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Survival and Health Care Burden of Children With Retinoblastoma in Europe

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Invited Commentary page 1071

Supplemental content

IMPORTANCE Studies on the epidemiology of retinoblastoma (RB) could lead to improvement in management.

OBJECTIVE To estimate the incidence and survival of RB in European children and the occurrence of second primary tumors (other than RB) in these patients.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used population-based data from 81 cancer registries in 31 European countries adhering to the European Cancer Registries (EUROCARE-6) project. Data collection took place between January 2000 and December 2013. European children aged 0 to 14 years diagnosed with RB were included. Data were analyzed from May to November 2023.

EXPOSURES Diagnosis of RB with *International Classification of Diseases for Oncology, Third Edition* (*ICD-O-3*), morphology coded 9510-9514 (retinoblastoma) and malignant behavior (fifth digit of morphology code, 3).

MAIN OUTCOME AND MEASURES Annual incidence (per million children aged 0-14 years), 5-year survival (%), and the standardized incidence ratio (SIR) of subsequent malignant neoplasms.

RESULTS The study included 3262 patients (mean [SD] age, 1.27 [1.63] years; 1706 [52%] male and 1556 [48%] female) from 81 registries. Of these, 3098 patients were considered in trend analysis after excluding registries with incomplete time coverage: 940 in 2000 to 2003, 703 in 2004 to 2006, 744 in 2007 to 2009, and 856 in 2010 to 2013. The estimated overall European incidence rate was 4.0 (95% CI, 3.9-4.1). Rates among countries varied from less than 2 million to greater than 6 million per year. No time trend of incidence was observed in any area. The overall European 5-year survival was 97.8% (95% CI, 95.5-98.9; 3180 cases). Five-year survival was lower in Estonia and Bulgaria (<80%) and 100% in several countries. Twenty-five subsequent malignant neoplasms were recorded during follow-up (up to 14 years), with an SIR of 8.2 and with cases occurring at mean ages between 1.3 and 8.9 years across different sites. An increased risk was found for hematological tumors (SIR, 5) and bone and soft tissue sarcomas (SIR, 29).

CONCLUSIONS AND RELEVANCE This study showed RB incidence remained stable at 4.0 per 1 000 000 European children aged 0 to 14 years from 2000 to 2013, but estimates varied among countries and differences in survival across countries persist. These data might be used to monitor RB management and occurrences of second tumors. The findings suggest future registry studies should aim to collect standardized RB stage at diagnosis and treatment to interpret disparities and potentially improve surveillance.

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Retinoblastoma (RB) is a very rare cancer in infancy and childhood, with estimates of new patients diagnosed annually worldwide ranging from approximately 4400 to 19 000.[1,2] In Europe, the number of new annual diagnoses is around 277, and the prevalence of adult individuals who were diagnosed with retinoblastoma in childhood is 5329.[3,4] RB is very aggressive and life-threatening if left untreated, but it is almost always curable if detected at an early stage when the disease is confined to the eye.[5] Early diagnosis and prompt treatment are vital to preserve the patient's life, eyes, and vision. Furthermore, a risk of subsequent malignant neoplasms (SMNs) following a first diagnosis has been reported,[6-9] requiring a dedicated surveillance program for these children. External beam radiation therapy was standard RB therapy until it became clear that patients faced a small but increased risk of SMNs with this treatment, which also affects the eye and anatomy of the orbit itself. Currently, radiation therapy is mostly avoided due to fear of SMNs and the availability of newer treatment alternatives, such as intra-arterial and intravitreal chemotherapies.[10] With the abandonment of external beam radiation therapy, the risk for SMN s should decrease further.[11]A global cross-sectional study including half of all documented RB cases worldwide in 2017 found that children from low- and middle-income countries, where the main global RB burden lies,[1] presented at an older age with more advanced disease and demonstrated a smaller proportion of familial history of retinoblastoma. This is likely because a rather high proportion of affected patients do not reach reproductive age with consequent inability to transmit the genetic heritage to the next generation.[2] The same study group showed profound inequity in survival of children depending on the national income level of their country of residence. In high-income countries, death from retinoblastoma is rare, whereas in low-income countries, the estimated 3-year survival is just under 60%.[12] Although essential treatments are available in nearly all countries, early diagnosis and treatment in low-income countries are key to improving survival outcomes.

