The Incidence of Trilateral Retinoblastoma: A Systematic Review and Meta-Analysis

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• PURPOSE: To estimate the incidence of trilateral retinoblastoma in patients with retinoblastoma.
• DESIGN: Systematic review and meta-analysis.
• METHODS: We searched Medline and Embase for scientific literature published between January 1966 and July 2015 that assessed trilateral retinoblastoma incidence. We used a random-effects model for the statistical analyses.
• RESULTS: We included 23 retinoblastoma cohorts from 26 studies. For patients with bilateral retinoblastoma the unadjusted chance of developing trilateral retinoblastoma across all cohorts was 5.3% (95% confidence interval [CI]: 3.3%–7.7%); the chance of pineal trilateral retinoblastoma was 4.2% (95% CI: 2.6%–6.2%) and the chance of nonpineal trilateral retinoblastoma was 0.8% (95% CI: 0.4%–1.3%). In patients with hereditary retinoblastoma (all bilateral cases, and the unilateral cases with a family history or germline *RB1* mutation) we found a trilateral retinoblastoma incidence of 4.1% (95% CI: 1.9%–7.1%) and a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8%–6.2%). To reduce the risk of overestimation bias we restricted analysis to retinoblastoma cohorts with a minimum size of 100 patients, resulting in adjusted incidences of 3.8% (95% CI: 2.4%–5.4%), 2.9% (95% CI: 1.9%–4.2%), and 0.7% (95% CI: 0.3%–1.2%) for any, pineal, and nonpineal trilateral retinoblastoma, respectively, among patients with bilateral retinoblastoma. Among hereditary retinoblastoma we found an adjusted trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2%–6.7%) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4%–5.6%).
• CONCLUSION: The estimated incidence of trilateral retinoblastoma is lower than what is reported in previous literature, especially after exclusion of small cohorts that were subject to overestimation bias in this context. (Am J Ophthalmol 2015;160(6): 1116–1126. © 2015 by Elsevier Inc. All rights reserved.)

UNTIL THE AGE OF ABOUT 7 YEARS PATIENTS WITH hereditary retinoblastoma are at risk of having an intracranial midline primitive neuroectodermal tumor diagnosed, and among patients diagnosed since 1995 more than 95% have developed trilateral retinoblastoma before the age of 5 years.[1–3] In histopathologic analysis these tumors look similar to corresponding retinal tumors. When unilateral or bilateral retinoblastoma and an intracranial midline primitive neuroectodermal tumor both occur in a patient, this is referred to as trilateral retinoblastoma, which can be found in the pineal gland (pineal trilateral retinoblastoma) in about three-quarters of cases; in the remaining patients it develops in other midline brain regions (nonpineal trilateral retinoblastoma), usually the suprasellar and parasellar region, although other brain regions have been reported also.[3–5]

In a recent meta-analysis we showed that survival has improved considerably in the last 2 decades, from hardly any to almost half of all patients.[3] Favorable survival after pineal trilateral retinoblastoma depended strongly on early detection and small tumor size. The improved survival after trilateral retinoblastoma was highly associated with the use of (improved) chemotherapy regimens, especially high-dose chemotherapy with stem cell rescue.[3]

Previous radiotherapy for retinoblastoma, especially before the age of 12 months, has been associated with a potentially higher incidence of pineal trilateral retinoblastoma in patients with hereditary retinoblastoma, even though the pineal gland is usually not (directly) within the field of radiation.[6] Whether previous systemic chemotherapy is protective of developing trilateral retinoblastoma is still being debated.[7–10]

There have been numerous reports on trilateral retinoblastoma incidence, but these studies are quite heterogeneous. Some are referral-based, others population-based. The only previously published study summarizing incidence data across studies reported an incidence of 5%–15% among patients with bilateral retinoblastoma.[2]

The objective of this study is to provide an overview of, to critically analyze, and to provide pooled summary estimates of published incidence data for pineal and nonpineal trilateral retinoblastoma.

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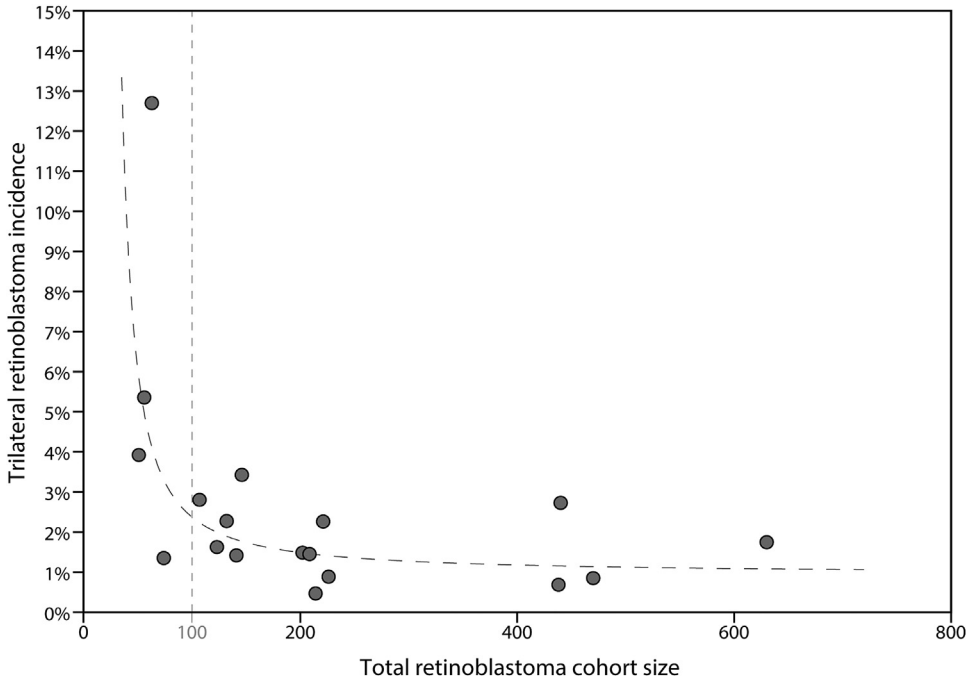

FIGURE 1. Trilateral retinoblastoma incidence vs the size of the cohorts of patients with unilateral or bilateral retinoblastoma. The estimated curve in this figure is an S-curve with a fit of $R^2 = 0.44$, $P = .0027$.

