

Incidence and survival of retinoblastoma in the Netherlands: a register based study 1862-1995

Annette C Moll, D Joop Kuik, Lex M Bouter, Willem Den Otter, P Dick Bezemer, Jan Willem Koten, Saskia M Imhof, Bertus P Kuyt, Karel E W P Tan

Abstract

Aim—The aim of this study was to determine the (time trends in) incidence and survival of hereditary (familial and sporadic) and non-hereditary retinoblastoma for male and female patients born in the Netherlands between 1862 and 1995.

Method—The national retinoblastoma register was updated and now consists of 955 patients. The missing dates of death were obtained from the municipal registers and the Central Bureau of Genealogy in The Hague. Mortality was compared with the Dutch vital statistics.

Results—From 1862 to 1995 no significant differences in incidence for retinoblastoma were found in the hereditary subgroups. Further, no significant differences between males and females were found, both overall and in the hereditary subgroups. The average incidence of retinoblastoma increased until 1944, probably due to incompleteness of the register, and stabilised after 1945 (1 per 17 000 live births). From 1900 to 1995 the standardised mortality ratio increased for hereditary retinoblastoma patients from 2.9 to 9.0 and decreased for non-hereditary retinoblastoma patients from 1.9 to 1.0.

Conclusion—Although survival for retinoblastoma was significantly better after 1945 than before, in comparison with the Dutch population the mortality between 1900 and 1990 increased for the hereditary and decreased for the non-hereditary retinoblastoma patients.

(*Br J Ophthalmol* 1997;81:559-562)

Retinoblastoma is a rare paediatric eye tumour which occurs in a hereditary and a non-hereditary form. All bilateral (familial or sporadic) cases and the familial unilateral cases can be considered to be hereditary (30%–40% of the cases).¹ In familial cases the patient inherits the retinoblastoma mutation from a carrier parent and in sporadic bilateral cases from a healthy parent in whom a new germinal mutation has occurred.

The incidence of retinoblastoma reported in the literature ranges from 1:10 000 in South Africa to 1:34 000 in the Netherlands (Table 1).¹⁻²¹ These extreme values come from hospital populations and are based on very crude estimations and are therefore probably inaccurate.¹ During the past years it has often been discussed whether there has been any

change in the incidence of this malignant disease.^{22, 23} The survival rate of retinoblastoma improved in the last century,²⁴ mostly because of Wardrop's recommendation to enucleate a retinoblastoma eye.²⁵ As a consequence, hereditary retinoblastoma patients were able to have offspring and this presumably led to a gradual increase in the incidence of hereditary retinoblastoma in the population.

Furthermore, there is still a discussion in the literature regarding the sex predominance of retinoblastoma patients. Pendergrass and Davis⁷ found no difference in the incidence of retinoblastoma between males and females. Naumova and Sapienza²⁶ found a significant overrepresentation of males among bilateral sporadic cases.

Neel²⁷ and Vogel¹ discussed a possible viral aetiology of retinoblastoma. A seasonal variation in births of children with non-hereditary retinoblastoma would suggest that the disease is possibly influenced by certain environmental agents such as viral infection.

The National Retinoblastoma Register of the Netherlands offers the unique opportunity to analyse the above mentioned controversies in the literature. Therefore, the purposes of this study were to determine for hereditary (sporadic and familial) and non-hereditary retinoblastoma patients: (1) the (time trends in) incidence, (2) the difference in incidence between males and females, (3) the difference in incidence between different months, (4) time trends in survival, (5) the difference in survival between male and female patients.

Methods

The National Retinoblastoma Register of the Netherlands^{28, 29} was used in the updated version.³⁰ It can be regarded as virtually complete for patients born from 1945 to date.¹⁷ We gathered the dates of birth and death of the 955 registered Dutch retinoblastoma patients born from 1862 to 1995. If possible, missing dates of death of patients were obtained with the help of the municipal registers and the Central Bureau of Genealogy in The Hague.

