Retinoblastoma in Great Britain 1963–2002

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ABSTRACT

Aim: This paper describes the epidemiology and family history status of 1601 children with retinoblastoma in Great Britain diagnosed 1963–2002 and summarises the practical consequences for diagnosis and counselling of developments in molecular genetics.

Methods: Incidence rates were analysed according to year of diagnosis and tumour laterality. Cases were classified as heritable or non-heritable on the basis of laterality and family history of the disease.

Results: There were 998 unilateral cases, 581 bilateral and 22 of unknown laterality. Bilateral cases tended to be diagnosed at a younger age than unilateral. All bilateral cases are regarded as heritable, and 35% had a family history of the disease. 7% of the unilateral cases had a family history and are therefore heritable. Thus, at least (41%) of our cases are heritable. This is an underestimate, since these data on family history are incomplete. For unilateral cases aged below 1 year, the reported incidence rate increased significantly ($p<0.0001$) by about 2.5% per year; for the age group 1–4 years, the average increase was about 0.5% per year (not significant).

Retinoblastoma is a malignant intraocular embryonal tumour of childhood. In Britain, approximately one in 20 000 children is affected; about 40 cases are diagnosed each year. The disease can be either unilateral or bilateral, the latter accounting for about 36% of cases in Britain. There are two forms of the disease: "heritable," that is those that carry a germ-line mutation in the RB1 gene, and "non-heritable." By "heritable," we mean transmissible to future generations. Bilateral retinoblastoma is invariably heritable, though in most cases there is no preceding family history of the disease. A minority of unilateral cases are also heritable; they will be classified as such if they have a family history of the disease or on the basis of molecular genetic analysis. The remaining unilateral cases are classified as non-heritable.

Children with retinoblastoma commonly present with either a white "cat's eye" reflex termed leucocoria (50%) or a squint (25%). Approximately 10% are detected at screening due to a family history of retinoblastoma. Pain is a rare presenting symptom, as is parental awareness of deterioration in the child's vision. The diagnosis of retinoblastoma is made on the characteristic clinical appearances when examined by an experienced ophthalmologist, backed up by ultrasonography.

In retinoblastoma genetics, the period 1960–2000 witnessed the progression from pedigree analysis to cytogenetics to molecular genetics, and retinoblastoma became a prototypic model for the study of hereditary predisposition to cancer. Knudson's "two-hit" hypothesis[1] stated the requirement for two rate-limiting genetic events (mutations) in retinoblastoma formation. These two mutational events were proposed to be the loss of both alleles of a tumour suppressor gene.[2] When these mutations are somatic (that is, occur in one retinal cell) the disease is non-heritable. If, however, the first mutation is germinal it will be present in all cells of an individual; such individuals have a heritable predisposition to the disease and often develop multifocal tumours. The cloning of the RB1 tumour suppressor gene[3] opened the molecular genetics era in retinoblastoma.

Molecular genetic analysis is used in assessment of risk for family members of retinoblastoma patients. This risk depends on whether the patient has a germ-line RB1 mutation. Genetic counselling in the absence of specific molecular information is provided using empirical risk information.[4] After the cloning of the RB1 gene, linkage analysis and subsequently direct mutation analysis permitted accurate definition of carrier risk and genetic counselling of patients; presymptomatic testing including prenatal testing also became possible.[5–7]

Clinical screening for retinoblastoma involves frequent ophthalmological examination under anaesthetic (EUA) of at-risk children (ie, those with an affected first-degree relative) usually until the age of five. Molecular analysis is able to identify carriers and non-carriers of RB1 mutations, thus preventing unnecessary EUAs; management of patients in this way has been shown to be more cost-effective.[8] Since the 1990s, genetic testing has become part of standard management of at-risk family members, thereby avoiding the need for clinical screening of non-carrier unaffected family members.

Molecular analysis is of great importance, especially in unilateral sporadic cases where tumour tissue is available.[9 10] Identification of the RB1 mutations in tumour, and checking the patients' blood for those mutations, permits the identification of heritable cases. Molecular analysis has indicated that over 15% of patients in this group are germ-line mutation carriers; see Z Onadim unpublished results, http://www.bartsandthelondon.nhs.uk/Retinoblastoma, and Lohmann *et al*.[10]

Some of the RB1 mutations identified also offer information on expression and penetrance of the disease. Some mutations give rise to low-penetrance retinoblastoma seen in families with mostly unilaterally affected and/or unaffected carrier members.[11] There have also been reports on abnormalities of other genes related to progression in retinoblastoma.[12]

Analysis of RB1 molecular changes in retinoblastoma has already produced practical consequences for diagnosis, identification of carrier status and presymptomatic prediction of disease.