Several single-country studies on the epidemiology of RB have been conducted during the last decades,[13-28] most being population-based studies showing fairly stable incidence or, in Europe, an increased trend over the period from 1978 to 1997.[29] In high-income countries, the evolution of treatment modalities, as well as the early detection of tumors and access to specialized centers, has resulted in survival rates exceeding 95%, also allowing globe salvage in many cases.[29] In Europe, 15-year survival for retinoblastoma has been reported to be 97%, with a cure fraction of 99%.[4,30]

Approximately 40% of RB cases worldwide are heritable, resulting from a germline mutation in the *RB1* gene.[5,6] Survivors of heritable retinoblastoma have an increased risk of SMNs, particularly bone and soft tissue sarcomas, uterine leiomyosarcoma, melanomas, and radiotherapy-related central nervous system tumors.[7-9] While annual skin examination is recommended for RB survivors, there is still a debate on the use of whole-body magnetic resonance imaging, including the search of pinealoblastoma.[31]

To our knowledge, the last Europe-wide study on the frequency and outcomes of RB using data from population-based cancer registries was conducted using incident data up to 2002.[32] To improve the knowledge on the epidemiology of this rare tumor in Europe, we conducted a comprehensive study on incidence, survival, and SMN occurrence in children with RB diagnosed between 2000 and 2013, using population-based data from European cancer registries participating in the European Cancer Registries (EUROCARE-6) project.

Key Points

Question What are the incidence and survival of European children with retinoblastoma (RB)?

Findings In this cohort study including 3262 European children, RB incidence was estimated as stable at each year from 2000 through 2013, and 5-year survival was high; both incidence and survival varied across countries. A small number of secondary malignant neoplasms were recorded during follow-up (up to 14 years).

Meaning In European children, RB incidence was stable between 2000 and 2013. Incidence and survival estimates will inform surveillance, which could be improved if registries collect standardized RB stage at diagnosis.

Methods

Data Collection

We analyzed pseudonymized data collected from population-based cancer registries after approval by the ethics committee of the National Cancer Institute of Milan, including waiver of consent. We hold these data in trust from each participating registry for the statistical analyses agreed on in the EUROCARE-6 protocol.[33] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed.

We obtained data between January 2000 and December 2013 on 3262 patients aged 0 to 14 years who were diagnosed with RB from 81 cancer registries in 31 European countries participating in the EUROCARE-6 study, with follow-up through December 2014. The year 2013 was the most recent available, while the years before 2000 were covered by a substantially lower number of cancer registries with more than 40% fewer cases. We analyzed malignant cases with *International Classification of Diseases for Oncology, Third Edition* (*ICD-O*-3) morphology coded 9510-9514 (retinoblastoma) and malignant behavior (fifth digit of morphology code, 3).[34] We did not select specific topography codes to overcome any possible incorrect site coding, since the origin of RB is restricted to embryonic ocular tissue but can be metastatic and may also arise as a trilateral tumor (ie, including both eyes and intracranial tissues, usually in the pineal or, in about one-fourth of cases, suprasellar region[35]). Finally, for our analyses carried out on individual data, we used the following information on patients with RB: sex, date of birth and/or age at diagnosis, date of diagnosis, vital status and date of death, date of last vital status ascertainment, geographic region or cancer registry, and occurrence of a following primary tumor (other than RB) after RB with a follow-up to a maximum of 14 years. Bilateral tu-

mors were considered as a single case. Given the rarity of the disease, we aggregated countries in 5 European regions. The definition of region was already specified in Gatta et al,[36] with the inclusion of Cyprus in Southern Europe and the Czech Republic in Eastern Europe and the exclusion of Sweden from Northern Europe, which does not provide data due to national data protection policies.

Statistical Analyses

Crude incidence rates were estimated as the number of cases per 1 000 000 persons per year with 95% CIs. To be comparable with most population-based incidence studies, the case incidence year was that of the year of diagnosis. Incidence rate was calculated as the number of cases divided by the number of person-years in the geographical area, stratified by sex and age for the given period. Incidence rates, age-adjusted for the European standard population, were calculated by sex, age group, and country or region. Incidence trends of adjusted rates by period of diagnosis (ie, 2000-2003, 2004-2006, 2007-2009, and 2010-2013) were calculated from 3098 cases after excluding 24 registries that did not cover all 4 periods. There were 913 patients in 2000 to 2003, 670 in 2004 to 2006, 720 in 2007 to 2009, and 795 in 2010 to 2013.