Retinoblastoma was regarded to be hereditary if at least one of the following criteria was met: bilateral retinoblastoma, family history for retinoblastoma (then the parent would be carrier of the defect in the retinoblastoma gene), or a defect in the retinoblastoma gene was found in chromosomal/DNA analysis of the patient. Sporadic hereditary retinoblastoma patients are the first cases known in a family. Some sporadic unilateral retinoblastoma pa-

Department of
Ophthalmology, Vrije
Universiteit,
Amsterdam,
Netherlands
A C Moll
S M Imhof
K E W P Tan

Department of
Epidemiology and
Biostatistics, Vrije
Universiteit,
Amsterdam,
Netherlands
D J Kuik
L M Bouter
P D Bezemer

Department of
Functional
Morphology, Utrecht
University,
Netherlands
W Den Otter
J W Koten

Department of Human
Genetics, Vrije
Universiteit,
Amsterdam,
Netherlands
B P Kuyt

Correspondence to:
A C Moll, MD, Department
of Ophthalmology, Free
University Hospital, De
Boelelaan 1117, 1081 HV
Amsterdam, Netherlands.

Accepted for publication
11 March 1997

Table 1 Incidence figures of retinoblastoma cited in the literature

Population	Time period	No of cases	Incidence*	Reference
Africa				
Bantu, South Africa	1955-75	80	1:10 000	Freedman and Goldberg, 1976 ²
Malawi	1975	20	1:10 000	BenEzra and Chirambo, 1976 ³
America				
USA	1969-71	59	1:18 000	Devesa, 1975 ⁴
Michigan, USA	?	49	1:20 000	Falls and Neel, 1951 ⁵
Ohio, USA	?	126	1:24 000	Macklin, 1961 ⁶
USA	1974-6	70	1:18 000	Pendergrass and Davis, 1980 ⁷
Asia				
Hokkaido, Japan	1945-57	69	1:24 000	Matsunaga and Ogyu, 1959 ⁸
Nagasaki, Japan	1965-86	34	1:16 000	Takano <i>et al</i> , 1991 ⁹
Australia, New Zealand				
Australia	1956-76	80	1:17 000	O'Day <i>et al</i> , 1977 ¹⁰
New Zealand	1948-77	100	1:18 000	Suckling <i>et al</i> , 1982 ¹¹
Europe				
Denmark	1928-57	118	1:19 000	Bech and Jensen, 1961 ¹²
Finland	1950-64	?	1:16 000	Tarkkanen and Tuovinen, 1971 ¹³
France	1951-60	295	1:28 000	Briard-Guillemot <i>et al</i> , 1974 ¹⁴
Germany	1934-51	48	1:29 000	Vogel, 1979 ⁵
Great Britain	1962-80	431	1:23 000	Sanders <i>et al</i> , 1988 ¹⁵
The Netherlands	1927-9	?	1:34 000	Hemmes, 1931 ¹⁶
The Netherlands	1945-70	486	1:16 000	DerKinderen <i>et al</i> , 1990 ¹⁷
Northern Ireland	1938-56	23	1:27 000	Stevenson and Martin, 1957 ¹⁸
Norway	1950-73	75	1:17 000	Horven, 1973 ¹⁹
Sweden	1958-71	88	1:18 000	Kock and Naeser, 1973 ²⁰
Middle East				
Riyadh, Saudi Arabia	1982-6	22	1:12 000	Al-Idrissi <i>et al</i> , 1991 ²¹

*Incidence in number of retinoblastoma patients per live births.

tients might be classified incorrectly as non-hereditary, since approximately 10% of the hereditary retinoblastoma patients are affected unilaterally.¹

STATISTICAL ANALYSES

The total annual number of live births by sex in the Netherlands is available until 1994.³¹ The cumulative incidences of the different retinoblastoma subgroups (sporadic hereditary, familial hereditary, and non-hereditary) were calculated in 5 year birth cohorts. The number of liveborn retinoblastoma patients was divided by the number of live births in the Netherlands in the same period (irrespective of the moment of diagnosis). Linear regression analyses were performed to detect a significant trend in incidence for the different retinoblastoma groups from 1862 to 1995.

Difference in incidence between sexes was investigated by testing the percentage of males in the retinoblastoma group against percentages of males and females in the same birth cohort in the Dutch population, using the binominal distribution. Sex differences between the retinoblastoma subgroups were compared with the χ^2 test for contingency tables.

Differences in incidence between months were investigated for each retinoblastoma subgroup, using a multinomial distribution, with the (relative) monthly birth frequencies of the Dutch population as variables.

The age at diagnosis was not always available for the patients born before 1945. Therefore, the survival curves are based on age since birth instead of in years after diagnosis. Survival was described with Kaplan-Meier curves, using the Mantel-Cox (log rank) test to determine differences in survival curves among the groups of interest.