METHODS

WE PERFORMED THIS SYSTEMATIC REVIEW AND META-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[11,12]

• **SEARCH STRATEGY:** We searched Medline (PubMed) and Embase for English, Dutch, and German literature published from January 1, 1966 through July 15, 2015, evaluating trilateral retinoblastoma cases. We also considered alternatively found studies for inclusion (eg, through checking references in included studies). The search was similar to the search we used in our systematic review and meta-analysis on survival of patients with trilateral retinoblastoma.[3] To ensure a sensitive search, we included only keywords corresponding to the target condition (including retinoblastoma, pineoblastoma, pineal, suprasellar, parasellar, sellar, ectopic, and brain), without any delimiters. For the detailed search see Supplemental Table 1 (available at AJO.com).

• **STUDY SELECTION AND DATA EXTRACTION:** Two authors (M.C.J. and A.C.M.) independently reviewed article titles and abstracts for eligibility. Discrepancies were resolved by consensus. Subsequently the same 2 authors independently reviewed eligible full-text articles for inclusion in the systematic review and meta-analysis. Again, discrepancies were solved by consensus.

We included studies in the systematic review and meta-analysis if (1) the study mentioned the number of patients with trilateral retinoblastoma (can also be 0, as long as authors mentioned evaluating for trilateral retinoblastoma cases), if (2) articles reported details and size of the retinoblastoma cohort in which patients with trilateral retinoblastoma were seen (eg, number of patients with trilateral retinoblastoma diagnosed in a cohort of patients with retinoblastoma during a certain period), and if (3) the full-text article could be obtained. We excluded studies from the systematic review if (1) the article was a review or meta-analysis, and if (2) studies included overlapping incidence data. Two authors (M.C.J. and W.A.K.) independently extracted incidence data. Discrepancies were resolved by consensus. We have defined hereditary retinoblastoma as patients with bilateral retinoblastoma, known familial retinoblastoma, or a detected germline mutation in *RB1*.

• **DATA SYNTHESIS AND STATISTICAL ANALYSIS:** Ideally, we would present the cumulative incidence of trilateral retinoblastoma until a certain age (eg, up to 5 years) in comparable retinoblastoma cohorts; however, most studies only provided the total number of patients with retinoblastoma and the number of trilateral retinoblastoma cases they found in their cohort. Therefore we are restricted to the calculation of a percentage of cases that developed trilateral retinoblastoma divided by total retinoblastoma cohort from a certain time period. This method unfortunately does

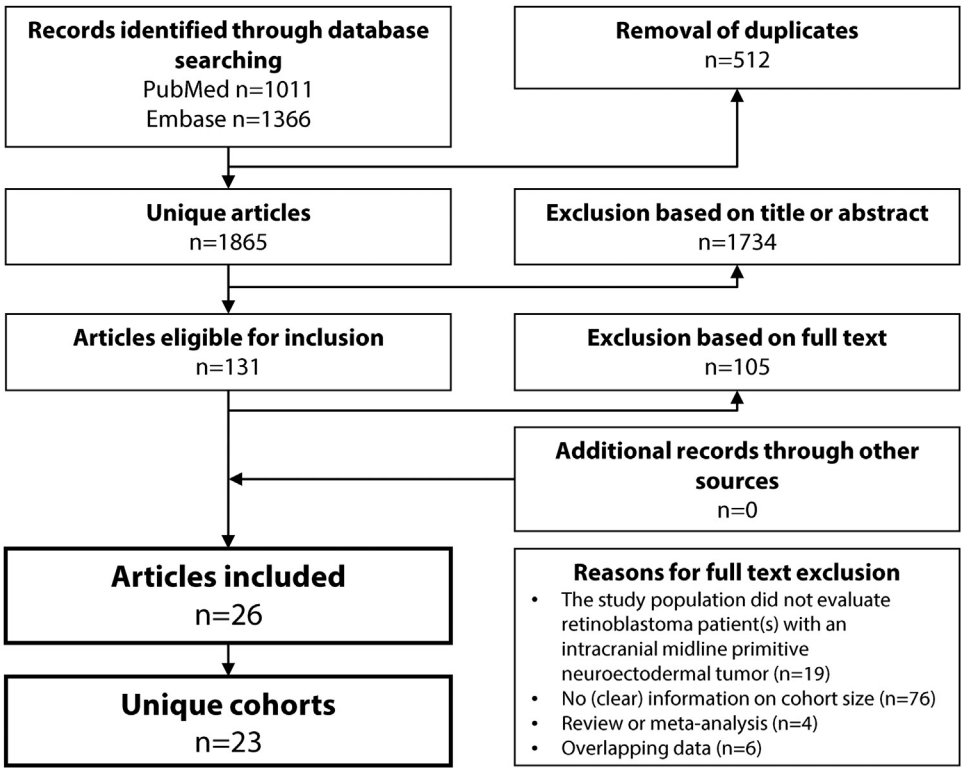

FIGURE 2. Flow chart of the total number of articles found with PubMed and Embase and subsequent inclusion and exclusion of articles, leading to the number of included articles and retinoblastoma cohorts that contained information on trilateral retinoblastoma incidence.

not take into account the effect of patients lost to follow-up (ie, assuming that of all patients with retinoblastoma it is unequivocally known whether they developed trilateral retinoblastoma or not).

