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Cancer mortality in long-term survivors of retinoblastoma

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ABSTRACT

This study examined long-term cause-specific mortality among 998 Dutch retinoblastoma survivors, diagnosed from 1862 to 2005, according to follow-up time, treatment and heredity. After a median follow-up of 30.8 years, only cause-specific mortality for second malignancies among hereditary retinoblastoma survivors was statistically significantly increased with 12.8-fold. Risk of death from second malignancies among non-hereditary survivors was not increased. Mortality rates of second malignancy among hereditary patients were non-significantly elevated with 1.6-fold for treated with radiotherapy, compared to those treated otherwise. Standardised mortality ratios (SMRs) for second malignancy among hereditary patients increased during the first three decades after retinoblastoma diagnosis. Whereas these risks decreased after three decades, the absolute excess risk (AER) increased significantly, up to 23.2 excess cases per 1000 patients/year after five decades of follow-up. Fifty years after retinoblastoma diagnosis the cumulative mortality from any second malignancy was 17.3% for hereditary patients. Very long-term follow-up of retinoblastoma patients revealed an emerging excess risk of mortality in hereditary retinoblastoma survivors. This implies that lifelong follow-up is needed, whereas at the same time, patients and their physicians must be alerted to the increased second malignancy risks.

1. Introduction

Retinoblastoma is a rare childhood cancer of the eye. The disease is caused by a *RB1* gene mutation in all patients with bilateral retinoblastoma, as well as in 10% of those with unilateral retinoblastoma.[1] Nowadays children diagnosed with retinoblastoma in the western world have excellent cure rates (up to 99%).[2] However, hereditary retinoblastoma survivors are at an exceptionally high risk of developing subsequent primary malignancies in childhood and adolescence.[3–13] So far, little information is available on long-term excess mortality among survivors of retinoblastoma.[7,14,15] Published studies include few patients with more than 50 years of follow-up, implying that mortality risk of retinoblastoma survivors has been hardly examined at ages during which death rates increase in the general population.

The national retinoblastoma registry of the Netherlands includes 1068 retinoblastoma patients diagnosed since 1862. Therefore, the registry offers a unique opportunity to analyse cause-specific mortality after long-term follow-up in a large group of retinoblastoma survivors, according to treatment and heredity.

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2. Materials and methods

2.1. Study population

The cohort analysed in this study has been described previously.[13] In brief, the cohort includes 1068 Dutch retinoblastoma patients diagnosed from 1862 to 2005. For each patient data were collected concerning demography, family history of retinoblastoma, tumour laterality, treatment for retinoblastoma (including radiotherapy fields and energy type, and chemotherapeutic agents), second and subsequent cancers and date and (underlying) cause of death. If a cohort member had died, the date, the place of death and the death certificate number were recorded. Information on the cause of death was obtained from Statistics Netherlands for all deceased cohort members up to June 2007. All causes of death in The Netherlands are coded by trained nosologists at Statistics Netherlands who use the International Classification of Diseases,[16] applicable to the particular calendar period. For this study, all registered causes of death coded on the basis of earlier revisions were reclassified according to the 10th revision.

Mortality rates in The Netherlands have been available since 1875, although only few causes of death were distinguished at that time. Throughout the decades, more and more causes of death were added to the ICD-classification and detailed cause-specific mortality rates were available since 1961. However, for skin melanoma and breast cancer reference rates were available since 1901.[17]

From the 1068 Dutch retinoblastoma patients, we excluded six patients because they apparently had retinomas (tumours with spontaneous growth arrest), 29 patients who died before 1901, and four patients with an unknown birth date, which left 1029 (96%) retinoblastoma patients eligible for this study. After extensive follow-up procedures,[13] we had to exclude 31 (3%) patients who were lost to follow-up.