Complete survival analysis was estimated from 2380 patients, estimating survival up to 5 years, irrespective of the date of diagnosis. Five-year observed survival was provided by the actuarial method with the period approach by age group, sex, country or region, and period of diagnosis observed (ie, absolute survival was used instead of relative survival for European children, since only a few deaths from other causes occurred). Incidence and observed survival trends were estimated for Europe as a whole and for single countries. We conducted *z* tests comparing the first and last point of the trends.

The number of SMNs among the cohort of RB survivors was compared with their expected number estimated from the overall European pool incidence rates, matched by site, sex, and age. The common end point for both expected and observed second tumors was December 31, 2013.

The confidence intervals for the observed-to-expected ratios were calculated based on the χ^2 distribution, in accordance with Sahai et al.[37] standardized incidence ratios were determined when the 95% CI did not include 1. Excess risk was estimated as the difference between observed and expected incidence rates. Data were analyzed from May to November 2023.

Results

The study included 3262 patients (mean [SD] age, 1.27 [1.63] years; 1706 [52%] male and 1556 [48%] female) from 81 registries. Of 2712 cases with information on laterality, 769 (28.4%) had bilateral lesions. Most cases were diagnosed within 5 years of age (3132 of 3262 [96%]), and 1370 of 3262 (42%) were diagnosed in the first year of life.

Table 1 shows the main data quality indicators by country. Overall, only 1 case was diagnosed from death certificates only. Sixty-five percent (1468 of 3262) were microscopically verified, although the proportions varied from 16% to 100%. Most cases were recorded in Denmark, Italy, and Poland. The quality of follow-up for vital status was good, since only 4% of cases (130 of 3262) were censored before 5 years of follow-up.

Incidence

The overall European incidence rate (age-standardized per 1 000 000 person-years, age 0-14 years) was estimated to be 4.0 (95% CI, 3.9-4.1; 3262 cases). Rates were lower than 2.0 in Cyprus, Denmark, and Austria and higher than 6.0 in Belgium (**Figure 1**). Incidence rates did not differ by sex (male, 4.2; 95% CI, 3.9-4.5; 1706 cases vs female, 3.9; 95% CI, 3.7-4.1; 1556 cases), while rates were higher in infants and in those aged 0 to 4 years (10.6; 95% CI, 10.2-11.0; 3127 cases) compared to those aged 5 to 9 years (0.4; 95% CI, 0.3-0.5; 122 cases). Table 1 provides the corresponding incidence rate by country. The eFigure in Supplement 1 shows incidence trends from 2000 to 2013. Rates did not vary between the 4 incidence periods in any European region. However, the Eastern European region had lower incidence rates than other regions throughout the study.

Survival

Figure 2 shows 5-year survival for all registries, with numerical data presented in eTable 1 in Supplement 1. The overall EU average was estimated to be 97.8% (95% CI, 95.5-98.9; 3180 cases). Five-year survival was 100% in 10 countries, including 3 countries of Northern Europe and 3 of the 4 UK nations, but less than 70% in Bulgaria and less than 80% in Estonia.

Table 2 shows 5-year survival by age bands and sex over the 3 periods. Survival remained very high across all subgroups. Five-year survival improved in the age group 1 to 4 years overall.

Risk of SMNs

Table 3 shows the observed and expected number of SMNs for each site (only the first 2 digits of the *ICD-O-3* code), with absolute excess risk reported per 10 000 children. An increased risk was found for hematological tumors (standardized incidence ratio, 5) and bone and soft tissue sarcomas (standardized incidence ratio, 29). The table also shows the time intervals at which SMNs were diagnosed. An increased risk was found for hematological tumors and sarcomas. Of the 3 cases of central nervous system cancer, 2 had a morphological codification as glioma not otherwise specified, 2 had a primitive neuroectodermal tumor, and 1 had pineoblastoma of ventricle. Another pineoblastoma was included in the endocrine glands category. Further specification of SMNs is given in eTable 2 in Supplement 1.

