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Risk of third malignancies and death after a second malignancy in retinoblastoma survivors

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ABSTRACT

Retinoblastoma patients have a strongly increased risk of second malignancies, and survivors with a third or subsequent malignancy are increasingly observed. However, it has not been examined whether survivors who developed a second malignancy have a greater risk of a subsequent malignancy. On the basis of the Dutch retinoblastoma registry, the risk of a third malignancy was compared with cancer risk in the Dutch population. Cox model analysis with a time-dependent covariate was used to compare the subsequent malignancy risk and survival among patients with and without a second malignancy. Risk of a third malignancy was increased 8-fold compared with the general population. The hazard ratio (HR) of a third malignancy after a second malignancy was more than 7-fold increased compared to the risk of a second malignancy after retinoblastoma. Radiotherapy increased the risk 3-fold. A third malignancy was associated with worse survival compared with survival of patients only diagnosed with a second malignancy (HR = 5.0). Survivors of retinoblastoma who already developed a second primary malignancy have an even higher risk of subsequent primary malignancies than retinoblastoma survivors without a second malignancy. Treating physicians and patients should be aware of this higher risk.

1. Introduction

The most common intraocular malignancy of infancy and childhood is retinoblastoma. Retinoblastoma patients can be classified into two groups: non-hereditary and hereditary. Hereditary retinoblastoma patients are those who have bilateral disease, a positive family history and/or a germline mutation in the *RB1* gene. Those with unilateral disease, no family history and no mutation found in the *RB1* gene have non-hereditary retinoblastoma. It has been well documented in large cohort studies that survivors of hereditary retinoblastoma have a strongly increased risk of second primary malignancies.[1–11] Since modern cancer treatment protocols have increased survival of patients who developed second primary malignancies, survivors with a third or subsequent malignancy are also increasingly observed. Until now, only one

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study specifically reported on the incidence and survival of third and additional malignancies.[12] However, no study has reported on the magnitude of the risk and survival of a third cancer among retinoblastoma patients. It might be speculated that those patients who already developed a second malignancy are more prone to develop subsequent malignancies, for example because of specific mutations in the *RB1* gene. Therefore, the cohort of Dutch retinoblastoma patients was used to evaluate whether retinoblastoma survivors who have already developed a second primary malignancy have a greater risk of a third malignancy, compared to the risk of a second malignancy in retinoblastoma survivors. We also evaluated to which extend a third malignancy affected survival.

2. Material and methods

2.1. Study population

This study is based on the Dutch Retinoblastoma Register. Methods used for follow-up have been described elsewhere.[7] In total, data of 1028 Dutch retinoblastoma patients diagnosed from 1862 to 2005 were collected. Data collected concerned demography, family history of retinoblastoma, tumour laterality, treatment for retinoblastoma, second and subsequent cancers, date and (underlying) cause of death, and when available mutations in the *RB1* gene.

The occurrence of any subsequent cancer was ascertained by pathology reports, hospital or physician records or death certificates. Pineoblastomas were excluded because a pineoblastoma is histologically identical to a retinoblastoma.[13] Basal cell carcinomas of the skin were also excluded because they are not registered in the Netherlands Cancer Registry.[14] Tumours were classified as in the field of radiation if they originated in the lids, orbits, periocular sinuses, temporal bones or skin overlying the temporal bone region. All other locations were classified as outside the field of radiation.

For this study we included all 1028 Dutch retinoblastoma patients of whom data were available. Of these 1028 retinoblastoma patients, 129 patients developed a second primary malignancy and consequently were at risk for a third primary malignancy.

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

Third primary malignancy risk was quantified using various measures. Time at risk for a third primary malignancy began at diagnosis of a second primary malignancy and ended on the date of third primary malignancy diagnosis, emigration, the date last known to be alive, the date of death or the closing date of our study (30th June, 2007), whichever occurred first.

The risk of a third primary malignancy in retinoblastoma survivors was first compared with cancer risk in the Dutch population. The expected number of third malignancies, taking into account the person-years of observation, was determined using age-, sex- and calendar year-specific incidence rates from the Eindhoven Cancer Registry and from the Netherlands Cancer Registry.[15–17] Cancer incidence data for the whole country were not available for the total study period. The standardised incidence ratio (SIR) was calculated as the ratio of the observed number of third primary malignancies to the expected number. The 95% confidence interval (CI) was calculated based on the Poisson distribution. The absolute excess risk (AER) was calculated by subtracting expected from observed third primary malignancies and dividing this figure by the accumulated number of person-years (expressed per 10,000 person-years).

A Cox model with a time-dependent covariate, allocating follow-up time for each patient to the 'no second primary malignancy' group until second primary malignancy occurrence, was conducted to compare the subsequent cancer risk among patients with and without a second primary malignancy. For this analysis, time at risk ended either at the date of third primary malignancy diagnosis, the date of the second primary malignancy for patients who did not develop a third malignancy or the predetermined censoring date (30th June, 2007), whichever occurred first. To compare survival after a third primary malignancy with that after a second primary malignancy, a Cox model with a time-dependent covariate, allocating follow-up time for each patient with a second primary malignancy to the 'no third primary malignancy' group until a third primary malignancy occurred, was used. For this analysis, time at risk ended at the date of death or the predetermined censoring date (30th June, 2007), whichever occurred first. The fit of the models was evaluated using residual-based graphical methods and goodness-of-fit test statistics. All *P* values were two sided; the statistical significance level was set at a $P < .05$.

Cox models were fitted with the use of Stata statistical software. All other analyses were fitted with the use of SPSS statistical software.

3. Results

The study population comprised 1028 retinoblastoma patients. The median follow-up time from the date of retinoblastoma diagnosis for all patients was 28.6 years (range = 0–89.7). Subject characteristics are shown in Table 1. Among 129 patients a second primary malignancy was diagnosed, of whom eleven patients subsequently developed a third primary malignancy. The second malignancies in this study were diagnosed between April 1941 and February 2007, and the third malignancies were diagnosed between June 1996 and June 2007. Median age at diagnosis of a third malignancy was 42.7 years (range = 16.3–77.5). All third primary malignancies occurred within 20 years after second primary malignancies diagnosis. In total, 70 second malignancies and 10 third malignancies were confirmed by pathology reports. In 59 cases the second malignancy and in one case the third malignancy could be confirmed by death certificate only. Table 2 describes the cancer diagnoses for the second and third malignancies separately. In the second primary malignancy group as well as in the third primary malignancy group, epithelial cancers were the most frequently observed malignancies, followed by soft tissue sarcoma, bone cancer, skin melanoma and other cancers, respectively. Of all second