Patients with bilateral disease, a positive family history of retinoblastoma or a defect in the *RB1* gene found in chromosomal/DNA analysis were classified as hereditary (39.6%). Patients with unilateral retinoblastoma, no family history of retinoblastoma or no defect found in the *RB1* gene were classified as non-hereditary (60.4%).

This study was approved by the Medical Ethics Committees of all participating hospitals, and was conducted in accordance with the principles of the Helsinki declaration.

2.2. Statistical analysis

A comparison was made between cause-specific mortality in retinoblastoma survivors and the Dutch population. In this person-years type of analysis, the ratio of the observed (O) to the expected (E) number of deaths in the study population was determined using age-, sex- and calendar period-specific mortality rates from Statistics Netherlands. To estimate standardised mortality ratios (SMRs) of breast cancer and skin melanoma, follow-up for mortality began on 1st January 1901, when reference rates for breast cancer and melanoma became available. For all other causes of death the comparison with mortality rates in the general population was restricted to those patients who were still alive in 1960, or born after 1960 ($n = 849$). Consequently, in analyses on causes of death other than breast cancer and skin melanoma, time at risk began on 1st January 1961. Follow-up ended at the date of death, date of emigration or the closing date of our study, whichever occurred first.

The SMR was calculated as the ratio of the observed to the expected number of deaths, and a 95% confidence interval (CI) was calculated based on the Poisson distribution.[18] Absolute excess risk (AER) is the most appropriate risk measure to judge which specific causes contribute most to excess mortality. The AER was calculated by subtracting the expected number of cases from the number observed, divided by person-years at risk multiplied by 1000. Multivariable Cox regression analysis was performed to quantify the effects of heredity and treatment on mortality, adjusting for confounders. Cox models were fitted using SPSS statistical software (SPSS, Chicago, IL). Cumulative risks of death by type of retinoblastoma and treatment were calculated with adjustment for competing risks of death due to other causes using S-plus statistical software (Insightful, Seattle, WA), including user-written functions.[19]

3. Results

Table 1 shows the general characteristics of the study population; retinoblastoma patients diagnosed between 1862 and 2005, who were at risk of death between January 1901 and June 2007. The median follow-up time for hereditary retinoblastoma survivors was 25.8 years (range = 0.13–79.9 years). For non-hereditary retinoblastoma survivors, the median follow-up was 34.2 years (range = 0.01–89.7 years). Most of the hereditary patients (56.2%) were treated with radiotherapy for their retinoblastoma, whereas only 6.3% of the non-hereditary patients were treated with radiotherapy. Most of the non-hereditary patients (88.2%) were treated with surgery alone. Chemotherapy was used with or without combination of radiotherapy for about 18.8% of the hereditary patients and in 2.8% of the non-hereditary patients. Of the 849 retinoblastoma patients with follow-up from January 1961, 60 (7.1%) were diagnosed with retinoblastoma from 1891 to 1929, 417 (49.1%) from 1930 to 1969 and 372 (43.8%) from 1970 to 2005. Percentages of hereditary and non-hereditary patients were similar to those for all patients (39.7% versus 60.3%, respectively). The median follow-up time for retinoblastoma patients at risk of death after 1960 was 30.8 years (range = 0.13–79.9 years) for hereditary retinoblastoma patients and 39.1 years (range = 0.01–89.7 years) for non-hereditary retinoblastoma patients.

Table 2 shows observed numbers of cause-specific deaths among hereditary and non-hereditary retinoblastoma patients, and provides separate data with SMRs for those who died after January 1, 1961. A total of 332 deaths were observed, for which 316 death certificates were obtained (95%). By far the most important cause of death was retinoblastoma ($n = 156$, 47.0%). Of these retinoblastoma deaths, more than 70% occurred before 1961. Seven patients suffered from fatal pinealoblastoma. For these patients the cause of death was recorded as retinoblastoma. Fig. 1 shows that retinoblastoma death impressively decreased over time.

Among the 849 retinoblastoma survivors at risk of death after January 1, 1961, a total of 182 deaths were observed.