Table 1 Cases of retinoblastoma by age, sex and laterality: England, Scotland and Wales 1963–2002

Age at diagnosis (years)	Unilateral			Bilateral			All cases		
	Males	Females	Total	Males	Females	Total	Males*	Females*	Total*
0	117	109	226	204	174	378	322	286	608
1	115	138	253	79	56	135	197	198	395
2	122	118	240	34	15	49	157	137	294
3	63	75	138	7	3	10	73	79	152
4	33	37	70	4	1	5	38	38	76
0–4	450	477	927	328	249	577	787	738	1525
5–9	35	31	66	0	2	2	36	33	69
10–14	5	0	5	0	2	2	5	2	7
All ages	490	508	998	328	253	581	828	773	1601

*Includes 22 cases where laterality is unknown.

There is now the potential to affect patient management by identification of other genomic changes that could be prognostic factors or therapeutic targets.

METHODS

Ascertainment of cases

We ascertained cases of retinoblastoma diagnosed between 1963 and 2002 from the population-based National Registry of Childhood Tumours (NRCT).[13] Oxfordshire Research Ethics Committee (Oxfordshire REC C, Ref 07/Q1606/45) approved the use of the data reported in this study in 2007.

Laterality

Cases of bilateral retinoblastoma are usually recognised as such soon after the initial diagnosis of retinoblastoma in one eye. Cases that were originally unilateral were categorised as bilateral if a tumour subsequently developed in the second eye.

Assigning heritability status to cases

We have classified cases as (1) "heritable," bilateral cases and those with a family history of the disease or (2) "non-heritable," unilateral (or of unknown laterality) with no known family history; some of these will be heritable, but germ-line carriers among them will not always be identified as such.

Incidence

Age-specific incidence rates are given as annual numbers of cases per million children. These are based on nationally compiled annual data by sex and single year of age. We have also estimated cumulative incidence rates, defined to be the risk of retinoblastoma by age 15 years; this is essentially the same as lifetime risk.

Time trends in incidence

Incidence rates at ages 0 and 1–4 years were calculated for single calendar years and for 5-year calendar periods. To assess whether there were long-term time trends in the incidence rates, we estimated an average annual percentage change (AAPC) for each group using standard Poisson regression methods with the assumption that the change, if any, was a constant, year-on-year proportionate increase or decrease.

Statistical methods

Statistical analyses were carried out using STATA software.[14] We have taken the value $p<0.05$ as being statistically significant.

RESULTS

Age, sex and laterality

There were 1601 cases of retinoblastoma diagnosed between 1963 and 2002. Numbers of cases by age, sex and laterality are shown in table 1. Of these cases, 51.7% were males, 48.3% females, 62.3% unilateral, 36.3% bilateral and 1.4% of unknown laterality.

The age at diagnosis (calculated for 1579 cases of known laterality) varies by laterality as shown in table 1.

Annual incidence rates are shown in table 2. The incidence rates for the age-group 0–14 years for unilateral, bilateral and all retinoblastoma (including those of unknown laterality) were 2.2, 1.3 and 3.5 per million, respectively. The corresponding cumulative rate estimates for the first 15 years of life were 32.9, 19.3 and 53.0 per million.

Table 2 Retinoblastoma: annual incidence rates per million by age, sex and laterality, England, Scotland and Wales 1963–2002

Age at diagnosis (years)	Unilateral			Bilateral			All cases		
	Males	Females	Total	Males	Females	Total	Males*	Females*	Total*
0	7.6	7.4	7.5	13.3	11.9	12.6	21.0	19.5	20.3
1	7.4	9.4	8.4	5.1	3.8	4.5	12.8	13.4	13.1
2	7.8	8.0	7.9	2.2	1.0	1.6	10.1	9.2	9.7
3	4.0	5.0	4.5	0.4	0.2	0.3	4.7	5.3	5.0
4	2.1	2.5	2.3	0.3	0.1	0.2	2.4	2.5	2.5
0–4	5.8	6.4	6.1	4.2	3.4	3.8	10.1	10.0	10.0
5–9	0.4	0.4	0.4	–	0.0	0.0	0.5	0.4	0.4
10–14	0.1	–	0.0	–	0.0	0.0	0.1	0.0	0.0
All ages	2.1	2.3	2.2	1.4	1.1	1.3	3.5	3.4	3.5

Rates <0.05 are shown as 0.0.
*Includes 22 cases where laterality is unknown.
–, zero cases.