In addition to performing unadjusted analysis, we calculated adjusted estimates by including cohorts of at least 100 patients with retinoblastoma, to prevent overestimation bias. Most small cohorts published specifically after encountering at least 1 trilateral retinoblastoma and thus led to a report irrespective of how many patients without trilateral retinoblastoma had been seen (ie, an arbitrary cohort of patients with retinoblastoma with a certain start and end date will have been constructed around the patient(s) with trilateral retinoblastoma that were encountered). The limit of 100 patients was based on visual evaluation of a plot of the incidence of trilateral retinoblastoma against the total sample size across studies (Figure 1). Typically, an unselected patient population contains 40% of bilateral retinoblastoma, and thus we considered also a cohort of at least 40 bilateral retinoblastomas to be large enough to guard for overestimation bias.

To assess the extent of this bias we compared data from developed vs developing countries, as one would expect follow-up to be more complete in developed countries (ie, higher chance to find a trilateral retinoblastoma). This might lead to an underestimation of trilateral retinoblastoma incidence in the developing countries. Pooling data from different retinoblastoma cohorts also assumes comparability of these cohorts.

To evaluate changes in trilateral retinoblastoma incidence over time we used a cutoff at the year 1995. We chose this cutoff because around (or maybe even before) 1995 treatment of retinoblastoma started to shift from radiotherapy to chemotherapy.[13]

We used a random-effects model to calculate summary estimates of trilateral retinoblastoma incidence.[14,15] A random-effects model is used for meta-analyses to account for heterogeneity between studies. For each analysis we calculated I^2 to evaluate heterogeneity among included studies; I^2 ranges from 0 to 100% with increasing heterogeneity.[16] For the random-effects analyses we used MetaXL (version 2.1; EpiGear, Wilston, Australia) and SAS (Proc MIXED, version 9.3; SAS, Cary, North Carolina, USA). The forest plots were created with Illustrator CS6 (Adobe, San Jose, California, USA).

• **RISK OF BIAS AND STUDY QUALITY ASSESSMENT:** Two authors (M.C.J. and T.K.) assessed the risk of bias with a modified checklist that was developed for prevalence studies by Hoy and associates.[17] With the checklist 6 items that could lead to bias were assessed (Supplemental Table 2, available at AJO.com).[18,19]

TABLE 1. Basic Information About the Retinoblastoma Cohorts of All Included Studies That Presented Trilateral Retinoblastoma Incidence Data

Study	Inclusion Period	Country	Source of the Data	Type of Patients With Retinoblastoma	Age at Retinoblastoma Diagnosis (Months)	Patient Follow-up From Retinoblastoma Diagnosis (Months)	Percentage of Cohort With Unilateral Retinoblastoma	Percentage of Cohort With Bilateral Retinoblastoma	Percentage of Cohort With Familial Retinoblastoma	Study Cohort (Partly) Overlaps With
Amoaku et al[26]	1960–1994	United Kingdom	Population registry	Any	Mean 6, range 0.75–17		64%	36%	38[a]	
Antoneli et al[27]	1986–2003	Brasil	1 center	Any			60%	40%		
Azar et al[28]	1975–2001	Australia	2 centers	Any	Mean 17.9 (bilateral 22.6, unilateral 3.5)		60%	40%	11	
Bartuma et al[29]	2001–2011	Sweden	1 center	Hereditary	Mean 8, range 0–39	Mean 60, range 13–144	8%	92%	38	
Blach et al[22]	1979–1990	USA	1 center	Irradiated	Median 7, range <1–60	Median 68, range 4–153	17%	83%	27	
Chantada et al[10]	1988–2012	Argentina	1 center	Bilateral	Mean 13.9, range 0–114	Median 115, range 31–290		100%	14[a]	Moreno et al[30]
De Ioris et al[31]	1999–2009	Italy	1 center	Any	Median 10, range 0.5–73		58%	42%	14	
De Potter et al[32]	1972–1992	United Kingdom	1 center	Any			54%	46%	14	
Duncan et al[33]	1990–1998	USA	2 centers	Any		Mean 44.8, range 0–139	≥63%	≤37%		
Helveston et al[34]	1967–1987	USA	1 center	Any	Unilateral 23, bilateral 10[b]		59%	41%		
Imhof et al[23]	1971–1993	Netherlands	1 center	Irradiated	Mean 5, range 1–216	Mean 148, range 48–276				Moll et al[6]
Jubran et al[35]	1991–1999	USA	1 center	Any						
Jurkiewicz et al[36]	1996–2008	Poland	1 center	Any	Unilateral median 22, bilateral median 12					
Kingston et al[37]	1954–1983	United Kingdom	2 centers	Any			31%	69%		
Klufas et al[24]	2006–2010	USA	1 center	Treated with intraarterial chemotherapy		Median 17.5, range 8–36				
Lim et al[38]	2001–2009	Malaysia	1 center	Any						
Lim et al[39]	1997–2010	Singapore	1 center	Any	25.7, SD 19.9 (unilateral mean: 30.2, SD 21.4, bilateral mean: 15.4, SD 9.6)	Median 36, range 0–156	69%	31%		

Continued on next page

TABLE 1. Basic Information About the Retinoblastoma Cohorts of All Included Studies That Presented Trilateral Retinoblastoma Incidence Data (*Continued*)

Study	Inclusion Period	Country	Source of the Data	Type of Patients With Retinoblastoma	Age at Retinoblastoma Diagnosis (Months)	Patient Follow-up From Retinoblastoma Diagnosis (Months)	Percentage of Cohort With Unilateral Retinoblastoma	Percentage of Cohort With Bilateral Retinoblastoma	Percentage of Cohort With Familial Retinoblastoma	Study Cohort (Partly) Overlaps With
Lueder et al[40]	1924–1985	USA	1 center	Any			67%	33%	14	Lueder et al[41]
Lueder et al.[41]	1924–1989	USA	1 center	Any					14	Lueder et al[40]
Moll et al[6]	1970–1997	Netherlands	Population registry	Hereditary						Imhof et al[23]
Moreno et al[30]	2000–2009	Argentina	Population registry	Any	Unilateral median 26 (IQR 13–42), bilateral median 10 (IQR 5–19)		68%	32%		Chantada et al[10]
Popovic et al[25]	1990–2001	Switzerland	1 center	Any			49%	51%		
Provenzale et al[42]	1985–2002	USA	1 center	Any			52%	48%		
Ramasubramanian et al[8,21]	2000–2012	USA	1 center	Any	Mean 21, median 13, range 0–91		53%	47%	11	
Scott et al[43]	1970–1990	USA	1 center	Any	Mean 15.8 (nonhereditary mean 20.5, hereditary mean 11.7)		52%	48%		
Shields et al[20]	1995–1999	USA	1 center	Any	Mean 14, median 8, range 1–87	Mean 33, range 0–67	48%	52%	18	

IQR = interquartile range; SD = standard deviation.

