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Incidence and survival of retinoblastoma in Taiwan: a nationwide population-based study 1998–2011

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ABSTRACT

Objective To study the epidemiology of retinoblastoma in Taiwan from 1998 to 2011.

Design This was a retrospective population-based cohort study using the Taiwan National Health Insurance Research Database.

Results The present study included 154 patients (92 males, 62 females) with retinoblastoma and the documented overall retinoblastoma incidence was 1 in 17 373 live births without a notable trend over the study period. The incidence per million live births examined by gender was 65.8 for males and 48.5 for females. The age-specific sex ratio increased from 1.4 at age younger than 1 year to 3.0 above age 4 years. Enucleation was performed in 109 (70.8%) children with retinoblastoma, and it was more prevalent in males than in females (77.2% vs 61.3%, p=0.0335). Multivariate Cox regression analyses with adjustment for diagnostic age, sex, and birth year elucidated that enucleation was a significant factor associated with survival (OR 0.27, 95% CI 0.10 to 0.61).

Conclusions The incidence of retinoblastoma in Taiwan exhibited no marked trend over time. There were more cases of males than females and the male-to-female rate ratio increased with age. Survival outcome was significantly associated with the intervention of enucleation.

INTRODUCTION

Retinoblastoma is the most frequent paediatric eye cancer. It is very aggressive and life-threatening if untreated, but it is curable if detected at an early stage.[1] Early diagnosis and prompt treatment are vital for children with this devastating eye malignancy in order to preserve their life and sight.

Population-based studies of the epidemiology of retinoblastoma have been conducted in several countries, such as the USA,[2 3] Great Britain,[4] Europe,[5] Singapore,[6] Japan[7] and Korea.[8] The incidence rates of retinoblastoma ranged approximately 40–60 per million live births worldwide, which corresponds to 1 per 16 000–24 000 live births.[2 3 5–9] Taiwan has reported an incidence of 1 per 21 691 live births during 1979–2003,[9] but no updated information on retinoblastoma is available for the past decade. Additionally, survival rates for retinoblastoma vary among different countries and races. The overall 5-year survival is 83%–97% in some developed countries such as Great Britain,[4] Mexico,[10] Singapore[6] and USA,[11] but much lower (20%–48%) in developing countries such as Africa and India.[12 13]

Retinoblastoma management in the past decades aimed to save the life, eye, vision and cosmetics of the child, in order of priority. Current therapeutic measures for retinoblastoma include enucleation (eye removal), external beam radiotherapy, systemic chemotherapy for metastasis and chemoreduction with or without focal tumour consolidation using various focal therapies, such as thermotherapy, cryotherapy, laser photocoagulation and plaque radiotherapy.[1 14–17] Recently, intra-arterial chemotherapy and intravitreal chemotherapy have evolved as impressively effective therapies for managing advanced and refractory retinoblastoma because of their ability to save globes which would have been enucleated.[17–20] However, the modality of enucleation still remains a vital option for retinoblastoma treatment, especially for the eye with intraocular retinoblastoma of International Intraocular Retinoblastoma Classification (IIRC) group E.[21]

This study aimed to update the incidences of retinoblastoma in Taiwan between 1998 and 2011 using a nationwide population-based data set. We also investigated the survival of patients with retinoblastoma and its associated factors.

MATERIALS AND METHODS

Data sources

The data of this population-based study were obtained from the Taiwan's National Health Insurance Research Database (NHIRD). Taiwan started a National Health Insurance (NHI) programme in 1995 that provides health care for more than 99% of the entire population. The NHIRD contains detailed information on inpatient and outpatient claims, such as demographic data, dates of clinical visits, diagnostic codes, details of prescriptions and expenditure amounts. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code was used in the NHIRD to define diagnostic diseases. However, personal information, including lifestyle, habits or family history, is not available from the NHIRD. The Institutional Review Board of our institution has reviewed and approved this study. No informed consent was necessary because this study analysed the secondary data.

