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CLINICAL STUDY

Retinoblastoma in Taiwan: incidence and survival characteristics from 1979 to 2003

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Abstract

Purpose **To describe the incidence and survival rate of patients with retinoblastoma in Taiwan over a 25-year period, from 1979 to 2003.**
Methods **Cases of retinoblastoma have been reported to the Taiwan National Cancer Registry (TNCR) since 1979. Retinoblastoma data from 1979 to 2003 were retrieved from the TNCR databank for analysis of both the incidence and survival rate. Trends in the incidence rate were estimated by calculating the annual percentage change (APC).**
Results **From 1979 to 2003, a total of 380 patients (182 [47.9%] females) with retinoblastoma were identified. Of the 380 cases, 359 patients (94.5%) were diagnosed before 5 years of age. The average annual age-standardized incidence rate was 4.45 per million in children under 10 years of age and 8.58 per million in children under 5 years of age. There was a significant increasing trend in the incidence rate over the study period with an APC of 2.3% ($P = 0.035$). Before the implementation of Taiwan's National Health Insurance (NHI) Program in 1995, the mean age at diagnosis was 4.8 ± 13.3 years and the 5-year survival rate was 74.7%. After implementation of the NIH Program, the mean age at diagnosis decreased to 1.6 ± 2.1 years ($P < 0.001$) and the 5-year survival rate increased to 84.7% ($P = 0.063$).**
Conclusions **We report the first population-based study on retinoblastoma in Taiwan. There was a significant increasing trend in the incidence rate from 1979 to 2003. Since the implementation of Taiwan's NHI, the mean diagnostic age decreased.**
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Keywords: retinoblastoma; incidence; survival rate; Taiwan

Introduction

Retinoblastoma is the most common primary intraocular malignancy in children.[1] The incidence rate of retinoblastoma ranges from 1 in 15 000 to 1 in 20 000 live births worldwide,[2] and survival rate varies by country. In developed countries, the survival rate has increased from 30% in the 1930s to more than 90% in the 1990s, mainly because of advances in the therapeutic strategy.[3] In Taiwan, an earlier clinic-based study indicated that the survival rate of children with retinoblastoma increased after implementation of Taiwan's National Health Insurance (NHI) Program.[4] The influence of the NHI Program on diagnosis and survival, however, has not yet been assessed in a population-based study.

Population-based data on the epidemiology of retinoblastoma have been reported for Europe,[5] Singapore,[6] and Japan.[7] In Taiwan, the incidence rate of retinoblastoma has increased during the past two decades.[8] Therefore, we analysed the incidence trends and survival characteristics of retinoblastoma using the population-based data from the Taiwan National Cancer Registry (TNCR) obtained during 1979–2003.

Materials and methods

The TNCR, founded in 1979 by the Department of Health, is a population-based registry in which the data of cancer patients in hospitals with at least 50 beds are collected and recorded throughout the country. The registry items include patient name, national identification number, sex, age, date of diagnosis, date of death, diagnostic methods, and mode of management. The diagnostic methods were recorded as one of the following: clinical signs, laboratory data, imaging findings, endoscopic

findings, exploratory surgery findings, cytologic findings, hematopathology findings, histopathology findings, and postmortem findings. The mode of management was recorded as none, surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, supportive care, Chinese medicine, and other treatments. Duplications of the data were avoided because of the unique national identification number of Taiwanese residents. Cases of retinoblastoma, having the code 95103 according to the International Classification of Disease for Oncology,[9] were identified. In this study, data of patients with retinoblastoma between January 1979 and December 2003 collected from the TNCR were analysed.

The age- and sex-specific incidence rates were estimated based on the number of new cases per million population using mid-year population counts.[10] The annual age-standardized incidence rate was calculated by the direct method, using the 2000 world standard population as a standard.

The trends in the incidence rate for children stratified by sex under 5, 10, and 14 years of age were estimated by calculating the annual percentage change (APC) from 1979 to 2003. By definition, the APC formula represents the average percentage of increase or decrease in cancer incidence rate per year: $APC = 100 \times (e^m - 1)$, where $m = (y-b)/x$, $y = \ln$ (incidence rate), $x =$ calendar year, and b is the intercept constant. The null hypothesis that was tested was $APC = 0$, that is, $m = 0$, with a two-sided α of 0.05.

