Retinoblastoma Incidence Patterns in the US Surveillance, Epidemiology, and End Results Program

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IMPORTANT. Several studies have found no temporal or demographic differences in the incidence of retinoblastoma except for age at diagnosis, whereas other studies have reported variations in incidence by sex and race/ethnicity.

OBJECTIVE. To examine updated US retinoblastoma incidence patterns by sex, age at diagnosis, laterality, race/ethnicity, and year of diagnosis.

DESIGN, SETTING, AND PARTICIPANTS. The Surveillance, Epidemiology, and End Results (SEER) databases were examined for retinoblastoma incidence patterns by demographic and tumor characteristics. We studied 721 children in SEER 18 registries, 659 in SEER 13 registries, and 675 in SEER 9 registries.

MAIN OUTCOMES AND MEASURES. Incidence rates, incidence rate ratios (IRRs), and annual percent changes in rates.

RESULTS. During 2000-2009 in SEER 18, there was a significant excess of total retinoblastoma among boys compared with girls (IRR, 1.18; 95% CI, 1.02 to 1.36), in contrast to earlier reports of a female predominance. Bilateral retinoblastoma among white Hispanic boys was significantly elevated relative to white non-Hispanic boys (IRR, 1.81; 95% CI, 1.22 to 2.79) and white Hispanic girls (IRR, 1.75; 95% CI, 1.11 to 2.91) because of less rapid decreases in bilateral rates since the 1990s among white Hispanic boys than among the other groups. Retinoblastoma rates among white non-Hispanics decreased significantly since 1992 among those younger than 1 year and since 1998 among those with bilateral disease.

CONCLUSIONS AND RELEVANCE. Although changes in the availability of prenatal screening practices for retinoblastoma may have contributed to these incidence patterns, further research is necessary to determine their actual effect on the changing incidence of retinoblastoma in the US population. In addition, consistent with other cancers, an excess of retinoblastoma diagnosed in boys suggests a potential effect of sex on cancer origin.

R etinoblastoma accounts for approximately 11% of cancers occurring in the first year of life, with 95% diagnosed before 5 years of age. The origin of retinoblastoma involves a 2-hit mutational inactivation of the retinoblastoma gene RB1 (OMIM 614041). In heritable cases (with a family history of retinoblastoma, known germline mutation, or multifocal disease), 1 hit is inherited as a germline mutation. Because only 1 additional hit is required in a somatic cell, heritable retinoblastoma occurs at a younger age relative to nonhereditary cases, which require 2 hits in somatic cells. Individuals with heritable retinoblastoma are also much more likely to develop multiple tumors, resulting in unilateral multifocal or bilateral disease, which has been used as a surrogate for heritable disease in the absence of RB1 mutation testing. With a well-established genetic origin, no significant changes in overall US retinoblastoma rates from the mid-1970s through 2004 have been reported. Analyses using incidence data through the 1990s, however, revealed increasing rates among children younger than 1 year. Higher incidence was also reported among females than males, blacks than whites, and white Hispanics than non-Hispanics. Cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) program are now available for 2005-2009. Our objective was to examine updated US retinoblastoma incidence patterns by sex, age at diagnosis, laterality, race/ethnicity, and year of diagnosis.
Methods

The coverage of the SEER program has expanded throughout the years from 9 to 13 and, most recently, to 18 population-based cancer registries for cases diagnosed since 1975, 1992, and 2000, respectively. The original SEER 9 registries included Atlanta, Georgia; San Francisco–Oakland, California; Detroit, Michigan; Seattle–Puget Sound, Washington; and Connecticut, Hawaii, Iowa, New Mexico, and Utah. The SEER 13 registries included the original 9 plus Los Angeles and San Jose–Monterey, California; rural Georgia; and the Alaska Natives registry. The SEER 18 registries added the rest of California, the rest of Georgia, Kentucky, Louisiana, and New Jersey. During 2000, the populations 5 years or younger were 1.8 million in SEER 9, 2.8 million in SEER 13, and 5.6 million in SEER 18. To analyze the most recent and largest SEER data set, we used the SEER 18 database. No institutional review board approval or informed consent was required for this study. We included cases classified as retinoblastoma according to the International Classification of Diseases for Oncology, Third Edition, morphology codes 9510/3 through 9513/3. Because family history is not available in SEER data, we used bilaterality as a surrogate of heritable retinoblastoma. After we excluded the few individuals with retinoblastoma among American Indian/Alaska Natives, of unknown race/ethnicity (n = 23), or of unknown laterality (n = 27), there were 721 children younger than 5 years diagnosed as having retinoblastoma.