The standardised mortality ratio (SMR) for the different retinoblastoma groups was calculated³² in 10 year mortality groups. An

SMR of 1.25 for example means 25% 'extra mortality' in the retinoblastoma patients in comparison with the Dutch population.³³ The Dutch mortality rates in age groups per calendar year of death were available from 1900 to date.³⁴ Confidence intervals (95% CI) were calculated using the logarithm of the SMR.³² In order to detect a trend in the SMR from 1900 to 1995 regression analyses on the logarithm of the SMR were done. This project was approved by the medical ethics committee of the Free University Hospital, Amsterdam, the Netherlands.

Results

HEREDITY

Sex and heredity of the retinoblastoma patients are shown in Table 2. Forty nine of the 350 hereditary retinoblastoma patients (14%) had the unilateral form; 320 of the 635 unilateral tumours were sited in the right eye and 296 in the left eye; in 19 unilateral cases the location of the tumour was unknown. The retinoblastoma subcohort 1945-94 has nearly the same composition as the total cohort (data not shown).

INCIDENCE BY SEX

In the period 1862-1995, no significant difference was found in incidence for retinoblastoma between males and females in the retinoblastoma subgroups (sporadic hereditary, familial hereditary, and non-hereditary). Furthermore, our investigation did not reveal any significant difference between the male/female ratio in various retinoblastoma subgroups and the Dutch population. Moreover, in the subcohort 1945-94 no significant difference in male/female ratio was found between the different retinoblastoma subgroups, or compared with the Dutch population (data not shown).

TIME TRENDS IN INCIDENCE

Figure 1 shows the number of retinoblastoma patients per 100 000 life births in 5 year cohorts in the Netherlands. The incidence of retinoblastoma increased significantly from 1862 to 1945. After 1945 there was no evidence of an increase in the total incidence of retinoblastoma, nor was there any significant change in incidence in the retinoblastoma subgroups (sporadic hereditary, familial hereditary, and non-hereditary retinoblastoma; data not shown). The average incidence of retinoblastoma after 1945 was 1:17 000 (95% CI; 1:15 500-1:18 500) (5.8 per 100 000) live births (range 13 000-25 000).

Table 2 Sex and heredity of patients in the National Retinoblastoma Register of the Netherlands from 1862 to 1995

Group	Male (%)	Female (%)	Total
Non-hereditary	318 (54.3)	268 (45.7)	586
Sporadic hereditary	130 (52.2)	119 (47.8)	249*
Familial hereditary	47 (46.5)	54 (53.5)	101†
Unknown	8	11	19
Total	503 (52.7)	452 (47.3)	955

*Including 29 unilateral patients.

†Including 20 unilateral patients.

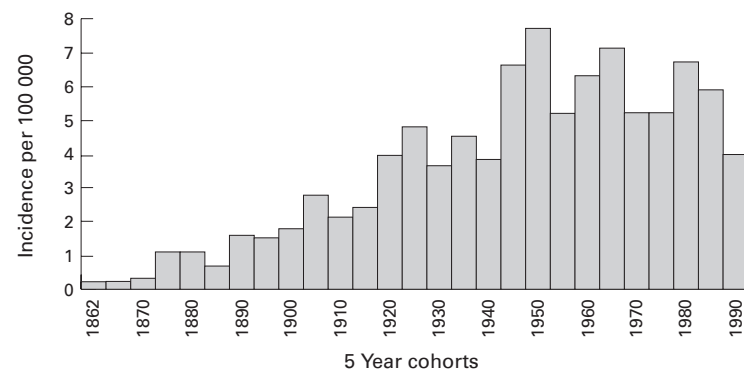


Figure 1 Incidence of retinoblastoma in the Netherlands in 5 year cohorts from 1862 to 1994. The incidence is expressed in number of retinoblastoma patients per 100 000 live births in the Netherlands in the same period (irrespective of the moment of diagnosis).

Table 3 Cumulative survival for the subcohorts of retinoblastoma patients: 1945–94

Group	No	Survival* until age 5	Survival* until age 35
Non-hereditary	395	91.8%	88.5%
Hereditary	242	87.2%	72.0%
Sporadic hereditary	164	87.4%	74.1%
Familial hereditary	78	86.8%	67.3%
Female	300	91.6%	84.3%
Male	337	88.7%	80.3%
All	637	90.1%	82.2%

*Survival per number of liveborn retinoblastoma patients.

