medicine Paris V Descartes,  
44 Paris, France, <sup>7</sup>Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Tel-Aviv  
45 University, Tel-Aviv, Israel <sup>8</sup>The Royal London Hospital, Barts Health NHS Trust, and Moorfields  
46 Eye Hospital NHS Foundation Trust, London, UK, <sup>9</sup>Department of Pediatric Ophthalmology,  
47 Hospital Vall d'Hebron, Barcelona, Spain, <sup>10</sup>University Hospital Centre "Mother Theresa", Tirana,  
48 Albania, <sup>11</sup>St Erik Eye Hospital, Stockholm, Sweden, <sup>12</sup>Bambino Gesù IRCCS Children's Hospital,  
49 Rome, Italy, <sup>13</sup>Pediatric Oncology Unit, Hospital Universitario y Politécnico La Fe, Valencia,  
50 Spain, <sup>14</sup>Institute of Pediatrics, Jagiellonian University Medical College, Childrens University  
51 Hospital of Krakow, Krakow, Poland, <sup>15</sup>Unit of Pediatric Hematology-Oncology, University  
52 Hospital CHUV, Lausanne, Switzerland, <sup>16</sup>University Hospital Essen, Department of  
53 Ophthalmology, University Duisburg-Essen, Essen, Germany, <sup>17</sup>The Filatov Institute of Eye  
54 diseases and Tissue Therapy, Odessa, Ukraine, <sup>18</sup>Cliniques Universitaires Saint-Luc, Brussel,  
55 Belgium, <sup>19</sup>Our Lady's Children's Hospital, Dublin, Ireland, <sup>20</sup>Centro Hospital Universitário de  
56 Coimbra, University of Coimbra, Coimbra, Portugal, <sup>21</sup>Hospital Sant Joan de Déu, Barcelona,  
57 Spain, <sup>22</sup>Eye Clinic, University Hospital "Alexandrovska", Department of Ophthalmology,  
58 Medical University, Sofia, Bulgaria, <sup>23</sup>Department of Ophthalmology, The Children's Memorial  
59 Health Institute, Warsaw, Poland, <sup>24</sup>Oncology Institute "Prof. Dr. Al. Trestioreanu" Bucharest,  
60 Romania, <sup>25</sup>Semmelweis University Budapest, Budapest, Hungary, <sup>26</sup>Institut curie, Paris, France,  
61 <sup>27</sup>Hospital Universitario Virgen Macarena, Sevilla, Spain, <sup>28</sup>Servicio Andaluz de Salud (SAS),  
62 Sevilla, Spain, <sup>29</sup>Department of Clinical Genetics, and Centre for Rare Disorders, Aarhus  
63 University Hospital, Aarhus, Denmark, <sup>30</sup>Division of Ophthalmology, Tel Aviv Sourasky Medical  
64 Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, <sup>31</sup>Retinoblastoma  
65 referral center, University of Siena, Siena, Italy, <sup>32</sup>University Childrens' Hospital, Bratislava,  
66 Slovakia, <sup>33</sup>Eye Department, Oslo university hospital, Oslo, Norway, <sup>34</sup>Institute for Oncology and  
67 Radiology, Belgrade, Serbia, <sup>35</sup>Birmingham Children's Hospital Eye Department, Birmingham  
68 Women's and Children's NHS Foundation Trust, Birmingham, UK, <sup>36</sup>Ophthalmology Department,  
69 Central Children's Hospital of Georgia, Tbilisi, Georgia, <sup>37</sup>Sackler Faculty of Medicine, Tel-Aviv  
70 University, Tel-Aviv, Israel, <sup>38</sup>University Hospital Brno, Masaryk University and ICRC/St. Anna  
71 University Hospital, Brno, Czech Republic, <sup>39</sup>East Tallinn Central Hospital, Tallinn, Estonia,  
72 <sup>40</sup>Children's Ophthalmology Department, Children's Hospital of Vilnius, University Hospital  
73 Santaros Clinic, Vilnius, Lithuania, <sup>41</sup>Clinical Center Of Vojvodina – University Eye Clinic, Eye  
74 Research Foundation Vidar – Latinović, Novi Sad, Serbia, <sup>42</sup>The Okhmatdyt National Children's  
75 Hospital, Kiev, Ukraine, <sup>43</sup>Department of Ophthalmology, University of Padova, Padova, Italy,  
76 <sup>44</sup>Department of Ophthalmology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer  
77 Center Amsterdam, Amsterdam, Netherlands, <sup>45</sup>N.N. Alexandrov National Cancer Centre of  
78 Belarus, Minsk, Belarus, <sup>46</sup>Moscow Helmholtz Research Institute of Eye Diseases, Moscow,