Survival time was defined as the time interval between the date of diagnosis and the date of death, or the cutoff date (31 December 2005) if the patient was still alive. The date of death was ascertained by death registration data sets from the Department of Health in Taiwan. Only TNCR cases recorded after 1984, however, were linked to the death registry database. Therefore, we were unable to determine the survival status of cases recorded before 1984, and thus only cases recorded after 1984 were included in the survival analysis.

Taiwan's NHI was established on 1 March 1995. By the end of 2003, more than 97% of the residents had joined the insurance programme.[11] Mean age at diagnosis and the 5-year survival rate before and after implementation of the Taiwan's NHI were compared. All analyses were conducted using the commercial statistical software SPSS (SPSS Inc., Chicago, IL, USA).

Results

A total of 380 cases with retinoblastoma were identified during 1979–2003 from the TNCR; 182 (47.9%) patients were females. Of the 380 cases, 362 (95.3%) were diagnosed based on pathologic findings, 12 (3.2%) on cytologic findings, and the remaining 6 (1.6%) on imaging findings. In the TNCR database, there were no further details regarding cytologic findings or imaging findings.

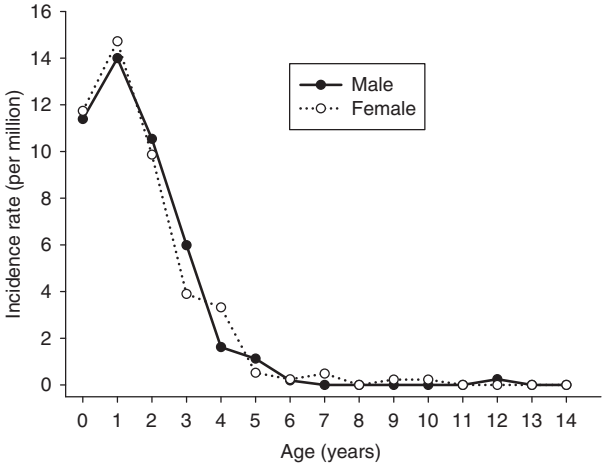

Figure 1 Age-specific incidence by single year of age and sex in children under 14 years of age from 1979 to 2003.

Age at diagnosis ranged from 0 to 81 years. Of the 380 cases, 359 (94.5%) and 365 (96.1%) were diagnosed before the age of 5 and 10 years, respectively. The incidence by year of age for boys and girls less than 14 years of age ($n = 366$) is shown in Figure 1. There was a unimodal distribution for both males and females with a peak at the age of 1 year. Before implementation of the NHI Program, mean age at diagnosis was 4.8 ± 13.3 years, which decreased to 1.6 ± 2.1 years after NHI implementation ($P < 0.001$).

The average annual crude incidence rate of retinoblastoma in Taiwan during 1979–2003 was 1 in 21 691 live births. The annual age-standardized incidence of retinoblastoma by sex for children under the age of 14 years from 1979 to 2003 is shown in Figure 2. The incidence rates did not differ significantly between males and females ($P = 0.898$). The annual age-standardized incidence rates of retinoblastoma in children under 5 years of age and in children under 10 years of age are shown in Figure 3. The average annual age-standardized rate of retinoblastoma was 8.58 per million population for children under 5 years of age and 4.45 per million population for children under 10 years of age. For children aged 14 years or younger, the average annual age-standardized rate was 2.90 per million population.

The average annual age-standardized incidence rates according to age groups of 0–4, 5–9, and 10–14 years in males were 8.56, 0.26, and 0.05 per million, respectively. For females, the average incidence rates according to age groups of 0–4, 5–9, and 10–14 years were 8.60, 0.29, and 0.04 per million, respectively. The incidence rates

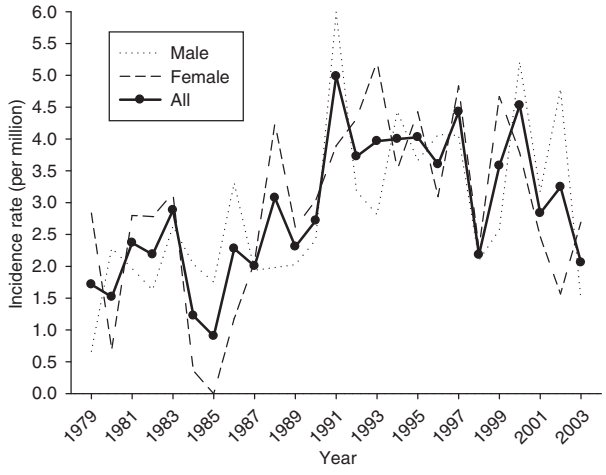

Figure 2 Age-standardized incidence rates of retinoblastoma by sex and whole population in children under 14 years of age from 1979 to 2003.