Study population and definitions

All enrolees who were first diagnosed with retinoblastoma (ICD-9-CM code: 190.5) were obtained from the entire population of inpatient data of the NHIRD. We only included patients who had applied for a catastrophic illness certificate of retinoblastoma (Registry of Catastrophic Illness Database, a subpart of the NHIRD) or received clinical treatment during the observation period to confirm the diagnostic accuracy of retinoblastoma.

At least two specialists validate the application of catastrophic illness certificates on the basis of careful examinations of medical records and laboratory and imaging studies. All the enrolled cases were born between 1998 and 2009, and were followed up until 2011 to ensure every case has been followed up for at least 2 years.

Statistical analysis

We calculated the incidences of retinoblastoma (per 1 million person-years) based on their birth year and further reported stratified analyses by sex and subperiods of calendar years between 1998 and 2009. The numerator of incidence was the number of incident cases within the respective birth year period. The denominator was the population of all infants born alive between 1998 and 2009 according to the Statistical Yearbook of the Interior from the Taiwan Department of Statistics. Male and female incidence was calculated from per male and female born children, respectively. Temporal trends of incidences were investigated using Poisson regression model. Crude and adjusted ORs with 95% CI were estimated for variables associated with overall mortality by using univariate and multivariate Cox regression models. Four variables including diagnostic age, sex, period of birth year and enucleation were analysed in the multivariate model. Data analysis was performed by using SPSS software, V.21 of the SPSS System for Windows (IBM Corporation, Somers, New York, USA). A two-tailed $p<0.05$ was considered significant.

RESULTS

Diagnostic age distribution

A total of 154 patients (92 males, 62 females) with retinoblastoma in Taiwan were identified from a population of children who were born alive between 1998 and 2009 based on the aforementioned criteria. The majority of cases appeared by 5 years of age, and no case was diagnosed later than 10 years of age (figure 1). The accumulated percentages of case numbers attained were 68.2%, 86.4% and 96.1% by 2, 3 and 5 years of life, respectively.

Trend of incidences during 1998–2009

The overall incidence of retinoblastoma was 57.56 per million live births (table 1), which corresponded to 1 per 17 373 live births. The incidence for males and females was 65.81 and 48.53 per million live births, respectively. Although the incidence for males was increased slightly across the study period, the female incidence seemed stable and Poisson regression analyses showed no significant change in the incidence rates of time trends for either males or females (figure 2).

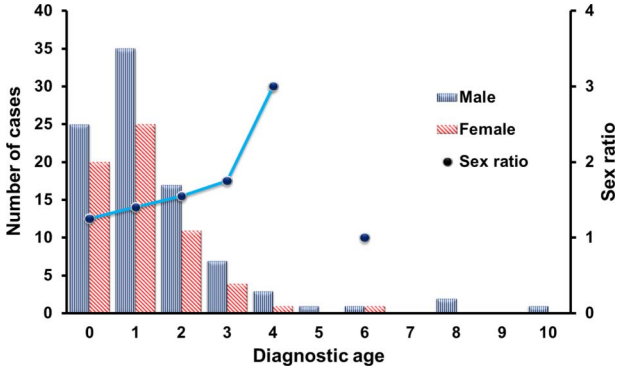

Figure 1 Number and sex ratio of the retinoblastoma cases by diagnostic age.

Table 1 Incidence of retinoblastoma in Taiwan from 1998 to 2009

Parameter	No. of cases	Percentage	Incidence rate*	Relative risk	95% CI
All patients	154	100.00	57.56	–	–
Sex					
Female	62	40.26	48.53	Ref.	–
Male	92	59.74	65.81	1.36	0.98 to 1.88
Birth year					
1998–2000	45	29.22	55.03	Ref.	–
2001–2003	35	22.73	49.96	0.91	0.58 to 1.41
2004–2006	38	24.68	63.85	1.16	0.75 to 1.79
2007–2009	36	23.38	64.04	1.16	0.75 to 1.80

*Incidence rate is the number of cases divided by per million live births.