79 Russia, <sup>47</sup>Yerevan State Medical University, Department of Oncology and Pediatric Cancer and  
80 Blood Disorders Center of Armenia, Hematology Center after R.H. Yeolyan, Yerevan, Armenia,  
81 <sup>48</sup>University Hospital Centre Zagreb, Zagreb, Croatia, <sup>49</sup>Department of Ophthalmology for  
82 Children and Adults, 2nd Faculty of Medicine, Charles University in Prague and Motol University  
83 Hospital, Prague, Czech Republic, <sup>50</sup>Head and Neck Tumors Department, SRI of Pediatric  
84 Oncology and Hematology of N.N. Blokhin National Medical Research Center of Oncology of  
85 Russian Federation, and Medical Academy of Postgraduate Education, Moscow, Russia, <sup>51</sup>The  
86 Royal London Hospital, Barts Health NHS Trust, and Moorfields Eye Hospital NHS Foundation  
87 Trust, London, UK, <sup>52</sup>Department of Pediatrics and Adolescent Medicine, Division of Pediatric  
88 Hematology/Oncology, Medical University of Graz, Graz, Austria, <sup>53</sup>NIHR Biomedical Research  
89 Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology and  
90 London Retinoblastoma Service, Royal London Hospital, London, UK, <sup>54</sup>Pediatric Hemato-  
91 Oncology, Hospital Universitario Infantil La Paz, Madrid, Spain, <sup>55</sup>Univ. Medical Centre Ljubljana,  
92 Univ. Eye Hospital Ljubljana, Ljubljana, Slovenia, <sup>56</sup>Department of Pediatric Hematology and  
93 Oncology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital,  
94 Prague, Czech Republic, <sup>57</sup>University Eye Clinic, Skopje, Macedonia, <sup>58</sup>Department of  
95 ophthalmology, Aarhus University Hospital, Aarhus, Denmark, <sup>59</sup>Children's Clinical University  
96 Hospital, Riga, Latvia, <sup>60</sup>Department of Ophthalmology, Medical University Graz, Graz, Austria,  
97 <sup>61</sup>S.Fyodorov Eye Microsurgery Federal State Institution, Moscow, Russia

98

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107 Correspondence to:

108 Andrew W. Stacey MD

109 Department of Ophthalmology

110 University of Washington

111 Seattle, Washington, USA

112 Email: [awstacey@uw.edu](mailto:awstacey@uw.edu)

113 Phone: +1 206 744 3225

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115 **Report**

116 Retinoblastoma is the most common intraocular malignancy. Its incidence has been reported  
117 between 1 case in 15,000 – 18,000 live births, or about 12, 6, or 4 cases per 1 million children  
118 under the age of 5, 10, or 15 years, respectively.<sup>1,2</sup> The aim of this study was to estimate the  
119 incidence of retinoblastoma across European countries within a one-year time frame. Data  
120 were collected through an international, multicenter, one-year cross-sectional analysis that has  
121 been previously described in detail.<sup>3</sup> Briefly, retinoblastoma treatment centers reported all new  
122 cases of retinoblastoma that were diagnosed between January 2017 and December 2017. The  
123 final analysis involved only those countries who described their data as “likely complete”.  
124 Two methods were used to estimate the incidence rate of retinoblastoma, the “live-birth”  
125 method and the “age-cohort”. Country population estimates and birth rates were retrieved  
126 from the World Bank Population Prospects and the United Nations database for 2017.