Age-adjusted (2000 US standard population) incidence rates were calculated using SEER*Stat software and expressed as retinoblastoma cases per 1 000 000 person-years. Rates were then stratified by sex, age at diagnosis, laterality, race/ethnicity (white, black, or Asian/Pacific Islander, with whites further categorized according to Hispanic ethnicity), and year of diagnosis.

We calculated male–female incidence rate ratios (IRRs) and racial/ethnic IRRs with white non-Hispanics as the reference group. The IRRs and their 95% CIs were calculated using SEER*Stat; an IRR is statistically significant if the 95% CI does not include 1.00. Although other SEER databases contained fewer registries and cases than SEER 18, for longer temporal perspectives, analyses were performed again in SEER 13 (1992-2009, n = 659) and SEER 9 (1975-2009, n = 679). Rates based on small numbers of cases are more unstable than those based on larger numbers; we have used a cut point of 10 cases to flag less stable rates.

Incidence trends were estimated using a weighted log-linear model to calculate annual percent changes (APCs) and 95% CIs using Joinpoint Regression software. Because the annual rates were based in many instances on small numbers of cases, we allowed at most one inflection, or joinpoint, indicating a statistically significant increase or decrease in the trend, to be fit when determining the trends in incidence. A trend was reported with a joinpoint if at least one segment had an APC estimate that was significantly different from zero. Two-sided tests for statistical significance were at the P < .05 level.

Results

During 2000-2009 in SEER 18, the total retinoblastoma incidence rate (per 1 000 000 person-years) was 13.2 among boys and 11.2 among girls, giving a significantly elevated male-female IRR of 1.18 (95% CI, 1.02 to 1.36) (Table). Incidence rates for unilateral cases were more than twice those for bilateral cases among boys and girls, and male-female IRRs were elevated but not significantly. Only the rate for bilateral cases among white Hispanic boys was significantly elevated compared with white Hispanic girls (IRR, 1.75; 95% CI, 1.11 to 2.91). Retinoblastoma incidence was uniformly lowest among white non-Hispanics, and only the male incidence of bilateral retinoblastoma among white Hispanics was significantly higher than among white non-Hispanics (IRR, 1.81; 95% CI, 1.22 to 2.79). The incidence rates for unilateral and bilateral retinoblastoma diagnosed at 1 to 4 years of age were significantly lower than those at younger than 1 year among both boys and girls.

To further understand the significant results in the Table, we compared incidence rates in SEER 13 during 1992-2000 and 2001-2009 (data not shown). Because of the small number of bilateral retinoblastoma cases diagnosed in SEER 13, cases were divided into 2 equal groups of 9 calendar years of diagnosis. Total retinoblastoma incidence among boys was nonsignificantly higher than among girls during 2001-2009 (IRR, 1.07; 95% CI, 0.85 to 1.32) and lower during 1992-2000 (IRR, 0.95; 95% CI, 0.77 to 1.18), reflecting a small increase in the rate among boys from 12.7 to 12.9 and a decrease among girls from 13.3 to 12.1. The recent excess bilateral retinoblastoma incidence among white Hispanic boys was due to a more rapid decrease in the incidence rates among white non-Hispanic boys from 3.9 to 2.7 (IRR, 0.69; 95% CI, 0.35 to 1.29) than the decrease among white Hispanic boys of 5.6 to 5.3 (IRR, 0.95; 95% CI, 0.50 to 1.81). There was also a more rapid decrease among white Hispanic girls from 4.3 to 3.6 (IRR, 0.84; 95% CI, 0.39 to 1.86) compared with white Hispanic boys.