Discussion

The population-based estimate of RB incidence and survival in Europe provided in this cohort study describes cases diagnosed since the year 2000. Incidence rates of 4.0 per 1 000 000 children were noted among those aged 0 to 14 years in the

Table 1. Data Quality of Retinoblastoma Cases Included in the Analysis From 2000 to 2013 by Country

Country	Cases, No.	DCO, No.	MV, %	Retina cases, unspecified morphology, No.[a]	Lost to follow-up <5 y, No.	Lost to follow-up <5 y, %	Laterality, No.		
							Unilateral	Bilateral	Unknown
Austria national	28	0	82	0	0	0	22	6	0
Belgium national	104	0	77	0	2	2	72	11	21
Bulgaria national	33	0	100	0	0	0	31	2	0
Croatia national	24	0	100	0	3	13	0	0	24
Cyprus national	1	0	0	0	0	0	1	0	0
Czech Republic national	40	0	100	2	0	0	34	4	2
Denmark national	23	0	96	21	1	4	16	5	2
Estonia national	5	0	100	0	0	0	4	1	0
Finland national	67	0	55	0	0	0	0	0	67
France national, childhood	695	0	62	0	10	1	480	215	0
Germany national, childhood	550	0	41	0	90	16	360	186	4
Hungarian national, childhood	74	0	76	0	3	4	48	24	2
Iceland national	2	0	100	0	0	0	2	0	0
Ireland national	53	0	87	0	0	0	0	0	53
Italy (CR pool)[b]	192	0	70	14	5	3	45	20	127
Latvia national	12	0	83	1	0	0	0	0	12
Lithuania national	13	0	100	0	0	0	0	0	13
Malta national	4	0	75	0	0	0	0	0	4
The Netherlands national	170	0	75	0	0	0	111	59	0
Norway national	42	0	55	0	0	0	28	13	1
Poland national	217	0	100	18	0	0	78	34	105
Portugal (CR pool)[c]	68	0	82	0	0	0	47	11	10
Slovakia national	26	0	100	0	0	0	17	9	0
Slovenia national	14	0	100	1	0	0	11	3	0
Spain (CR pool)[d]	198	1	44	0	6	3	134	9	1
Switzerland national, childhood	57	0	16	0	0	0	39	18	0
England national	474	0	71	3	0	0	323	128	23
Northern Ireland national	12	0	75	1	0	0	6	3	3
Scotland national	41	0	71	0	0	0	29	6	6
Wales national	23	0	70	5	0	0	5	2	16
Northern Europe	134	0	63	21	1	1	46	18	70
Central Europe	1618	0	56	1	102	6	1095	498	25
Eastern Europe	420	0	95	21	3	1	212	74	134
Southern Europe	487	1	62	14	14	3	275	40	223
UK/Ireland	603	0	73	9	0	0	363	139	101
European pool (81 CRs)	3262	1	66	66	120	4	1943	769	496

Abbreviations: CR, cancer registry; DCO, death certificate only; MV, microscopic verification.

[a] Not included in the analysis.

[b] Italy is not nationally covered. Italy was covered by Alto Adige, Barletta-Andria-Trani, Basilicata; Bergamo, Biella, Catania-Messina-Enna, Catanzaro, Province of Varese and Como, Cremona and Mantova, Ferrara, Firenze-Prato, Friuli Venezia Giulia, Genova, Latina, Province of Milan and Lodi, Modena, Monza and Brianza, Napoli 3 South, Nuoro, Palermo, Parma, Piacenza, Piemonte Childhood, Ragusa, Reggio Emilia, Romagna, Salerno, Sassari, Siracusa, Sondrio, Taranto, Trapani, Trento, Umbria, Veneto, and Viterbo registries.