[a]As percentage of the patients with bilateral retinoblastoma.

[b]Age at treatment; unknown if these are means or medians or some other measure.

RESULTS

WE IDENTIFIED 1865 UNIQUE STUDIES FROM DATABASE searches. We excluded 1734 articles based on title and abstract (Figure 2). We excluded 105 studies based on the full text; reasons for exclusion are shown in Figure 2. Twenty-six studies (3 pairs of studies had overlapping cohorts but provided different data of interest and were therefore included; see Table 1) met the inclusion criteria of this systematic review. Twenty-one studies (20 cohorts) were included in the meta-analysis. Tables 2 and 3 show the incidence data as reported in each included study.

• **UNADJUSTED ESTIMATES:** Twenty-six studies reported trilateral retinoblastoma incidence in 23 unique cohorts of patients with retinoblastoma, and in 15 studies (15 cohorts) bilateral could be distinguished from unilateral retinoblastoma (Table 2). Seven studies (6 cohorts) presented the trilateral retinoblastoma incidence in hereditary retinoblastoma, 3 studies (cohorts) reported trilateral retinoblastoma incidence after external beam irradiation for retinoblastoma, and 5 studies (cohorts) compared the incidence in patients with retinoblastoma with and without previous chemotherapy. Forest plots of the included studies (sorted by the midpoint of the study period) and the summary estimates are shown in Figure 3.

For unilateral and bilateral retinoblastoma combined, the unadjusted chance of developing a trilateral retinoblastoma across all studies is 2.1% (95% confidence interval [CI]: 1.4%–2.8%; 18 cohorts), the chance of developing pineal trilateral retinoblastoma is 1.7% (95% CI: 1.2%–2.3%; 19 cohorts), and the chance of a nonpineal trilateral retinoblastoma is 0.4% (95% CI: 0.2%–0.6%; 18 cohorts). For bilateral retinoblastoma the chance of developing a trilateral retinoblastoma is 5.3% (95% CI: 3.3%–7.7%; 14 cohorts); restricting calculations to pineal trilateral retinoblastoma resulted in an incidence of 4.2% (95% CI: 2.6%–6.2%; 15 cohorts) and restricting to nonpineal trilateral retinoblastoma gave an incidence of 0.8% (95% CI: 0.4%–1.3%; 14 cohorts). In hereditary retinoblastoma we found a trilateral retinoblastoma incidence of 4.2% (95% CI: 1.6%–7.7%; 5 cohorts) and a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8%–6.2%; 6 cohorts), and we did not calculate the nonpineal trilateral retinoblastoma incidence, as there were no cases in 5 retinoblastoma cohorts.

• **ADJUSTED ESTIMATES:** We adjusted for potential overestimation bias by restricting the analysis to cohorts that included at least 100 patients with retinoblastoma (Figure 1). We found incidences of 1.7% (95% CI: 1.2%–2.2%; 14 cohorts), 1.4% (95% CI: 1.0%–1.7%; 15 cohorts), and 0.3% (95% CI: 0.2%–0.6%; 14 cohorts) for any, pineal, and nonpineal trilateral retinoblastoma, respectively. In cohorts with only patient with bilateral retinoblastoma we found incidences of 3.8% (95% CI: 2.4%–5.4%; 10 cohorts), 2.9% (95% CI: 1.9%–4.2%; 11 cohorts) and 0.7% (95% CI: 0.3%–1.2%; 10 cohorts), respectively. Among patients with hereditary retinoblastoma we found a trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2%–6.7%; 4 cohorts) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4%–5.6%; 5 cohorts).

• **PERIOD ANALYSIS:** To analyze changes over time we created 2 groups with the year 1995 as the cutoff year (depending on the midpoint of the study period). Before the year 1995 unadjusted trilateral retinoblastoma incidence for unilateral and bilateral retinoblastoma combined was 2.5% (95% CI: 1.5%–3.8%) vs 1.5% (95% CI: 0.9%–2.2%) from the year 1995 onward ($P = .24$). The incidence of pineal trilateral retinoblastoma before the year 1995 was 2.2% (95% CI: 1.3%–3.4%) vs 1.2% (95% CI: 0.8%–1.8%) from 1995 onward ($P = .14$).

Restricted to patients with bilateral retinoblastoma, the unadjusted trilateral retinoblastoma incidence was 6.2% (95% CI: 3.2%–9.9%) before the year 1995 vs 3.7% (95% CI: 1.4%–6.9%) from the year 1995 onward ($P = .44$). The incidence of pineal trilateral retinoblastoma was 5.3% (95% CI: 2.7%–8.8%) before the year 1995 vs 2.9% (95% CI: 1.3%–5.1%) from the year 1995 onward ($P = .38$; Figure 3).