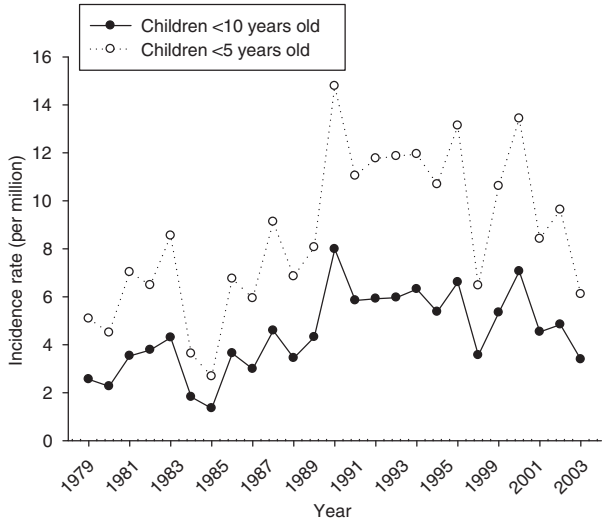

Figure 3 Age-standardized incidence rates of retinoblastoma in Taiwan from 1979 to 2003 in children under 5 years of age and in children under the age of 10 years.

according to age groups of 0–4, 5–9, and 10–14 years in the whole population were 8.58, 0.28, and 0.05 per million, respectively.

There was an increasing trend in the incidence rate. The APC was 2.3% for all patients ($P = 0.035$), 2.0% for male patients ($P = 0.054$), and 2.4% for female patients ($P = 0.195$). For children under 5 years of age and children under 10 years of age, the APC was 3.2 ($P = 0.004$) and 3.4% ($P = 0.003$), respectively. The APC was 3.5% ($P = 0.002$) for total patients under 14 years of age.

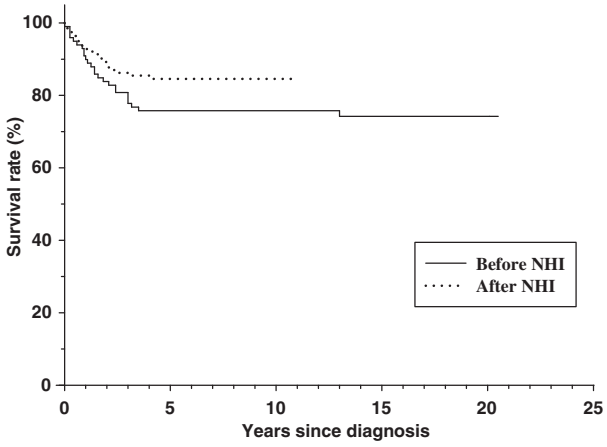

Figure 4 The survival curve of retinoblastoma before and after implementation of the Taiwan National Health Insurance Program in March 1995.

Information on the mode of management was complete and available on 123 cases during the last 8 years from 1996 to 2003. Of them, 76 cases (61.8%) received surgery only, 12 (10%) received surgery combined with chemotherapy, 2 (1.6%) received surgery combined with radiotherapy, 2 (1.6%) received surgery combined with chemotherapy and radiotherapy, 2 (1.6%) received surgery combined with other treatments, and 6 (4.9%) refused treatment. The remaining patients received radiotherapy only, chemotherapy only, chemotherapy combined with radiotherapy, or other treatments.

A total of 238 cases, diagnosed with retinoblastoma in or after 1984 were linked to the death registry database. Overall, the 5- and 10-year survival rates were 80%. All of the deaths occurred within the first 5 years after diagnosis. Figure 4 shows the survival rate before and after implementation of the NHI. Compared with the 5-year survival rate before and after implementation of the NHI, survival rate improved from 74.7 to 84.7%. This difference, however, was not statistically significant ($P = 0.063$, by a log-rank test).

Discussion

On the basis of the TNCR data, there was an increasing trend in the age-standardized incidence of retinoblastoma from 1979 to 2003. Earlier, we reported the incidence of retinoblastoma in children under the age of 5 and 10 years in Taiwan from 1979 to 1996.[8] The present analysis includes more cases over a longer period. Moreover, as the TNCR is continually updated and the data entries are regularly checked and corrected, the results reported in this study are believed to be more accurate and complete than in the earlier report.