INCIDENCE PER MONTH

The distribution of the retinoblastoma subgroups does not show significant differences over the 12 months of the year in comparison with the Dutch population. There appears to be a slight, but not significant excess of retinoblastoma affected newborns from December to May (data not shown).

SURVIVAL

In all, 287 of the 955 patients born between 1862 and 1995 had died; 640 patients were still alive and 28 patients could not be traced for follow up. Five hundred and thirty eight patients of the subcohort 1945–94 were still alive; 99 patients had died and eight patients could not be traced for follow up. Cumulative survival at 5 and 35 years of age for the different retinoblastoma subgroups is shown in Table 3. There was a significant difference in cumulative survival between hereditary and non-hereditary retinoblastoma ($p < 0.005$). The difference in survival between sporadic hereditary and familial hereditary survival was not significant. The difference in survival between male and female retinoblastoma patients was also not statistically significant.

The survival at 5 years ($p < 0.01$) and 35 years ($p < 0.01$) of age was significantly better for patients born after 1945 than for patients born before 1945. SMRs for the period 1898–1995 are given in Table 4. No trend in the SMR could be found for the total group of patients. However, for the hereditary patients the SMR increased significantly ($p = 0.007$), while for the non-hereditary patients a significant decrease trend was found ($p = 0.017$).

Table 4 Standardised mortality ratio (SMR) for retinoblastoma patients

Cohort	All RB	Hereditary	Non-hereditary
	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)
1898–1907	1.4 (0.7–2.6)	—	1.9 (1.0–3.7)
1908–17	2.7 (1.7–4.3)	2.9 (1.1–7.4)	2.7 (1.6–4.8)
1918–27	3.2 (2.2–4.7)	3.6 (2.1–6.2)	2.9 (1.7–5.0)
1928–37	3.3 (2.2–4.9)	4.5 (2.5–8.2)	2.4 (1.4–4.3)
1939–47	2.2 (1.4–3.3)	2.6 (1.3–5.0)	1.8 (1.0–3.2)
1948–57	2.6 (1.8–3.7)	3.3 (1.9–6.0)	2.1 (1.3–3.5)
1958–67	3.0 (2.1–4.3)	5.0 (3.0–8.0)	2.1 (1.3–3.5)
1968–77	2.6 (1.8–3.7)	5.5 (3.4–8.9)	1.6 (1.0–2.8)
1978–87	2.8 (2.0–3.9)	5.7 (3.6–9.0)	1.7 (1.0–2.9)
1988–95	3.1 (2.1–4.7)	9.0 (5.5–14.4)	1.0 (0.5–2.3)

RB = retinoblastoma.

95% CI = 95% confidence interval.

Discussion

HEREDITY

The percentage of hereditary and non-hereditary retinoblastoma (61.4% and 36.6%, respectively) was similar to the percentage published by Vogel.¹ In addition, he found that 10%–12% of the unilateral sporadic cases were in fact new germline mutants; we found a nearly similar percentage of 14.0.

INCIDENCE BY SEX

Several studies showed no sex differences in the incidence of retinoblastoma.^{5 11 35} Naumova and Sapienza²⁶ made an extensive compilation of the literature regarding sex and laterality of proved sporadic cases and found a significant overrepresentation of males among bilateral sporadic cases. For unilateral retinoblastoma they could not find such a difference. We could not confirm their first mentioned findings.

TIME TRENDS IN INCIDENCE

As discussed by Vogel¹ studies covering more recent periods tend to give higher values of incidence of retinoblastoma. The most obvious explanation is a more complete ascertainment in the more recent studies. This can also explain the increasing incidence we found in the period 1862–1944. It seems that especially in the period 1862–1900 the tumour was often not recognised and/or registered. Vogel¹ did not exclude that there has been a true increase in incidence of retinoblastoma. However, the incidence in the period 1945–94 did not change significantly in our study. Probably, in this period the tumour was diagnosed correctly and the register was really complete.

INCIDENCE PER MONTH

Earlier reports^{1 5 11 36} failed to show clustering of sporadic hereditary or non-hereditary retinoblastoma in specific months. Our data revealed fluctuations to some extent by month of birth, but this was not statistically significant.