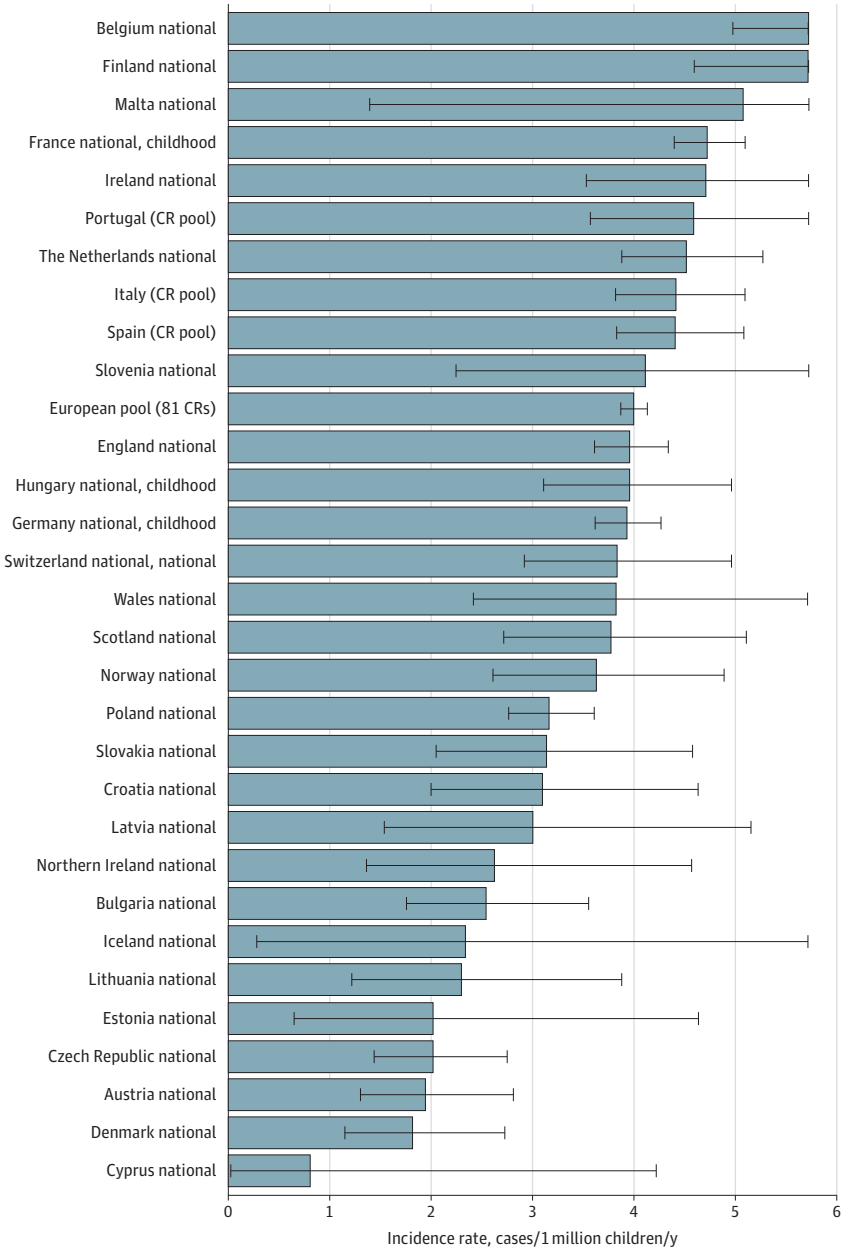
[c] Portugal is not nationally covered. Portugal was covered by Central Portugal, Northern Portugal, and Southern Portugal registries.

[d] Spain is not nationally covered. Spain was covered by Balearic Islands, Mallorca, Basque Country, Canary Islands, Castellon, Comunitat Valenciana, Girona, Granada, Murcia, Navarra, Spanish Childhood, (RETI-SEHOP), and Tarragona registries.

period from 2000 to 2013, with a large variability of incidence across countries. The overall European 5-year survival was 98%, with disparities across countries. Furthermore, for Europe we provided the risk of a subsequent tumor after RB within 14 years of diagnosis.

Higher incidence rates have been reported in non-European countries, including South America, the US (among White Hispanic individuals), and East and South-East Asia, with world age-standardized incidence rates between 5.1 and 6.0 per million. Lower rates have been reported in North Africa and

Figure 1. Age-Standardized Rates for Each Included Country and Pooled Across Europe