127 The formula used to calculate the live-birth incidence rate in each country was:

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$$129 \quad \text{Incidence (livebirth)} = \frac{\# \text{ Retinoblastoma cases in 2017}}{\text{Population in 2017} \times \text{Crude Birth Rate in 2017}}$$

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

$$132 \quad \text{Incidence (agecohort)} = \frac{\# \text{ Retinoblastoma cases in 2017}}{\text{Population Estimate age} < 5 \text{ years in 2017}} \times 1 \text{ Million}$$

133 Bootstrap sampling was used to estimate the distribution of each incidence rate. Linear  
134 regression analysis was conducted to identify factors that may affect the country-level  
135 incidence rate, including the following variables: age at diagnosis, proportion of bilateral cases,  
136 proportion of familial cases, proportion male, and per capita gross domestic product (GDP) for  
137 the year 2017 (World Bank database). Summary data were calculated for each country and  
138 European region (North, South, East, West). An alpha level of 0.05 was used.

139 From the original 40 countries (with 517 retinoblastoma patients), 24 countries were identified as  
140 representing "likely complete" national-level data, and all 294 patients from these 24 countries were  
141 included in the analysis (**Table 1**).

142 The number of live births for the year 2017 was calculated for each country and region (**Table**  
143 **1**). The combined data resulted in a live-birth incidence rate of 1 in 13,915 (CI: 12,315 - 15,150),  
144 or 7.2 per 100,000, live births in Europe. The analysis was repeated with the United Nations  
145 population data and similar outcomes were seen for each country and overall (1 in 13,844 live  
146 births, CI: 12,309 - 15,083). The highest live-birth incidence was seen in Northern Europe (1 in  
147 12,907 live births) whereas the lowest incidence rate was seen in Southern Europe (1 in 17,177  
148 live births, map in **Figure 1, available at [www.aaojournal.org](http://www.aaojournal.org)**).

149 The combined age-cohort incidence rate was 14.1 per million children <5 years old (CI: 12.9 -  
150 15.9), and 4.6 per million children <15 years old (CI: 4.1 – 5.2, **Table 1**). The age-cohort results  
151 were used in a linear regression analysis (full details in **Table 2, available at**  
152 **[www.aaojournal.org](http://www.aaojournal.org)**). There was no significant relationship between incidence rate and  
153 country GDP. The only variable that resulted in a significant association with incidence rate was

154 the proportion of familial cases ( $p=0.002$ ), which showed an increasing relationship between  
155 the proportion of familial cases presenting and the incidence rate within that country. A similar  
156 trend was present for the countries grouped by region (scatter plots demonstrated in **Figure 2**,  
157 **available at [www.aaojournal.org](http://www.aaojournal.org)**).

158 The incidence rates calculated in this study – 1 in 13,844 live births or 14.1 and 4.6 per 1 million  
159 children under age 5 and 15 years, respectively – are higher than those previously reported.  
160 While some studies have suggested stable incidence rates over many years through the early  
161 2000s,<sup>1,2,4</sup> recent national data from Finland documented an increase from approximately 1 in  
162 16,700 to 1 in 12,500 live births from 1990 to 2014.<sup>5</sup> The increase in Finland was not evident  
163 when familial retinoblastoma was excluded. Our study supports the conclusion that, even  
164 wider in Europe, the incidence of retinoblastoma has increased in recent decades because of an  
165 increasing number of familial patients.

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

172 One important finding from these data comes from two large countries included in the study  
173 whose completeness could not be verified: Italy and Germany. These countries reported high  
174 numbers of cases with the combined incidence for Italy (31 cases) and Germany (65 cases),

175 corresponding to 1 in 12,900 live births. If the data from the two largest countries with  
176 potential missing data were included in the study, they would further support the higher than  
177 previously reported incidence rate estimate, even though their results may be underestimates  
178 of their true incidence rates. In this study, Russia was the country with the largest number of  
179 patients (84) that was not included in the main analysis, but those data are known to be  
180 incomplete due to non-participation of some centers outside the capital, Moscow.