SURVIVAL

In 1809, Wardrop²⁵ advocated enucleation of a retinoblastoma containing eye as a lifesaving measure. It is the general opinion that early enucleation contributed to a better survival.²⁴ However, new treatment modalities (irradiation)

tion or coagulation) were developed to save life and preserve vision. Bishop and Madsen³⁷ reported an increase in the survival of retinoblastoma of 5% in 1869 to 81% in 1967. This study also showed an increasing survival. It should be stressed also that from 1900 the survival in the general population³⁴ increased dramatically. Taking this into account, it is clear from the trend analysis of the SMR that survival for the hereditary group could not follow the improvement in the general population.

The risk of death is significantly higher for a retinoblastoma patient than for an average member of the Dutch population, as all SMRs are larger than 1. In other words, the improved diagnostic technique and improved retinoblastoma treatment did not result in the same length of survival for the general Dutch population and patients with hereditary retinoblastoma, in particular. Mortality increased significantly compared with the mortality of the general population ($p=0.007$). In contrast, there was a significantly decreased 'extra mortality' of the non-hereditary patients ($p=0.017$). These findings can probably be explained by the hereditary retinoblastoma gene disorder. Hereditary retinoblastoma patients are vulnerable for second primary tumours and pineoblastomas.³⁰ Furthermore, treatment of hereditary (bilateral) retinoblastoma patients is more often irradiation than that of non-hereditary patients, because non-hereditary patients are mostly enucleated. DerKinderen *et al*³⁸ have shown that irradiation therapy is an extra risk factor for second primary tumours in hereditary retinoblastoma patients. This will lead to death in many cases. On the other hand no second primary tumours were induced by irradiation of non-hereditary retinoblastoma patients³⁹; consequently, non-hereditary retinoblastoma patients will be cured and survival will be improved.

This study was supported by grants from the Haak-Bastiaanse-Kuneman-stichting.

- 1 Vogel F. Genetics of retinoblastoma. *Hum Genet* 1979;52:1-54.
- 2 Freedman J, Goldberg L. Incidence of retinoblastoma in the Bantu of South Africa. *Br J Ophthalmol* 1976;60:655-66.
- 3 BenEzra D, Chirambo MC. Incidence of retinoblastoma in Malawi. *J Pediatr Ophthalmol* 1976;13:340-3.
- 4 Devesa SS. The incidence of retinoblastoma. *Am J Ophthalmol* 1975;80:263-5.
- 5 Falls HF, Neel JV. Genetics of retinoblastoma. *Arch Ophthalmol* 1951;46:367-89.
- 6 Macklin MT. A study of retinoblastoma in Ohio. *Am J Hum Genet* 1961;12:1-43.
- 7 Pendergrass TW, Davis S. Incidence of retinoblastoma in the United States. *Arch Ophthalmol* 1980;98:1204-10.
- 8 Matsunaga E, Ogyu. Genetic study of retinoblastoma in a Japanese population. *Jpn J Human Genet* 1959;4:156.