We further investigated temporal patterns in overall retinoblastoma incidence by race/ethnicity in all 3 SEER registry groups (Figure 1). Although in some instances the findings were based on small numbers of cases, Figure 1 shows each of the annual rates and the fitted trend lines. Some of the individual rates vary by more than 10-fold. Among white non-Hispanics, the trends were consistent in SEER 13 (APC, −2.1%; 95% CI, −4.4% to 0.2%) and SEER 18 (APC, −2.8%; 95% CI, −6.1% to 0.6%), although the trend among whites in SEER 9 was flat (APC, 0.1%; 95% CI, −0.7% to 1.0%). The incidence trends were also flat among white Hispanics (SEER 13: APC, 0.9%; 95% CI, −2.4% to 4.3%; SEER 18: APC, 0.3%; 95% CI, −5.3% to 6.5%) and blacks (SEER 9: APC, 0.1%; 95% CI, −1.3% to 1.5%; SEER 13: APC, −0.1%; 95% CI, −3.6% to 3.9%; and SEER 18: APC, −0.1%, 95% CI, −8.3% to 8.7%). Although not significant, the trends in incidence among Asian/Pacific Islanders were downward (SEER 13: APC, −1.0%; 95% CI, −5.0% to 3.2%; SEER 18: APC, −2.7%; 95% CI, −13.2% to 9.1%), similar to those among white non-Hispanics.
To investigate the temporal trends among all 3 SEER registry groups by age and laterality, we restricted the analysis to whites in SEER 9 for 1975-2009 and to white non-Hispanics for 1992 onward (Figure 2). Retinoblastoma diagnosed at younger than 1 year increased significantly during 1975-1984 in SEER 9 (APC, 6.2%; 95% CI, 0.3% to 12.5%) and then decreased sig-
nificantly during 1992-2009 in SEER 13 (APC, −3.1%; 95% CI, −5.6% to −0.5%) and nonsignificantly in SEER 18 (APC, −1.4%; 95% CI, −7.5% to 5.0%). No trends were significantly different from zero for cases diagnosed in patients at 1 to 4 years of age or for unilateral retinoblastoma, although SEER 18 rates among those 1 to 4 years old decreased by 3.6% per year (95% CI, −8.5% to 1.6%) and for unilateral disease by −3.9% per year (95% CI, −7.7% to 0.1%). Bilateral retinoblastoma incidence decreased significantly in SEER 13 during 1998-2009 (APC, −6.3%; 95% CI, −5.6% to −0.5%) and nonsignificantly in SEER 18 (APC, −0.9%; 95% CI, −8.5% to 6.3%). Bilateral retinoblastoma incidence also decreased significantly among those 1 to 4 years old (APC, −3.6% per year; 95% CI, −5.6% to −0.5%) in 2000-2009 compared with earlier years.

Discussion

The retinoblastoma incidence rate during 2000-2009 among boys in SEER 18 was significantly higher than that among girls (IRR, 1.18) (Table), in striking contrast to earlier reports of a female predominance.4,6,8,10 Further exploratory analyses revealed that this excess seems to have become apparent in 2000-2009 because of a small increase in male incidence and a decrease in female incidence. Explanation for the higher rate among boys is not readily apparent, but the elevated IRR is similar to that seen for other childhood tumors in SEER, such as acute lymphocytic leukemia (IRR, 1.18), central nervous system tumors (IRR, 1.11), and neuroblastoma (IRR, 1.06).17 Incidence rates for many adult-onset cancers are also higher in men than women, but it has been difficult to elucidate why these excesses exist.19 Further investigation is necessary to understand the effect of sex in cancer origin.

The additional retinoblastoma cases in 2004-2009 were especially valuable to estimate incidence rates for the Hispanic and Asian/Pacific Islander populations. Although US Census Bureau questionnaires now allow for multiple answers for race, extensive efforts have been made to bridge the multiple race responses into a single race for population estimates in SEER.20 The SEER registries also use the North American Association of Central Cancer Registries Hispanic Identification Algorithm to determine Hispanic ethnicity.21 The incidence rates in 2000-2009 did not differ significantly among white non-Hispanics, Asian/Pacific Islanders, or blacks. The higher rate among white Hispanic boys with bilateral retinoblastoma resulted from a less rapid incidence rate decrease among white Hispanic boys compared with the other racial/ethnic groups and sex. If there were errors in the Hispanic case and population estimates, one might have expected a similar excess among white Hispanic girls and those diagnosed as having unilateral retinoblastoma.