Dynamic diagnostic age-specific sex ratio across ages

The overall ratio of male-to-female incidence was 1.36 (table 1). The age-specific sex ratio increased from 1.4 at age younger than 1 year to 3.0 above age 4 years (figure 1).

Factors associated with fatality rate

The multivariate analysis that disclosed cases receiving enucleation showed significantly lower risk of death with an OR of 0.27 (95% CI 0.10 to 0.61), but the diagnostic age, sex and calendar year of the birth cohorts were not associated with fatality rate (table 2). Enucleation was performed in 109 (70.8%) children with retinoblastoma, and it was more prevalent in males than in females (77.2% vs 61.3%, $p=0.0335$).

DISCUSSION

This was a nationwide population-based study which may avoid selection bias and provide a reliable estimate of the incidence of a rare disease like retinoblastoma. This study demonstrated that 70% of the total cases were diagnosed before 2 years of age and as few as 4% of cases were identified after 5 years of age. There was a male predominance with a rising male-to-female sex ratio as age increases. The intervention of enucleation was associated with a significantly lower fatality, compared with that among those retinoblastoma victims without eye removal surgery.

The present work demonstrated that the incidence rate of retinoblastoma in Taiwan during 1998–2011 was 1 per 17 373 live births,[9] which is similar to that in other countries, such as 1 per 16 642 live births in Northern Europe,[22] 1 per 16 938 live

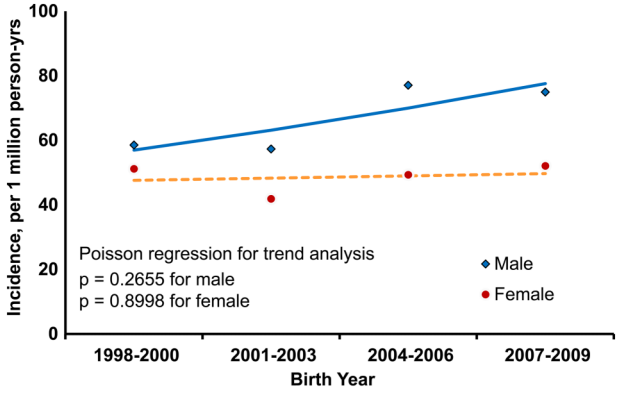

Figure 2 The incidence of retinoblastoma per 1 million patient-years. The solid line indicates male patients, and the dotted line indicates female patients.

Table 2 Multivariable logistic regression analysis of fatality for cases with retinoblastoma

	Survival (N=128)	Death (N=26)	Mortality (%)	Univariate analysis		Multivariate analysis	
				OR	95%CI	OR	95% CI
Diagnostic age							
<2 years	90	15	14.3	Ref.	–	Ref.	–
≥2 years	38	11	22.4	1.74	0.73–4.13	1.91	0.76 to 4.76
Sex							
Female	50	12	19.4	Ref.	–	Ref.	–
Male	78	14	15.2	0.75	0.32–1.75	0.90	0.37 to 2.23
Birth year							
1998–2004	63	17	21.3	Ref.	–	Ref.	–
2005–2011	65	9	12.2	0.51	0.21–1.24	0.47	0.19 to 1.18
Enucleation							
No	31	14	31.1	Ref.	–	Ref.	–
Yes	97	12	11.0	0.27	0.12–0.65	0.25	0.10 to 0.61

births in Korea,[8] 1 per 17 000 live births in the Netherlands,[23] 1 per 19 780 live births in Japan[7] and 1 per 18 000–24 000 live births in the USA.[2 3] But the present incidence was higher than the incidence of 1 per 21 691 live births reported in a previous study in Taiwan during 1979–2003.[9] This discrepancy of incidence may be due to a better accessibility to health care after the implementation of the NHI programme since 1995. One study has reported that the NHI improved the treatment and survival of patients with retinoblastoma in Taiwan,[24] because more cancer cases can be well treated without worry about the financial problems. Though the previous study has reported an increasing trend in the incidence of retinoblastoma over the 25-year study period (1979–2003) in Taiwan, the present study found that the trend of incidences of retinoblastoma was stable after the intervention of NHI in Taiwan.