The results of this study suggest that the incidence of retinoblastoma in Taiwan is lower than that reported in Europe. The annual age-standardized incidence rate from 1978 to 1997 in Europe[5] was 4.1 per million population in children under 14 years of age. In Asia, population-based studies on retinoblastoma have been reported for Singapore[6] and Japan.[7] In Singapore, the annual crude incidence rate is 2.4 per million population for children under the age of 10 years.[6] On the basis of the National Registry of Retinoblastoma in Japan from 1975 to 1982, the annual crude incidence is 1 in 19 780 live births.[7]

The increasing trend of the incidence rate is higher in Taiwan than in Europe (APC 1.4% in the general group and 0.8% in the paediatric group).[5] There are several possible reasons for this finding. First, improved access to medical care in Taiwan may have resulted in higher detection and diagnosis rates.[4,12,13] Taiwan's NHI is a government-sponsored NHI Program. At the end of 2003, more than 97% of Taiwan residents were enrolled and most (>97%) of the hospital and clinics in Taiwan belong to the insurance programme.[11] Children under the age of 3 years currently receive free medical care, and others receive subsidized medical care. Su *et al*[4] reported the effect of Taiwan's NHI on retinoblastoma in a medical centre. In their study, the average annual number of reported cases increased from 3.3 to 6.5 after NHI implementation, age at diagnosis decreased from 29 to 21 months, and there was a significantly higher 5-year cumulative survival rate after NHI implementation. Their results are consistent with our findings and suggest that the access to health care improved after NHI implementation. Moreover, although no comprehensive data have been collected in Taiwan to fully evaluate the NHI's effects on the access to health care, in one small cohort of 1025 adults, Cheng *et al*[12] reported that patients who were uninsured earlier had increased the number of their outpatient visits after beginning the NHI to the same level as those who were insured before implementation of the NHI. Aggregated hospital statistics indicate that the average hospital admission rate increased from 110 times per 1000 population in 1994 to 120 times per 1000 population in 1996.[13]

There are other possible reasons for the increasing incidence rate of retinoblastoma in Taiwan. The improved survival rate of retinoblastoma may increase the probability of inheritance of the *Rb1* gene, a tumour suppressor gene, which would contribute to the higher incidence rate.

The 5-year survival rate of retinoblastoma is 80% in Taiwan, which is lower than that reported in Europe (95%),[5] in the United States (>93%),[14] and in Japan (10-year survival rate was 86.7% in bilateral cases and 92.3% in unilateral cases),[7] but close to that reported in Singapore (3-year survival rate was 83%).[6] In this study, all of the deaths occurred within the first 5 years after diagnosis, a finding consistent with data from Singapore.[6] Despite the survival rate being lower in Taiwan compared with Western developed countries, Taiwan's NHI has contributed to earlier diagnosis, which may improve the survival rate.

The surgery rate of retinoblastoma in Taiwan was 61.8% from 1996 to 2003, which was higher than that in Singapore (47.7%)[6] and in Japan (48.5%),[7] indicating that surgery is the main strategy for retinoblastoma in Taiwan.

In this study, the diagnostic age of retinoblastoma cases ranged from 0 to 81 years. A total of 13 (3.4%) cases were diagnosed after the age of 20 years, and all of these diagnoses were based on histopathologic findings. It is very likely that these atypical cases were regressed retinoblastoma that had reactivated or undergone malignant changes of retinoma.[15] We were unable to obtain more detailed clinical information on these atypical cases because there was no other relevant information available in the TNCR database.

There are some limitations to this study. First, cases linked to the death registry database were only available for those diagnosed at the beginning of 1984, which limited the power of our survival analysis. Moreover, survival rate in patients receiving different treatments cannot be assessed and compared, because of the lack of complete information regarding treatment following diagnosis. Finally, we were unable to determine an association between survival rate and laterality or family history due to the lack of recorded relevant information in the TNCR. Further studies of retrospectively or prospectively collected data on family history and the laterality of retinoblastoma are needed and would improve the usefulness of the TNCR data.

In summary, these nationwide data suggest that the incidence rate of retinoblastoma increased between 1979 and 2003. Advances in medicine and accessibility to health care are expected to continue to improve the survival rate of retinoblastoma in Taiwan.

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