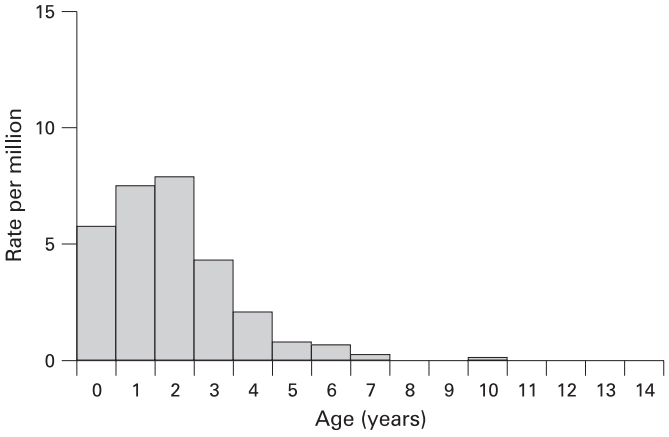

Figure 1 Unilateral retinoblastoma. Incidence rates by single year of age: England, Scotland and Wales 1963–1982.

In figs 1–4, incidence rates for unilateral and bilateral cases by age at diagnosis are shown for two separate 20-year periods: 1963–1982 and 1983–2002.

Time trends in incidence

The reported incidence rates for unilateral cases aged below 1 year increased from 5.8 per million in the earlier period to 9.5 per million in the later period; the rate for those aged 1–4 years increased from 5.4 per million to 6.1 per million.

The reported incidence rate for bilateral cases aged below 1 year increased from 11.4 per million in the earlier period to 14.0 in the later period; the rate for those aged 1–4 years decreased from 1.8 in the early period to 1.5 in the later period.

In figs 5–8, incidence rates in successive quinquenia are shown for unilateral and bilateral cases aged below 1 year and 1–4 years. Data for unknown laterality are excluded.

There was a significantly increasing trend for unilateral cases aged below 1 year (AAPC = 2.5%; $p<0.0001$); for the age group 1–4 years, the rate increased at an average of about 0.5% per year, though the trend was not statistically significant ($p = 0.09$) and not regular. For bilateral cases, no statistically significant trend was observed in either age group.

Heritability

Details of the cases by age, laterality, family history and heritability are shown in table 3.

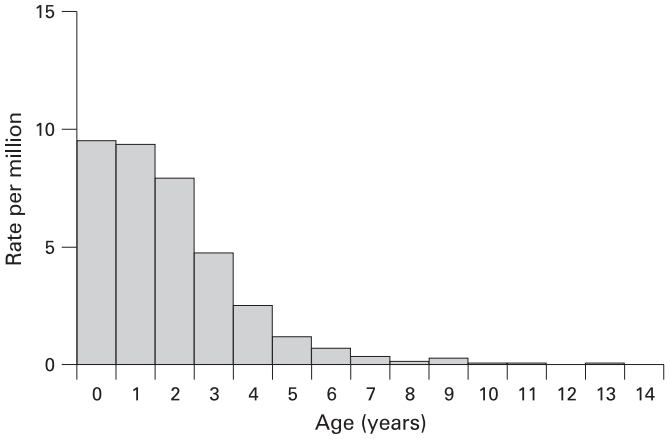

Figure 2 Unilateral retinoblastoma. Incidence rates by single year of age: England, Scotland and Wales 1983–2002.

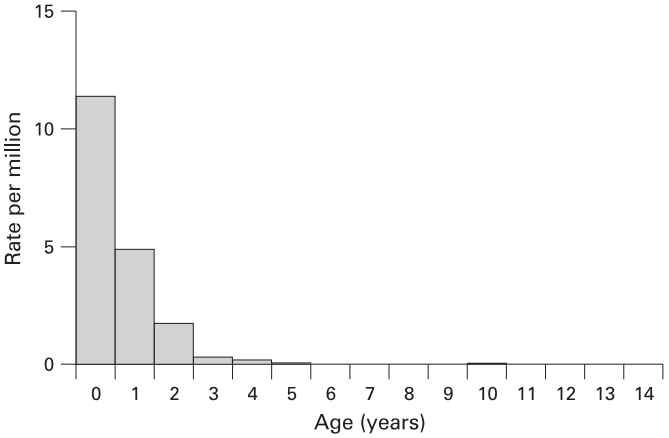

Figure 3 Bilateral retinoblastoma. Incidence rates by single year of age: England, Scotland and Wales 1963–1982.