• **EFFECT OF PREVIOUS THERAPY:** Four studies reported on trilateral retinoblastoma incidence in retinoblastoma cohorts who underwent previous systemic chemotherapy (Table 3). In a single-center study with 4 trilateral retinoblastoma cases an inverse association between chemotherapy and the development of pineoblastoma was reported ($P = .014$), with an incidence of 0.6% (1/180) and 8.6% (3/35), respectively, for patients who did and who did not receive previous chemotherapy for their retinoblastoma.[8] In a single-center study from the same center, but different period, 1 pineoblastoma was found in 18 hereditary patients with retinoblastoma who did not undergo chemotherapy, compared to none in 99 patients who did undergo chemotherapy.[20] However, in another single-center study with 3 trilateral retinoblastomas this association was reversed with an incidence of 1.9% (3/159) vs 0.0% (0/38), respectively ($P > .99$).[10]

Three studies specifically looked at trilateral retinoblastoma incidence in cohorts of patients with retinoblastoma who underwent external beam radiotherapy (Table 3). In a single-center study with 4 trilateral retinoblastomas a pineal trilateral retinoblastoma incidence of 1.7% (3/179) was found in the group of patients with nonirradiated hereditary retinoblastoma and an incidence of 2.8% (1/36) was found in the irradiated group ($P = .5$).[8,21] A single-center study with 6 trilateral retinoblastomas found that patients with bilateral retinoblastoma who underwent irradiation as treatment for their retinoblastoma had a 6.2%

TABLE 2. Incidence of Trilateral Retinoblastoma Among Unilateral and Bilateral Retinoblastoma, Bilateral Retinoblastoma, and Hereditary Retinoblastoma for Studies Included in the Meta-analysis

		Unilateral and Bilateral Retinoblastoma		Bilateral Retinoblastoma		Hereditary Retinoblastoma	
Study	Inclusion Period	Pineal	Nonpineal	Pineal	Nonpineal	Pineal	Nonpineal
Amoaku et al[26]	1960–1994	2.7% (4/146)	0.7% (1/146)	7.7% (4/52)	1.9% (1/52)		
Antoneli et al[27]	1986–2003	0.6% (3/470)	0.2% (1/470)	1.1% (2/186)	0.5% (1/186)		
Azar et al[28]	1975–2001	1.6% (2/123)	0.0% (0/123)	4.1% (2/49)	0.0% (0/49)		
De Ioris et al[31]	1999–2012	2.8% (3/107)	0.0% (0/107)	6.7% (3/49)	0.0% (0/49)		
De Potter et al[32]	1972–1992	2.0% (9/440)	0.7% (3/440)	4.0% (8/202)	1.5% (3/202)		
Duncan et al[33]	1990–1998	0.9% (2/226)	0.0% (0/226)			2.4% (2/85)[a]	0.0% (0/85)[a]
Helveston et al[34]	1967–1987	1.4% (1/74)	0.0% (0/74)	3.3% (1/30)	0.0% (0/30)		
Jubran et al[35]	1991–1999	1.4% (3/207)	0.0% (0/207)				
Jurkiewicz et al[36]	1996–2008	0.5% (1/202)	1.0% (2/202)				
Kingston et al[37]	1954–1983	1.3% (8/630)	0.5% (3/630)	1.9% (8/432)	0.5% (2/432)		
Lim et al[38]	2001–2009	1.4% (2/141)	0.0% (0/141)				
Lim et al[39]	1997–2010	3.9% (2/51)	0.0% (0/51)	12.5% (2/16)	0.0% (0/16)		
Lueder et al[40]	1924–1985	2.3% (3/132)	0.0% (0/132)	6.8% (3/44)	0.0% (0/44)	6.0% (3/50)	0.0% (0/50)
Lueder et al[41]	1924–1989	2.7% (4/143)				7.1% (4/56)	
Moll et al[6]	1970–1997					5.8% (7/121)	0.0% (0/121)
Moreno et al[30]	2000–2009	0.7% (3/438)	0.0% (0/438)	2.2% (3/139)	0.0% (0/139)		
Popovic et al[25]	1990–2001	1.8% (4/221)	0.5% (1/221)	3.7% (4/108)	0.9% (1/108)		
Provenzale et al[42]	1985–2002	11.1% (7/63)	1.6% (1/63)	23.3% (7/30)	3.3% (1/30)		
Ramasubramanian et al[8,21]	2000–2012	1.0% (4/408)		1.6% (3/193)		1.9% (4/215)	
Scott et al[43]	1970–1990	5.4% (3/56)	0.0% (0/56)	11.1% (3/27)	0.0% (0/27)	10.0% (3/30)	0.0% (0/30)
Shields et al[20]	1995–1999	0.5% (1/214)	0.0% (0/214)	0.9% (1/112)	0.0% (0/112)	0.9% (1/117)	0.0% (0/117)

The number of trilateral retinoblastoma patients divided by the size of the retinoblastoma cohort in parentheses.

[a]Duncan et al[33] reported that 83 had hereditary retinoblastoma, excluding the 2 pineal trilateral retinoblastoma cases that can be classified as having hereditary retinoblastoma on the basis of developing a midline primitive neuroectodermal tumor (they also presented a case with an "orbital midline primitive neuroectodermal tumor," but we are not convinced this is trilateral retinoblastoma).

(6/97) chance to develop trilateral retinoblastoma (5 pineal and 1 suprasellar); excluding the suprasellar tumor from the calculation resulted in a pineal trilateral retinoblastoma incidence of 5.2% (5/97).[22] Finally, in a single-center study with 5 cases a pineal trilateral retinoblastoma incidence of 5.7% (5/87) in patients with irradiated hereditary retinoblastoma was reported.[23]

• **RISK OF BIAS AND STUDY QUALITY ASSESSMENT:** Per-study scores on individual items of the risk-of-bias checklist (numbered from Q1 through Q6) can be found in Supplemental Table 2 (available at AJO.com), showing considerable risk of bias in terms of how much the cohort is population-like (Q1 and Q2) and the follow-up duration (Q4). To address assessment bias we compared trilateral retinoblastoma incidence in developed vs developing countries—the latter being potentially more prone to this type of bias, which would result in lower expected incidence numbers. This comparison indeed showed differences with unadjusted unilateral and bilateral trilateral retinoblastoma incidences of 2.3% (95% CI 1.6%–3.2%) vs 1.1% (95% CI 0.5%–1.9%; $P = .32$) and bilateral trilateral retinoblastoma incidences of 6.0% (95% CI 3.5%–9.2%) vs 2.6% (95% CI 0.4%–6.2%; $P = .50$) for developed and developing countries, respectively, though statistically not significantly different.