181 Limitations of this study include its method of data collection and its short duration. The latter  
182 limitation introduces bias and variability into the results, because the incidence rate of this rare  
183 cancer is not constant from one year to the next. However, the number of new cases used for  
184 this analysis (294 patients from 24 countries) is robust and larger than the number used for the  
185 recent 50 year-long analysis of incidence in Finland (213 patients) and 40 year-long analysis in  
186 Sweden (291 patients).<sup>2,5</sup>

#### 187 **Conclusion:**

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

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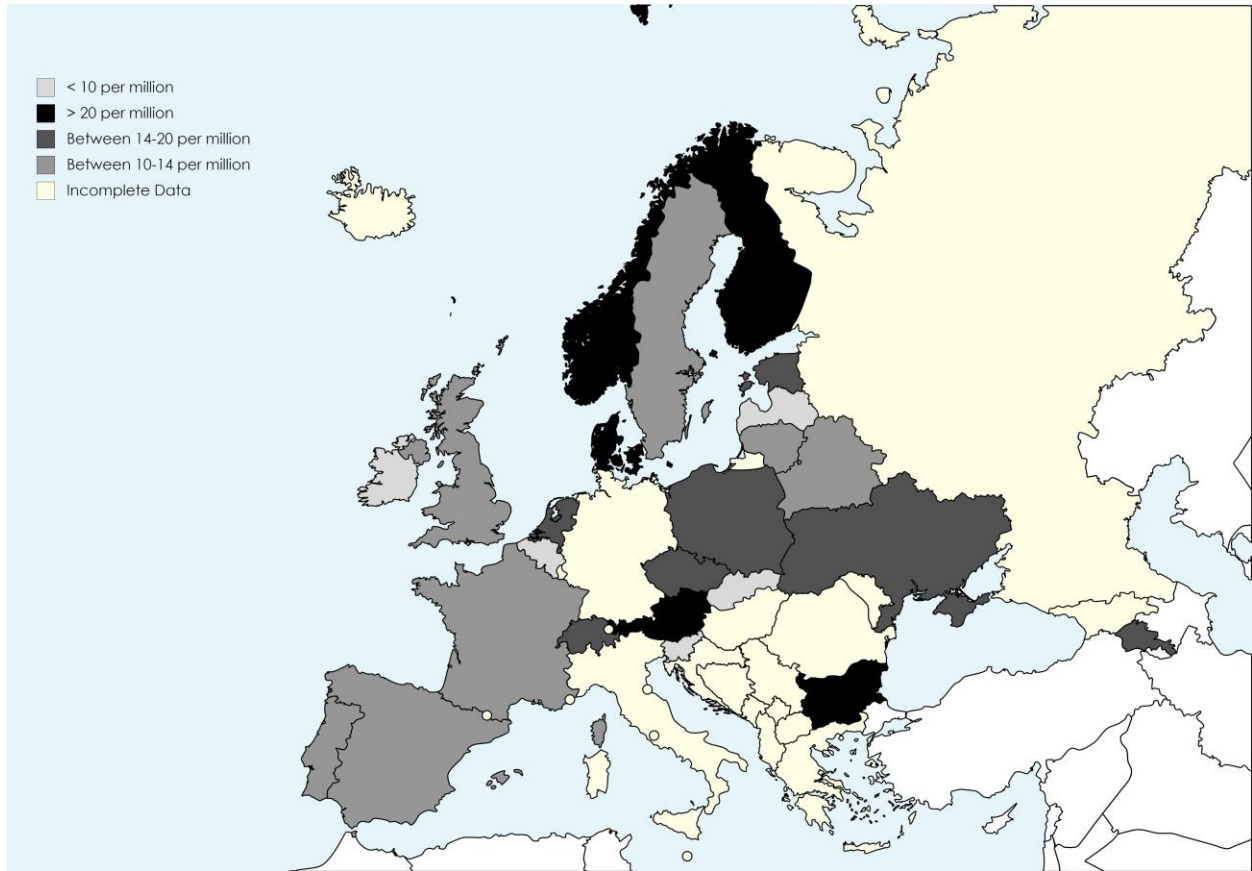
213 **Table 1: European Countries included in the analysis with the corresponding number of new patients and**  
 214 **calculated incidence rates. The data are grouped by region and completeness (countries with incomplete data**  
 215 **are listed in their region but no calculations were made with 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	-	-	-	-	-	-
		<b>TOTAL</b>	<b>190</b>	<b>1204935</b>	<b>13692</b>	<b>13496</b>	<b>14.6</b>	<b>5.2</b>
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
		<b>TOTAL</b>	<b>90</b>	<b>1161628</b>	<b>12907</b>	<b>13170</b>	<b>16.3</b>	<b>5.8</b>
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	-	-	-	-	-	-
		<b>TOTAL</b>	<b>84</b>	<b>498156</b>	<b>17177</b>	<b>17174</b>	<b>11.3</b>	<b>3.9</b>
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	-	-	-	-	-	-
		<b>TOTAL</b>	<b>153</b>	<b>1226331</b>	<b>14096</b>	<b>13783</b>	<b>14.1</b>	<b>4.8</b>
<b>OVERALL</b>		<b>517</b>	<b>4091051</b>	<b>7913</b>	<b>13844</b>	<b>14.1</b>	<b>4.6</b>	<b>4.6</b>