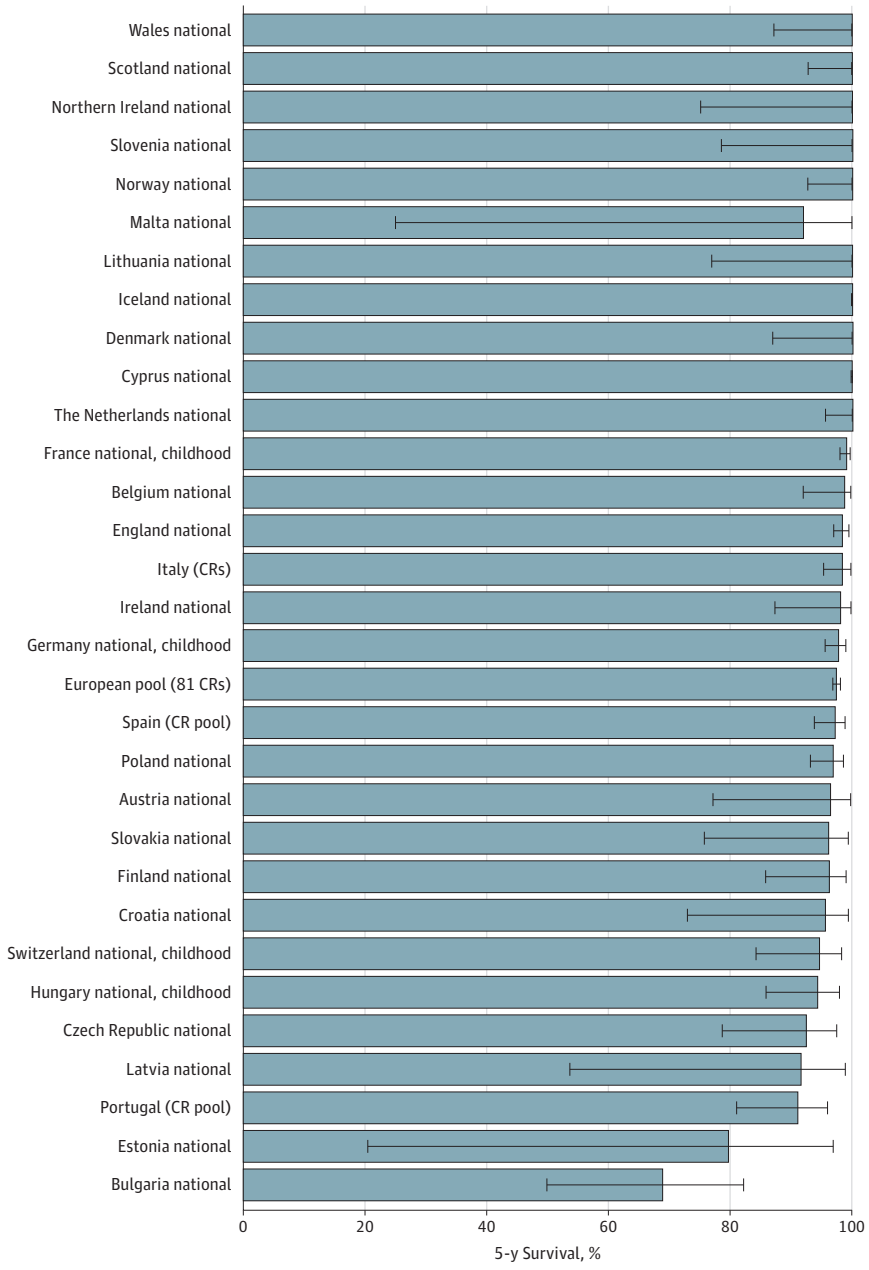


Countries are labelled as national when the registry has a national coverage, pool when estimates are derived from multiple registries with local coverage, and childhood when data are collected by specialized child registries. Age, 0-14 y; period of diagnosis, 2000-2013. The bars indicate the point estimates of incidence for each country and the whiskers indicate 95% CIs. CR indicates cancer registry.

among US Native American individuals (2.2 and 1.8, respectively).[29] Our data show low incidence rates in small countries, like the Nordic and the Baltic countries and Austria. Furthermore, the rate would increase only in Denmark if 66 tumors of the retina without pathological diagnosis were included in the analysis, without affecting the range of values. Migration to countries with centers of excellence may be a reason for low case ascertainment,[38] although most of the small countries with low recorded incidence have a retinoblastoma center[39] or have active members of the European Retinoblastoma Group.[40] Genetic differences across populations should also be considered.