DISCUSSION

THIS SYSTEMATIC REVIEW GIVES AN OVERVIEW OF STUDIES on trilateral retinoblastoma incidence. Our summary estimates (especially the adjusted ones) of trilateral retinoblastoma incidence in bilateral or hereditary retinoblastoma are considerably lower than previously summarized by Kivelä,[2] with an estimated incidence ranging from 5% to 15% in bilateral retinoblastoma, reflecting small cohorts in earlier studies. Even the unadjusted trilateral retinoblastoma incidence from this meta-analysis is lower and more precise (relatively narrow confidence intervals) than generally assumed in "literature"; to test this we evaluated the trilateral retinoblastoma incidence mentioned in the introduction and discussion of articles included in the meta-analysis on survival after trilateral retinoblastoma[3] (for obvious reasons, we excluded articles that assessed trilateral retinoblastoma incidence) (Supplemental Table 3, available at AJO.com).

TABLE 3. The Incidence of Trilateral Retinoblastoma Among Unilateral and Bilateral Retinoblastoma, Bilateral Retinoblastoma, and Hereditary Retinoblastoma for Studies That Assessed the Effect of Previous Chemotherapy or Radiotherapy on the Development of Trilateral Retinoblastoma

Study	Inclusion Period	Treatment for Retinoblastoma	Unilateral and Bilateral Retinoblastoma		Bilateral Retinoblastoma		Hereditary Retinoblastoma	
			Pineal	Nonpineal	Pineal	Nonpineal	Pineal	Nonpineal
Bartuma et al[29]	2001–2011	Systemic chemotherapy					0.0% (0/24)[a]	0.0% (0/24)[a]
Chantada et al[10]	1988–2009	Systemic chemotherapy			1.9% (3/159)	0.0% (0/159)		
		No systemic chemotherapy			0.0% (0/38)	0.0% (0/38)		
Klufas et al[24]	2006–2010	Intraarterial chemotherapy	1.1% (1/89)	0.0% (0/89)	1.4% (1/70)	0.0% (0/70)		
Ramasubramania et al[8,21]	2000–2012	Systemic chemotherapy	0.4% (1/252)				0.6% (1/180)	
		No systemic chemotherapy	1.9% (3/156)				8.6% (3/35)	
Shields et al[20]	1995–1999	Systemic chemotherapy	0.0% (0/142)	0.0% (0/142)	0.0% (0/95)	0.0% (0/95)	0.0% (0/99)	0.0% (0/99)
		No systemic chemotherapy	1.4% (1/72)	0.0% (0/72)	5.9% (1/17)	0.0% (0/17)	5.6% (1/18)	0.0% (0/18)
Blach et al[22]	1979–1990	Radiotherapy	4.3% (5/117)	0.9% (1/117)	5.2% (5/97)	1.0% (1/97)		
Imhof et al[23]	1971–1993	Radiotherapy	4.7% (5/106)	0.0% (0/106)			5.7% (5/87)	0.0% (0/87)
Ramasubramanian et al[8,21]	2000–2012	Radiotherapy					2.8% (1/87)	
		No radiotherapy					1.7% (3/179)	

The number of trilateral retinoblastoma patients divided by the size of the retinoblastoma cohort in parentheses.

[a]Twenty-four patients received a full course of systemic chemotherapy, 1 was previously treated elsewhere, and 2 did not receive (a full course of) chemotherapy; 1 of these latter 2 patients did develop trilateral retinoblastoma (location unspecified).

The lower estimates for trilateral retinoblastoma incidence we calculated potentially reduce the cost-effectiveness of screening for trilateral retinoblastoma in patients with retinoblastoma beyond baseline imaging. More than 50% of trilateral retinoblastomas are diagnosed at the time of retinoblastoma diagnosis (with baseline magnetic resonance imaging of the eyes and brain), suggesting that baseline screening for trilateral retinoblastoma might indeed be useful.[3]

The few studies that published on prior use of systemic chemotherapy and risk of developing trilateral retinoblastoma have shown conflicting results with respect to a potential decrease of trilateral retinoblastoma risk in patients with retinoblastoma. Whether intraarterial chemotherapy has an effect on the risk to develop trilateral retinoblastoma—theoretically improbable because systemic exposure to chemotherapy is very low—was only assessed in 1 relatively small cohort of 89 patients and does not allow for any conclusions on this issue.[24] Also, the few studies that looked at prior radiotherapy did not allow for any meaningful meta-analysis. Should previous radiotherapy (commonly used before the year 1995) be inductive and previous chemotherapy (increasingly used since the year 1995) protective, then we would expect to see a clear reduction of trilateral retinoblastoma incidence over time. The estimated incidences did slightly decrease after the year 1995, but the differences were not statistically significant (Figure 3). Alternatively, larger cohort sizes in later studies could partially explain this difference.

There is much heterogeneity between the studies reporting trilateral retinoblastoma incidence. Some studies looked at incidence data in a population (3 cohorts from 3 studies; see Table 1), but most are data from 1 or more (specialized) institutions, which—owing to referral bias—might have resulted in a higher trilateral retinoblastoma incidence, or maybe actually a lower incidence when children with trilateral retinoblastoma end up in different specialized pediatric neurooncology centers (Table 2). Also, some of the cohorts are from the same center. Other potential sources of heterogeneity are the choice of start date and end date (year) of the retinoblastoma cohort at risk, and loss to follow-up of patients in the cohort. The estimates in this study assume that of all patients with retinoblastoma in the cohort it is known whether they developed trilateral retinoblastoma, which might be considered appropriate because trilateral retinoblastoma develops relatively quickly (median interval 17 months) after