In our series, 653 cases were classified as heritable (40.8%) and 948 assumed to be non-heritable (59.2%).

Of the 653 heritable cases 71 (10.9%) were unilateral with a family history; these 71 cases constitute 7.1% of all unilateral cases. Of the 581 bilateral cases, 205 (35.3%) had a family history; one case of unknown laterality had a family history. As explained in the Methods section, the true numbers of unilateral cases that are heritable will be higher than those reported here.

DISCUSSION

Incidence rates

The incidence rates for unilateral and bilateral retinoblastoma shown in table 2 are similar to those for other developed countries.[15]

Detailed age distributions are presented in figs 1–4. The age distributions are different for unilateral cases in the two 20-year periods shown in figs 1, 2. This is largely because of the increasing rate at ages below 1 year shown in fig 5.

Time trends in incidence

The increase in incidence (mainly for unilateral cases aged below 1 year at diagnosis) reported in this paper could be real, or attributable to improvements in diagnosis of retinoblastoma, or to improved registration and ascertainment of cases. One consequence of this increase is that, as can be seen from figs 1, 2, it creates a marked difference in the two age distributions for

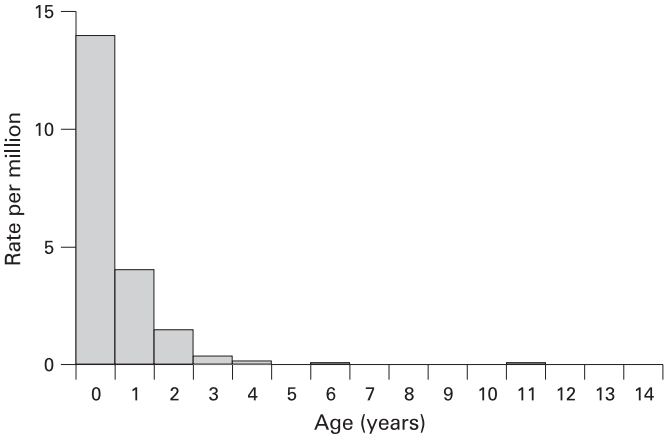

Figure 4 Bilateral retinoblastoma. Incidence rates by single year of age: England, Scotland and Wales 1983–2002.

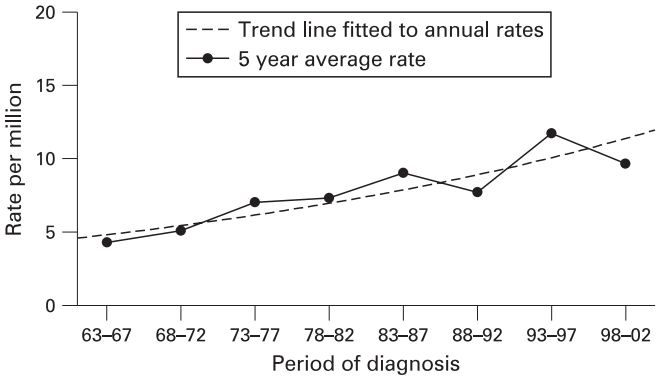

Figure 5 Unilateral retinoblastoma. Incidence at ages below 1 year: England, Scotland and Wales 1963–2002.

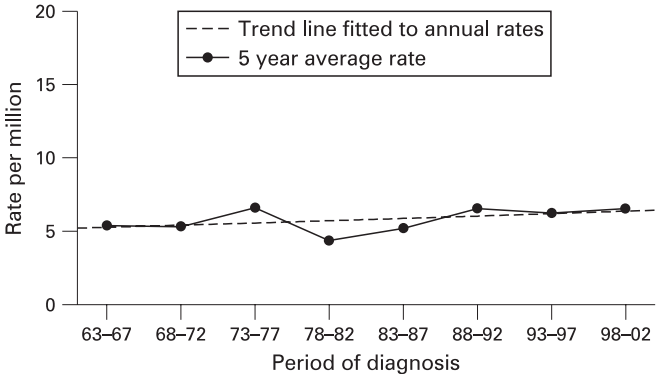

Figure 6 Unilateral retinoblastoma. Incidence at ages 1 to 4 years: England, Scotland and Wales 1963–2002.

the unilateral cases based on data from the two 20-year periods covered by the present study. Inferences concerning aetiology based on the shape of the age distributions must make due allowance for the trends in different age groups.