A major strength of our study is that SEER provides population-based data, avoiding the potential biases associated with clinic- or hospital-based case series. During 2000-2009 in SEER 18, the population aged 5 years or younger increased 9.3% from 5.6 million to 6.0 million. The increase varied considerably by racial/ethnic group with 31% among white Hispanics, 27% among Asian/Pacific Islanders, and 6% among blacks, whereas the white non-Hispanic population decreased 4%.17 The number of retinoblastoma cases would be expected to change accordingly; that is, for example, the observed number of cases among white Hispanics would have increased by 31% solely because of population growth, with no change in incidence rates. Rates in our analyses take into account the populations at risk and the number of cases to allow comparisons of risk across population groups. A limitation of our study is the rarity of retinoblastoma, which has made rigorous analyses difficult. However, although small numbers of retinoblastoma cases were reported to SEER annually in many instances, comparisons of...
the available SEER databases revealed informative temporal patterns (Figure 1 and Figure 2).

The increasing incidence of retinoblastoma during 1975-1984 among whites diagnosed as having retinoblastoma at younger than 1 year (Figure 2) is similar to a previous SEER study that reported an increasing incidence among children younger than 1 year during 1974-1991.6 The etiologic characteristics of retinoblastoma are supported by the different temporal patterns among white non-Hispanics (Figure 2), with notable decreases in all SEER 13 and SEER 18 registries since the 1990s and in SEER 9 since 1984 among those younger than 1 year and a more rapid decrease in SEER 13 for bilateral cases since 1998. In contrast, there was a steep decrease observed in SEER 18, followed by a less steep decrease in SEER 13, and almost no change in SEER 9 for unilateral cases among those 1 to 4 years of age. Although some patients with unilateral disease can inherit the genetic mutation, bilateral retinoblastoma requires a germline \( RB1 \) mutation and is usually diagnosed at younger than 1 year. Molecular genetic testing for \( RB1 \) mutations is now available. The use of highly sensitive allele-specific polymerase chain reaction results in rates of detection of \( RB1 \) mutations of 95% and 93% in bilateral and unilateral familial retinoblastoma patients, respectively.22 The American Society of Clinical Oncology recommends that genetic testing be offered when family history suggests genetic susceptibility to cancer and when testing will affect management.23 Approximately 10% of all retinoblastoma cases can be attributed to family history with autosomal dominant inheritance; the remaining heritable cases are due to de novo mutations.24 Thus, survivors of heritable retinoblastoma have a 50% risk of having a child with retinoblastoma. Prenatal testing is then clinically actionable as a termination, as a preterm delivery to begin treatment, or for initiation of early screening depending on the parents’ decision. However, a further limitation of our study is that SEER does not collect data regarding whether \( RB1 \) mutation testing was conducted for individual cases.

During the 1960s and 1970s, 3-year survival rates among patients with retinoblastoma were less than 80%.9,25 During the past several decades, the 5-year survival rates have increased significantly from 92.3% (1975-1984) to 96.5% (1995-2004).26 With improved survival of patients with retinoblastoma, more individuals with bilateral disease are surviving to potentially have children. Prenatal screening for retinoblastoma has become available since the early 1990s.27 Parents who survived retinoblastoma can test whether the fetus has inherited the mutant \( RB1 \) gene.28,29 Subsequent decisions after \( RB1 \) genetic testing can potentially explain the decrease in the retinoblastoma incidence rates we observed among white non-Hispanics diagnosed as having retinoblastoma at younger than 1 year since 1992 and among those with bilateral disease since 1998. In addition, improved technology and identification of \( RB1 \) carriers over time could contribute to the decreasing patterns among those 1 to 4 years old and those with unilateral disease. Although not significantly different, the SEER 18 APCs presented in Figure 1 similarly suggest possible differential uptake of these advances in medical technology by racial/ethnic group. The APC of −2.7 among Asian/Pacific Islanders was similar to the APC of −2.8 among white non-Hispanics, in contrast to the APCs of 0.3 for white Hispanics and −0.1 for blacks.

Conclusions

Although heritable retinoblastoma is most often diagnosed at younger than 1 year and presents as bilateral disease, further investigation is necessary to understand how the uptake of genetic testing and screening may affect retinoblastoma incidence in the United States.

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REFERENCES