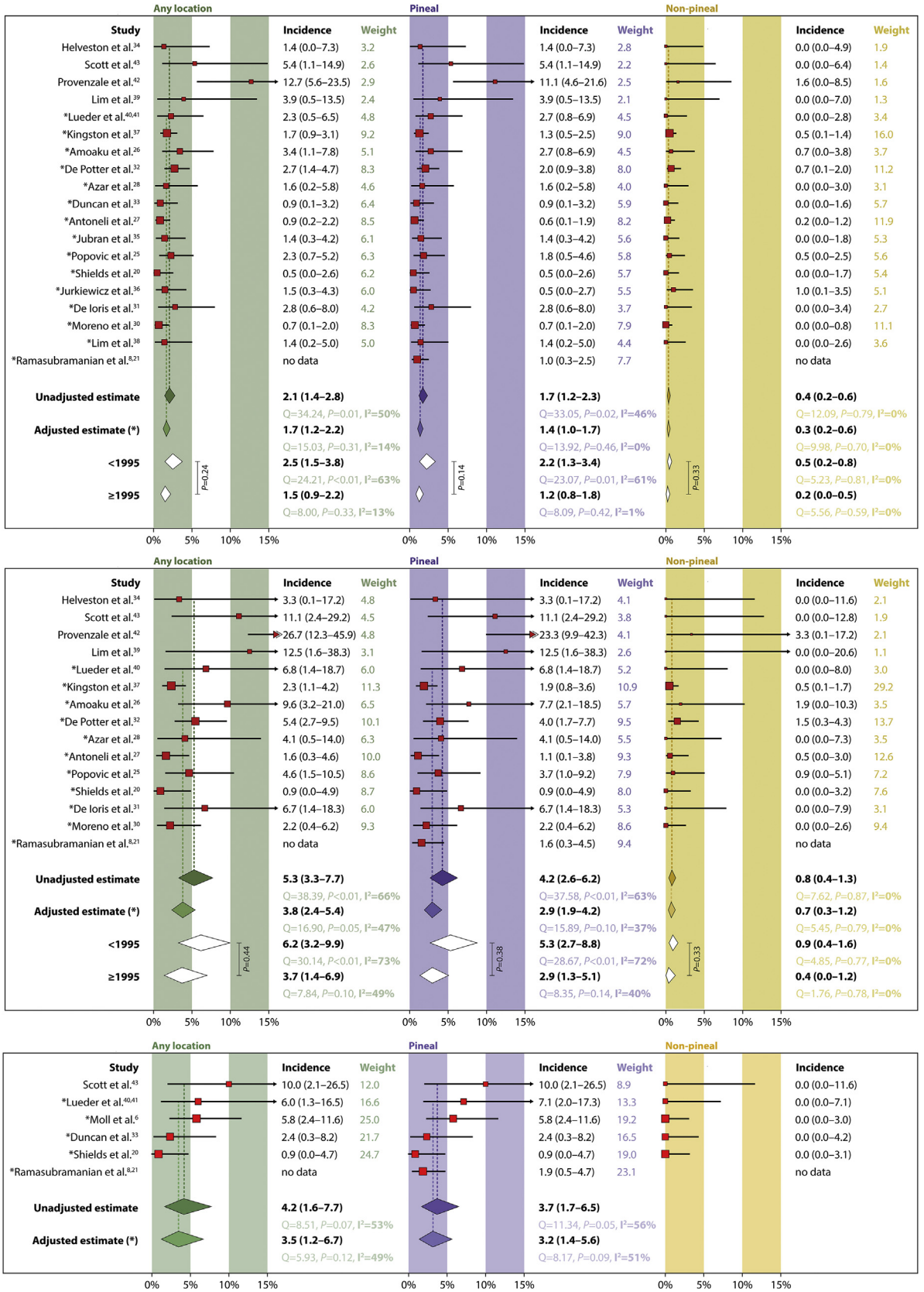

FIGURE 3. Forest plots of trilateral retinoblastoma incidence in cohorts of patients with (Top) unilateral and bilateral, (Middle) bilateral, and (Bottom) hereditary retinoblastoma. Incidence in percentages with a 95% confidence interval in parentheses.

retinoblastoma (since 1995 >95% are diagnosed with trilateral retinoblastoma before the age of 5 years).[3]

There is a risk that patients with asymptomatic trilateral retinoblastoma without histopathologic proof of disease might have been false-positive trilateral retinoblastoma cases (eg, benign pineal cysts[25]), causing an overestimation of trilateral retinoblastoma incidence. On the other hand, patients with retinoblastoma, especially those from several decades back, might have died from central nervous system metastases that were not recognized as trilateral retinoblastoma (ie, false negatives).

In summary the incidence of trilateral retinoblastoma is estimated to be substantially lower than previously reported in the literature concerning trilateral retinoblastoma, especially after adjusting for bias from small cohorts.

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Biosketch

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SUPPLEMENTAL TABLE 1. The Syntaxes Used to Obtain Articles That Reported Incidence of Trilateral Retinoblastoma With Pubmed and Embase

Pubmed search syntax[a]:

(''Retinoblastoma''[Mesh] OR retinoblastoma[tw] OR retinoma[tw] OR retinocytoma[tw]) AND (''Pinealoma''[Mesh] OR pinealoma[tw] OR pineoblastoma[tw] OR pinealoblastoma[tw] OR pineal[tw] OR trilateral[tw] OR ectopic[tw] OR brain[tw] OR sellar[tw] OR suprasellar[tw] OR parasellar[tw]) AND ((''1966/01/01''[PDAT] : ''3000/12/31''[PDAT]) AND (Dutch[lang] OR English[lang] OR German[lang])) NOT (''Animals''[Mesh] NOT ''Humans''[Mesh])

The Embase search syntax[a]:

('retinoblastoma' OR 'retinoblastoma'/exp OR retinoblastoma OR 'retinoma' OR 'retinoma'/exp OR retinoma OR 'retinocytoma' OR 'retinocytoma'/exp OR retinocytoma) AND ('pinealoma' OR 'pinealoma'/exp OR pinealoma OR pineoblastoma OR 'pinealoblastoma' OR 'pinealoblastoma'/exp OR pinealoblastoma OR pineal OR trilateral OR ectopic OR 'brain' OR 'brain'/exp OR brain OR sellar OR suprasellar OR parasellar) AND [humans]/lim AND [embase]/lim AND ([dutch]/lim OR [english]/lim OR [german]/lim) AND [medline]/lim AND [1966–2015]/py

[a]Both searches were performed on March 14, 2014 and updated on July 15, 2015.