Percentage of heritable cases

Of the total 1601 cases, 653 (ie, 41%) are known to be heritable. If, as has been suggested earlier, 15% of unilateral cases without a family history are heritable, the number of heritable cases would be about 790 (ie, 49%), though this could be an overestimate if there was some selection in cases for whom information on molecular genetics was available.

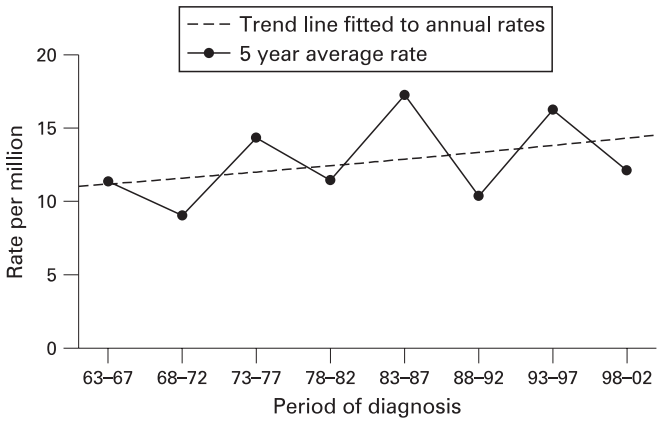

Figure 7 Bilateral retinoblastoma. Incidence at ages below 1 year: England, Scotland and Wales 1963–2002.

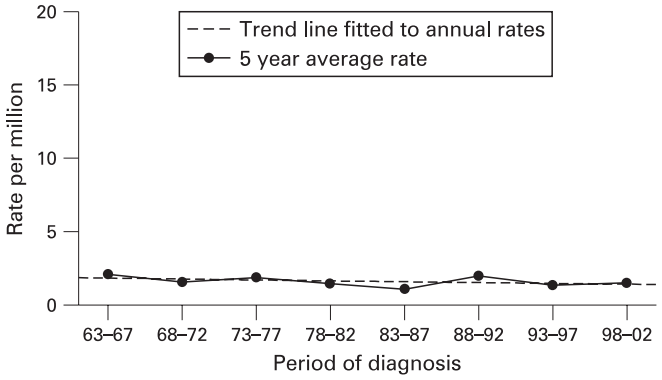

Figure 8 Bilateral retinoblastoma. Incidence at ages 1 to 4 years: England, Scotland and Wales 1963–2002.

Aetiological factors

There are international variations in incidence that could be due to differences in exposure to viruses, for example Orjuela *et al*,[16] though the evidence has been disputed by Gillison *et al*[17] and Hack *et al*.[18] It has also been suggested that they may be associated with variations in latitude and hence perhaps exposure to sunlight,[19] though this explanation has been questioned by Jemal *et al*.[20]

In summary, no environmental causes have been convincingly identified for either heritable or non-heritable retinoblastoma. The trend in incidence for unilateral cases, if it is not

Table 3 Number of cases with and without a family history (FH) of retinoblastoma, by age and laterality: England, Scotland and Wales 1963–2002

Age at diagnosis (years)	Unilateral			Bilateral			Unknown laterality			Total no of heritable cases
	+FH	No FH	Total	+FH	No FH	Total	+FH	No FH	Total	
0	33	193	226	166	212	378	0	4	4	411
1	18	235	253	26	109	135	0	7	7	153
2	11	229	240	6	43	49	1	4	5	61
3	4	134	138	1	9	10	0	4	4	14
4	3	67	70	3	2	5	0	1	1	8
0–4	69	858	927	202	375	577	1	20	21	647
5–9	2	64	66	1	1	2	0	1	1	4
10–14	0	5	5	2	0	2	0	0	0	2
All ages	71	927	998	205	376	581	1	21	22	653

merely due to improved ascertainment, suggests there may be an increasingly common exposure to an environmental factor.

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Competing interests: None.

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