Risk factors that have been associated with RB include advanced parental age, use of assisted reproductive technology, human papillomavirus infection, diet, sunlight exposure, direct fetal radiography exposure, and parental exposure to hazardous occupational substances. Of particular interest, paternal employment as a welder, mechanist, or related metal works have been associated with an increased risk of sporadic RB, as among farmers and other workers involved in agriculture.[41,42] Our study did not confirm a previous finding of increased trend in incidence found in a subset of European registries in 2017[43]; however, the methods used to compute incidence were different from the ones in

Figure 2. Five-Year Survival of Children Aged 0-14 Years With a Diagnosis of Retinoblastoma From 2000 to 2013 by Country



Countries are labelled as national when the registry has a national coverage, pool when estimates are derived from multiple registries with local coverage, and childhood when data are collected by specialized child registries. The bars indicate the point estimates of survival for each country and the whiskers indicate 95% CIs. CR indicates cancer registry.

our study. Furthermore, the population of patients was different in the 2 studies, as sampling was hospital-based in Stacey et al.[43]

Childhood cancer survival differences across European countries have been reported in international population-based studies[3,4] with lower survival in Eastern European countries and higher survival in Northern and Central countries in the same period as ours. Compared with other pediatric tumors, RB represents a disease with a curability of 99%, because currently available treatments are effective for localized and regional spread lesions and most metastatic tumors.[4] A diagnosis of early stage RB should be more likely in those countries, mainly in Europe and in other high-income countries. Many high-income countries have established neonatal or early pediatric screening programs, such as those assessing the pupillary red reflex, which may allow an early diagnosis of RB.[43] The absence of these programs may affect the incidence rates of RB in children leading to delayed onset and late stage at diagnosis.[2,44,45]

We also estimated the occurrence of SMNs up to a maximum of 14 years from diagnosis in survivors and found an absolute excess risk of nearly 11 per 10 000 children for all tumors. Higher risks were found for hematological malignancies and tumors of head and neck (all rhabdomyosarcomas), brain,

Table 2. Five-Year Survival by Age, Sex, and Period

Sex	Survival, % (95% CI)			
	2003 Estimate	2006 Estimate	2009 Estimate	2013 Estimate
Male				
0 y	98 (95-99)	99 (95-100)	99 (95-100)	99 (96-100)
1-4 y	96 (93-98)	96 (92-98)	97 (93-99)	99 (96-100)
5-9 y	100 (NE)	100 (NE)	100 (NE)	100 (NE)
10-14 y	NE	NE	100 (NE)	100 (NE)
Total	97 (95-98)	97 (95-99)	98 (96-99)	99 (97-100)
Female				
0 y	99 (95-100)	98 (93-99)	99 (94-100)	98 (94-99)
1-4 y	96 (92-98)	93 (89-96)	97 (92-99)	98 (95-100)
5-9 y	100 (NE)	100 (NE)	91 (51-99)	100 (NE)
10-14 y	NE	NE	NE	NE
Total	97 (95-99)	95 (92-97)	98 (95-99)	98 (96-99)
Male and female				
0 y	99 (97-100)	99 (96-99)	99 (97-100)	99 (97-100)
1-4 y	96 (94-97)	95 (92-97)	97 (94-98)	99 (97-99)
5-9 y	100 (NE)	100 (NE)	95 (0.70-0.99)	100 (NE)
10-14 y	NE	NE	100 (NE)	100 (NE)
Total	97 (96-98)	96 (95-98)	98 (96-99)	99 (98-99)

Abbreviation: NE, not estimable.

Table 3. Subsequent Malignant Neoplasms After Diagnosis of Retinoblastoma: Observed and Expected Number of Neoplasms for Each Site