SUPPLEMENTAL TABLE 2. Risk-of-Bias Assessment With a Modified Checklist by Hoy and Associates[17] of the Studies That Assessed the Incidence of Trilateral Retinoblastoma and Were Included in This Systematic Review and Meta-analysis

Author	Q1	Q2	Q3	Q4	Q5	Q6
Amoaku et al[26]	1	2	2	0	2	1
Antoneli et al[27]	2	0	2	2	2	1
Azar et al[28]	2	0	2	0	0	0
Bartuma et al[29]	0	0	0	1	2	0
Blach et al[22]	0	0	0	2	2	1
Chantada et al[10]		0	2	2	0	1
De Ioris et al[31]	2	0	2	0	2	1
De Potter et al[32]	0	0	2	0	2	1
Duncan et al[33]	1	0	2	1	2	1
Helveston et al[34]	2	0	2	0	2	1
Imhof et al[23]	0	0	2	2	2	1
Jubran et al[35]	0	0	2	0	2	1
Jurkiewicz et al[36]	0	0	2	0	0	1
Kingston et al[37]	0	0	2	0	2	1
Klufas et al[24]	0	0	0	0	2	0
Lim et al[38]	0	0	2	0	2	1
Lim et al[39]	0	0	2	1	2	1
Lueder et al[40]	0	0	2	0	2	1
Lueder et al[41]	0	0	2	0	2	1
Moll et al[6]		2	2	2	2	1
Moreno et al[30]	0	2	2	0	2	1
Popovic et al[25]	0	0	0	0	2	1
Provenzale et al[42]	0	0	2	0	2	1
Ramasubramanian et al[8,21]	0	0	0	0	2	1
Scott et al[43]	0	0	2	0	2	1
Shields et al[20]	0	0	2	0	2	0

0 = high risk, 1 = intermediate risk, 2 = low risk.

Q1. Was the study's target population a close representation of the national population in relation to relevant variables? (Based on Marees et al.,[18,19] ie, 39.4% bilateral cases)

0 points: proportion of bilateral deviates considerably (≥6 percentage points [%pts]) from population-like or undefined.

1 point: proportion of bilateral deviates slightly (3–6 %pts) from population-like.

2 points: proportion of bilateral population-like (<3 %pts).

Q2. Was the sampling frame a true or close representation of the target population? (eg, hospital-based: high risk, population-based: low risk)?

0 points: hospital-based or undefined.

2 point: national or regional population.

Q3. Was some form of random selection used to select the sample, OR was a census undertaken?

0 points: selected cases (eg, based on type of therapy or undefined).

2 points: consecutive cases.

Q4. Was the likelihood of patients missing from follow-up minimal? Was the length of the shortest prevalence period for the parameter of interest appropriate? (ie, adequate length of follow-up to observe the outcome)

0 points: median follow-up <2.5 years or undefined.

1 point: median follow-up ≥2.5 but <5 years.

2 points: median follow-up ≥5 years.

Q5. Was an acceptable case definition used in the study?

0 points: temporal clustering of cases with increasing follow-up or unclear.

2 points: no evidence of temporal clustering of cases with increasing time period.

Q6. Was the way of trilateral retinoblastoma assessment appropriate (eg, histopathology, cerebrospinal fluid and on imaging: treatment response to therapy or disease progression)?

0 points: undefined.

1 point: clinical diagnosis including imaging.

2 points: based on histopathology.

SUPPLEMENTAL TABLE 3. Trilateral Retinoblastoma Incidence Mentioned in the Introduction or Discussion of Articles Since 2000 Included in our Meta-analysis on Trilateral Retinoblastoma Survival,[1] Excluding Articles That Assessed Trilateral Retinoblastoma Incidence

Study	Year	Retinoblastoma Population	Incidence of Trilateral Retinoblastoma	Source According to Authors
Bonci et al[2]	2013	Bilateral	8%–10%	Kivelä[3]
Dai et al[4]	2008	Unilateral or bilateral	3%	Bader et al,[5] Amoaku et al,[6] De Potter et al,[7] Pesin et al[8]
Dimaras et al[9]	2011	Unilateral or bilateral	3%	De Potter et al[7]
D'Elia et al[10]	2014	Sporadic unilateral	<0.5%	De Potter et al[7]
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Dunkel et al[11]	2010	Bilateral	6%	Blach et al[12]
Huddleston et al[13]	2013	Genetic form	3%–9%	Blach et al,[12] Shields et al[14]
Ibarra et al[15]	2000	Unilateral	0.5%	Kingston et al,[16] De Potter et al,[7] Blach et al[12]
		Bilateral	4%–10%	
James et al[17]	2010	Unilateral or bilateral	1.5%–5%	Provenzale et al[18]
Kamaleshwaran et al[19]	2014	Sporadic unilateral	<0.5%	Kivelä[3]
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Kivela et al[20]	2003	Hereditary	5%–15%	Kivelä,[3] Kingston et al,[16] Blach et al,[12] De Potter et al[7]
Raizis et al[21]	2013	Unspecified	<1%	Antoneli et al[22]
Rodjan et al[23]	2012	Sporadic unilateral	<0.5%	De Potter et al,[7] Kivelä[3]
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Popovic et al[24]	2006	Unspecified	4%–8%	Kingston et al,[16] De Potter et al,[7] Shields et al[25]
Popovic et al[26]	2007	Sporadic unilateral	<0.5%	Kivelä[3]
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Shah et al[27]	2013	All	3%	Shields et al[28]
		Unilateral	0.5%	
		Bilateral	2%–11%	
Skrypnyk et al[29]	2004	Unspecified	5%	De Potter et al[7]
Tsuruta et al[30]	2011	All	3%	De Potter et al[7]
Wright et al[31]	2010	Genetic form	3%–9%	Blach et al[12]

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