217 **Table 2: Linear regression analysis of potential predictors of higher incidence rate of retinoblastoma in 24**  
 218 **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
	<b>Total</b>	<b>14.6</b>	<b>19.1</b>	<b>0.07</b>	<b>0.21</b>	<b>0.58</b>	
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
	<b>Total</b>	<b>16.3</b>	<b>22.1</b>	<b>0.11</b>	<b>0.34</b>	<b>0.54</b>	
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
		<b>Total</b>	<b>11.3</b>	<b>17.7</b>	<b>0.07</b>	<b>0.45</b>	<b>0.41</b>
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
		<b>Total</b>	<b>14.1</b>	<b>18.7</b>	<b>0.08</b>	<b>0.40</b>	<b>0.52</b>
<b>Overall</b>	p-value		0.11	0.002	0.85	0.58	0.105

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



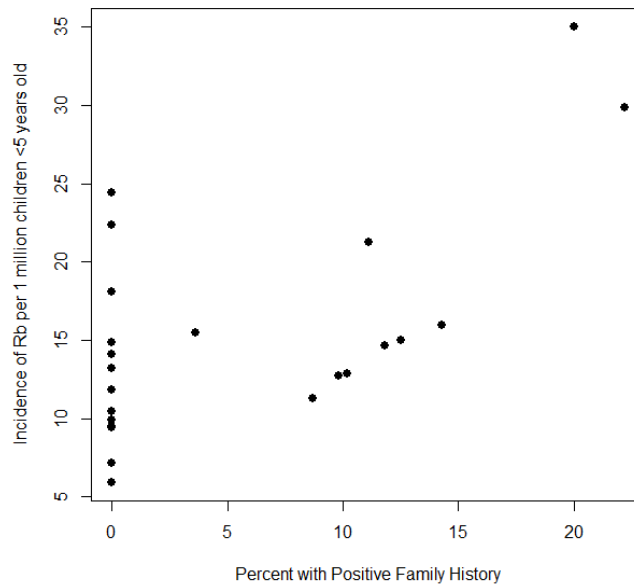
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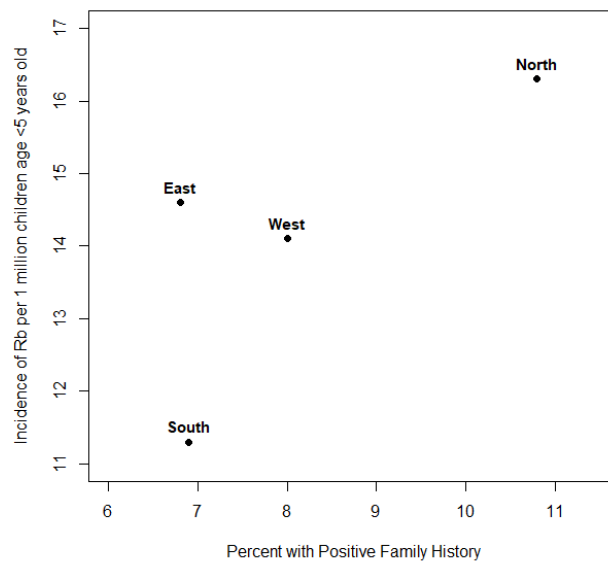
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226 **Figure 2:** Scatterplot of retinoblastoma incidence in 2017 per 1 million children <5 years against  
227 percent of new patients with familial retinoblastoma in (A) 24 European countries that reported  
228 “likely complete” data and (B) in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



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