Tumor site	Neoplasms, No.		Observed/expected, ratio	95% CI	*P* value	Excess risk, cases/10 000 children/y	Mean age at event, y	Follow-up, mo			
	Observed	Expected						6-11	12-59	60-119	≥120
All sites but eye	25	3.06	8.2	5.3-11.7	<.001	10.68	6.43	0	11	12	2
Nose, nasal cavity, and middle ear	2	0.01	253.6	30.7-916.0	<.001	0.97	3.37	0	2	0	0
Bones and joints	8	0.12	64.9	28.0-127.8	<.001	3.83	2.00	0	0	6	2
Soft tissue, including heart	2	0.22	9.2	1.1-33.3	.01	0.87	7.21	0	0	2	0
Kidney and renal pelvis	1	0.2	5.1	0.1-28.4	.5	0.39	5.66	0	0	1	0
Brain	3	0.43	6.9	1.4-20.3	<.001	1.25	5.68	0	2	1	0
Endocrine system	2	0.18	11.2	1.4-40.3	<.001	0.89	5.87	0	1	1	0
Non-Hodgkin lymphoma	1	0.2	5	0.1-28.1	.50	0.39	2.91	0	1	0	0
Leukemia	5	0.97	5.2	1.7-12.0	<.001	1.96	5.08	0	4	1	0
Acute lymphocytic leukemia	1	0.77	1.3	0.0-7.2	.76	0.11	1.25	0	1	0	0
Acute myeloid leukemia	2	0.13	15.7	1.9-56.7	<.001	0.91	7.58	0	1	1	0
Acute monocytic leukemia	2	0.01	143.9	17.4-519.7	<.001	0.97	4.5	0	2	0	0
Miscellaneous	1	0.09	11	0.3-61.1	.17	0.44	5.67	0	1	0	0

bone, and soft tissues. We also found that 25 cases of SMN were present in bilateral retinoblastoma, 14 of which were heritable RB. Subsequent malignant neoplasms in children with heritable RB are due to the presence of a mutation in the *RB1* tumor suppressor gene and to therapeutic choices. In a review by Fabius et al,[45] the standardized incidence ratio for secondary malignancies varied between 11.4 and 20.4 among survivors with heritable RB and 1.2 to 1.85 among those with nonheritable RB. In Fabius et al,[45] age at onset of SMN was younger than 10 years for most cases of leukemia and lymphoma and appeared before adolescence for sarcomas, whereas melanomas and carcinomas appeared in young adults. Central nervous system tumors were found both in adolescents and young adults in that study. The length of follow-up in our study was limited to 14 years, not yet sufficient to investigate SMN occurrence in adolescents and young adults. Among studies not using population-based data, a study by Schonfeld et al[46] estimated that 1 in 3 patients with hereditary RB will develop SMN by the age of 50 years, as opposed to none with nonhereditary RB.

Despite high survival rates in high-income countries, children surviving RB have a lower quality of life and have reported difficulties in activities of daily living.[47] Flegg at al[48] conducted a research prioritization initiative with engagement of people affected by RB, clinicians, and researchers to determine the top 10 RB research priorities in Canada. They found that achieving an earlier diagnosis, which should increase the proportion diagnosed with earlier stage disease, and conducting second cancer screening for heritable RB survi-

vors were the top priorities. Other priorities concerned long-term follow-up, including of second cancers, and the formation of international consortia and registries. Surveillance using EUROCARE-6 can contribute to reaching these goals.

Strengths and Limitations

Limitations of this investigation include the partial availability of RB stage. A wider use of the Toronto Paediatric Cancer State Guidelines in childhood cancer registration[49] will improve the registration of clinical variables, such as stage at diagnosis, treatment, and other prognostic factors. Another limitation is the latency in data collection, which is inherent in large-scale, centralized studies. Moreover, not all registries provided data across all periods, leading to incidence and survival trends being based on registries with incident data throughout the study time frame, which are the majority. These limitations may reduce the certainty of the evidence of our estimates. A further limitation of our study is that the results may be influenced by or associated with genetic predispositions among ethnic groups.

Strengths of this investigation include its relatively large number of cases evaluated and a standardized Europe-wide data collection. According to the recommendations of the European Network of Cancer Registries, *ICD-O-3* code 9510 can be used for retinoblastomas without requiring histological confirmation. This could potentially explain the differences between countries regarding histological verification and the column of tumors of the retina without morphological codification of retinoblastoma. These are likely to be cases receiving medical treatment and not registered, by mistake, as retinoblastoma. However, only Denmark would double its rate after their inclusion, appearing more similar to the other Nordic countries.

Conclusions

We found stable incidence of 4.0 per 1 000 000 children aged 0 to 14 years in the period from 2000 to 2013, with a large variability of incidence across countries. High survival for children with RB were noted in Europe, with higher risk with respect to the children population of SMNs in RB survivors. Multinational initiatives that collect RB stage and primary treatment, linking clinical and cancer registries, are warranted to improve RB surveillance.

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