One recent paper has predicted the incidence trends of retinoblastoma in the Asia-Pacific region, based on the assumption that the incidence of retinoblastoma among live-born children is uniform in all countries.[25] The predicted number may be used as a surrogate to evaluate the completeness of registration for retinoblastoma. Interestingly, the predicted number by its formulation is 160, close to the observed number of 154 in our study.

The retinoblastoma incidence rate among boys was higher than that among girls (table 1), which is consistent with the study of Wong *et al*[3] but different from some previous studies of no sex difference.[2 6 13 23] One explanation for this sex difference might be related to cultural behaviour. For example, sons are more favoured than daughters in Taiwan,[26] which might cause more male children to be brought to medical care than female children, corresponding to our observation that females significantly underwent less enucleation than males. It could consequently result in a higher mortality in females than males (table 2). Therefore, the small difference between the predicted number (n=160) and observed number (n=154), which suggests a little under-reporting, might be predominantly from girls as a result of son preference in Taiwan.[26] Notably, we found that the male-to-female rate ratio of retinoblastoma was age dependent and increased gradually from 1.4 in children aged 0–1 years to 3.0 above age 4 years. The true reason for the changing sex rate ratio is not clear, but this type of dynamic phenomenon in the sex rate ratio has already been noted in other childhood diseases such as infantile hypertrophic pyloric stenosis and intussusception.[27 28] The sex difference of the incidences of retinoblastoma and other childhood diseases may be genetically related.[29] However, the underlying mechanism requires further investigation.

Enucleation is the curative treatment for this devastating eye cancer, particularly for cases with clinical features suggesting a risk of extraocular spread.[30] However, the choice of performing enucleation or not may be complex because it involves several factors including clinical situations and families' preference. For example, some parents refuse enucleation because of their belief in alternative treatments, culture and social stigma.[30] The multivariate regression model in our study showed that the surgical intervention of enucleation was significantly associated with the decrease in mortality (OR=0.27, 95% CI 0.10 to 0.61). Early identification of this childhood eye tumour is essential in order to reduce morbidity and mortality related to this ocular malignancy.[1] A previous study found that if enucleation was performed longer than 3 months after diagnosis, it would result in worse outcome.[31] Some developed countries have justified the use of chemoreduction and local therapy because these interventions allow the patient to avoid radiation-related secondary malignancies that develop in as many as 11% of irradiated patients after 30 years.[32] However, enucleation in low-resource countries, where most children with retinoblastoma live, is often the only available curative treatment.[33 34] Even in resource-rich countries, the evidence-based curative therapy for IIRC Group E eyes is enucleation.[21]

There were some limitations of this present study. First, this was a retrospective study to analyse reimbursement data which did not include family history and personal information like lifestyle, socioeconomic status, living area, signs or symptoms at presentation, pathologic report and genetic information. Therefore, we were unable to recognise the familial cases and the investigation of risk factors associated with mortality was inevitably affected. Second, the cancer stage and laterality were not available in the current ICD-9-CM system that prohibited us to analyse the outcomes of retinoblastoma that involved unilateral or bilateral eyes. We hope the ICD-10-CM can provide more detailed clinical information in the future. Finally, the sample size in this study might be too small to show a statistical significance; however, that does not mean absence of clinical importance.

Conclusions

In conclusion, this nationwide population-based study has updated the overall retinoblastoma incidence in the past decade

in Taiwan to 1 in 17 373 live births. The incidence exhibited no marked trend over time after the implementation of NHI in 1995. There were more male cases than female cases and the male-to-female rate ratio rose with age. The survival outcome was significantly associated with the intervention of enucleation.

Contributors All authors have contributed equally to the research, from the title to drafting of work, methodology and approval of manuscript and accept full responsibility and accountability for the same.

Competing interests None declared.

Ethics approval Institutional Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital has reviewed and approved this study.

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