- 9 Takano J, Akiyama K, Imamura N, Sakuma M, Amemiya. Incidence of retinoblastoma in Nagasaki Prefecture, Japan. *Ophthalmic Paediatr Genet* 1991;12:139-44.
- 10 O'Day J, Billson FA, Hoyt GS. Retinoblastoma in Victoria. *Med J Aust* 1977;2:428-32.
- 11 Suckling RD, Fitzgerald PH, Stewart J, Wells E. The incidence and epidemiology of retinoblastoma in New Zealand: a 30-year survey. *Br J Cancer* 1982;46:729-36.
- 12 Bech K, Jensen OA. Bilateral retinoblastoma in Denmark, 1928-1957. *Acta Ophthalmol* 1961;39:561-8.
- 13 Tarkkanen A, Tuovinen E. Retinoblastoma in Finland 1912-1964. *Acta Ophthalmol* 1971;492:93-300.
- 14 Briard-Guillemot ML, Bonaiti-Pellie C, Feingold J, Frezal J. Etude génétique du retinoblastoma. *Humangenetik* 1974;24:271-84.
- 15 Sanders BM, Draper GJ, Kingston JE. Retinoblastoma in Great Britain 1969-80: incidence, treatment, and survival. *Br J Ophthalmol* 1988;72:576-83.
- 16 Hemmes GD. Untersuchungen nach dem Vorkommen von Glioma retinae bei Verwandten von mit dieser Krankheit Behafteten. *Klin Monatsbl Augenheilkd* 1931;86:331-5.
- 17 DerKinderen DJ, Koten JW, Tan KEWP, Beemer FA, Van Romunde LKJ, Den Otter W. Parental age in sporadic hereditary retinoblastoma. *Am J Ophthalmol* 1990;110:605-9.
- 18 Stevenson AC, Martin VAF. Retinoblastoma, occurrence of the condition in Northern Ireland. *Brit J Prev Soc Med* 1957;11:29-35.
- 19 Horven I. Retinoblastoma in Norway. *Acta Ophthalmol* 1973;51:103-9.
- 20 Kock E, Naeser P. Retinoblastoma in Sweden 1958-1971. *Acta Ophthalmol* 1973;57:344-50.
- 21 Al-Idrissi I, Al-Kaff A, Senft SH. Cumulative incidence of retinoblastoma in Riyadh, Saudi Arabia. *Ophthalmic Paediatr Genet* 1991;13:9-12.
- 22 Muir KR, Smith H, Parkes SE, Willshaw H, Harry J, Mann JR, Stevens MC. Increasing incidence of retinoblastoma? *Arch Dis Childh* 1990;65:915.
- 23 Parkes SE, Amoaku WM, Muir KR, Willshaw HE, Mann JR. Thirty years of retinoblastoma (1960-1989) changing patterns of incidence. *Paediatr Perinat Epidemiol* 1994;8:282-91.
- 24 Shields JA, Shields CL. Retinoblastoma. In: *Intraocular tumors, a text and atlas*. Philadelphia: WB Saunders, 1992:305-91.
- 25 Wardrop J. *Observations on the fungus Haematodes*. Edinburgh: Constable, 1809.
- 26 Naumova A, Sapienza C. The genetics of retinoblastoma, revisited. *Am J Hum Genet* 1994;54:264-73.
- 27 Neel JV. Mutations in the human population. *Methodol Human Genet* 1962;203-24.
- 28 Schappert-Kimmijser J, Hemmes GD, Nijland R. The heredity of retinoblastoma. *Ophthalmologica* 1966;151:197-213.
- 29 DerKinderen DJ. A new concept of oncogenesis with an evaluation in retinoblastoma. Thesis, Utrecht, 1987.
- 30 Moll AC, Imhof SM, Koten JW, Bezemer PD, Kuik DJ, Bouter LM, *et al*. Second primary tumors in patients with hereditary retinoblastoma: a registered-based follow-up study 1945-1994. *Int J Cancer* 1996;67:515-9.
- 31 Centraal Bureau voor de Statistiek. *Statistiek van de loop der bevolking*. The Hague, 1936-1994.
- 32 Rothman KJ. *Modern epidemiology*. Boston: Little, Brown, 1986:232.
- 33 Bouter LM, Van Dongen MCJM. *Epidemiologisch onderzoek*. Houten/Antwerp: Bohn Stafleu Van Loghum, 1991:37.
- 34 Centraal Bureau voor de Statistiek. *Sterftecijfers 1990-1994*. The Hague.
- 35 Jensen RD, Miller RW. Retinoblastoma: epidemiological characteristics. *N Engl J Med* 1971;285:307-11.
- 36 Matsunaga E, Minoda K, Sasaki MS. Parental age and seasonal variation in the births of children with sporadic retinoblastoma: a mutation-epidemiologic study. *Hum Genet* 1990;84:155-8.
- 37 Bishop JO, Madsen EC. Retinoblastoma: Review of current status. *Surv Ophthalmol* 1975;19:342-66.
- 38 DerKinderen DJ, Koten JW, Nagelkerke NJD, Tan KEWP, Beemer FA, Den Otter W. Non-ocular cancer in patients with hereditary retinoblastoma and their relatives. *Int J Cancer* 1988;41:499-504.
- 39 Imhof SM, Moll AC, Hofman P, Mourits M Ph, Schipper J, Tan KEWP. Second primary tumors in patients treated with megavoltage external beam irradiation for retinoblastoma. (Submitted for publication)



Incidence and survival of retinoblastoma in the Netherlands: a register based study 1862 – 1995

Annette C Moll, D Joop Kuik, Lex M Bouter, et al.

Br J Ophthalmol 1997 81: 559-562

doi: 10.1136/bjo.81.7.559

Updated information and services can be found at:

<http://bjo.bmj.com/content/81/7/559.full.html>

These include:

References

This article cites 25 articles, 4 of which can be accessed free at:

<http://bjo.bmj.com/content/81/7/559.full.html#ref-list-1>

Article cited in:

<http://bjo.bmj.com/content/81/7/559.full.html#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Epidemiology](#) (766 articles)

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>