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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

Table 1 – Characteristics of study population.

Characteristics[a]	Total group		Patients diagnosed with a second primary malignancy only		Patients diagnosed with a second and a third primary malignancy	
	No. of patients	%	No. of patients	%	No. of patients	%
Total no. of cases	1028	100	118	100	11	100
Sex						
Male	543	52.8	66	55.9	4	36.4
Female	485	47.2	52	44.1	7	63.6
Laterality						
Unilateral	692	67.3	41	34.7	4	36.4
Bilateral	336	32.7	77	65.3	7	63.6
Treatment for retinoblastoma						
Surgery alone	702	68.3	62	52.5	4	36.4
Radiotherapy	196	19.1	37	31.4	6	54.5
Radiotherapy and chemotherapy	66	6.4	16	13.6	1	9.1
Chemotherapy	25	2.4	1	0.8	0	0
Other[b]	39	3.8	2	1.7	0	0
Vital status						
Alive	667	64.9	36	30.5	6	54.5
Dead	361	35.1	82	69.5	5	45.5
Dead due to a subsequent cancer	85	23.5	80	97.6	5	100

Percentages may not run up to 100 due to rounding.

[a] In the total group 69 patients (36 males and 33 females) with unilateral retinoblastoma were indicated as having the hereditary form of retinoblastoma. In the group patients only diagnosed with a second malignancy 13 (eight males, five females), and in the group patients also observed with a third malignancy one female was indicated as hereditary. Of all hereditary unilateral cases, 56 were treated with surgery alone, seven with radiotherapy, one with radiotherapy and chemotherapy, two with chemotherapy, and of three the treatment was unknown. Except for one patient (treatment unknown, only a second malignancy), all patients diagnosed with a subsequent malignancy were treated with surgery alone. A total of 24 hereditary unilateral patients died (12 due to a second malignancy).

[b] Other treatments include: 13 patients who did not receive any treatment (retinoblastoma patients diagnosed before 1930); three patients treated with photocoagulation, and 23 patients of whom the treatment is unknown (17 cases had unilateral retinoblastoma).

Table 2 – Cancer site specific data of study population.

	Diagnosed as second primary malignancy ($n = 129$) No. of cancers (%)	Diagnosed as third primary malignancy ($n = 11$) No. of cancers (%)
Cancer site[a]		
Soft tissue	28 (21.7)	3 (27.3)
Bone cancer	18 (14.0)	2 (18.2)
Skin melanoma	14 (10.9)	2 (18.2)
Epithelial cancer[b]	56 (43.4)	4 (36.4)
Other[c]	13 (10.1)	0 (0)

[a] Of all second malignancies diagnosed among hereditary unilateral subjects, three were soft tissue, one skin melanoma, nine epithelial cancers and one other cancer (leumaemia). Only one soft tissue sarcoma was diagnosed as a third malignancy among a hereditary unilateral subject.

[b] Epithelial cancers include cancers of lung, breast, bladder, prostate, cancer of the digestive organs (stomach, colon, small intestine, rectum and pancreas), and cancers of uterus, ovary and kidney and other unspecified or unknown cancers of the urinary organs.

[c] Other cancers include three cancers not otherwise specified, two brain cancers (no pinealoblastoma), two non-Hodgkin lymphomas, two leukaemia's, one Hodgkin lymphoma, one multiple myeloma, one squamous cell carcinoma of skin and one other malignant neoplasm of skin.

primary malignancies diagnosed, 22 (36.7%) were located within the field of radiation, whereas only 1 (9%) third primary malignancy was located within the field of radiation. Data of the 11 patients who developed a third primary malignancy are presented in Table 3.

In patients who developed a second primary malignancy after hereditary retinoblastoma, the risk of a third primary malignancy was increased 8-fold (standardised incidence ratio (SIR) = 8.5; 95% CI = 3.7–16.7) compared to the general population, with an excess of 202 malignancies per 10,000 person-years. Also, an increased risk was observed among non-hereditary retinoblastoma subjects (SIR = 6.0; 95% CI, 1.3–17.7; absolute excess risk (AER) = 403 per 10,000 person-years). All third primary malignancies occurred within 20 years after second primary malignancy diagnosis.

Table 3 – Data of the 11 retinoblastoma subjects who were observed with a third malignancy.

Subject No.	Gender	Laterality of retinoblastoma[a]	Treatment for retinoblastoma	Site of second malignancy (Location)	Age (years) at second malignancy diagnosis	Site of third malignancy (Location)	Age (years) at third malignancy diagnosis	Vital status
1	Male	Unilateral	Surgery	Epithelial (Lung)	69.9	Epithelial (Bladder)	77.5	Alive
2	Female	Unilateral	Surgery	Epithelial (Bladder)	69.8	Soft tissue (Retroperitoneum)	70.2	Alive
3	Male	Unilateral	Surgery	Other (Chronic lymphoid leukaemia)	58.0	Epithelial (Nasopharynx)	60.5	Dead
4	Male	Unilateral	Surgery	Soft tissue (Orbita)	55.7	Epithelial (Lung)	59.6	Dead
5	Female	Bilateral	Radiotherapy	Epithelial (Breast)	42.8	Soft tissue (Uterus)	54.8	Alive
6	Female	Bilateral	Radiotherapy	Skin melanoma (Knee)	36.9	Soft tissue (Uterus)	42.0	Alive
7	Female	Bilateral	Radiotherapy	Bone (Knee)	18.4	Bone (Femur)	35.8	Dead
8	Female	Bilateral	Radiotherapy	Soft tissue (Bladder)	32.5	Epithelial (Uterus)	42.7	Alive
9	Male	Bilateral	Radiotherapy	Skin melanoma (Arm)	25.5	Skin melanoma (Back)	38.5	Dead
10	Female	Bilateral	Radiotherapy and chemotherapy	Bone (Femur)	25.9	Skin melanoma (Trunk)	33.4	Alive
11	Female	Bilateral	Radiotherapy	Soft tissue (Zygoma)	8.0	Bone (Orbita)	16.3	Dead

[a] Of the unilateral patients, one patient (subject No. 2) had family members with retinoblastoma and was therefore indicated as hereditary. The other three unilateral patients had no family members with the disease and were indicated as non-hereditary cases. For these patients no DNA analysis was available.

Adjusted for retinoblastoma type and treatment, the subsequent cancer risk after a second primary malignancy was increased more than 7-fold (HR = 7.6; 95% CI = 3.9–14.8) (Table 4). Treatment with radiotherapy or a combination of radiotherapy and chemotherapy statistically significantly increased the risk of subsequent malignancy (HRs of 2.9 and 4.5, respectively). Age did not confound the association between cancer history (only retinoblastoma versus retinoblastoma and a second primary malignancy) and the risk of a subsequent malignancy.

The occurrence of a third malignancy was associated with worse survival compared with having only a second malignancy. Adjusted for type of malignancy, a third malignancy increased the risk of death 5-fold (HR = 5.0; 95% CI = 1.7–15.2).

In 2 of the 11 third primary malignancy patients a fourth and a fifth primary malignancy developed. Both patients were females, had hereditary retinoblastoma and were the first in the family. The first patient had bilateral retinoblastoma, which was treated with radiotherapy and subsequently developed a Ewing sarcoma of the knee, osteosarcoma of the femur, mucoepidermoid carcinoma of right parotid and an unspecified cancer type of ethmoid. The other patient had unilateral retinoblastoma, which was treated with surgery only and subsequently developed a bladder carcinoma, soft tissue sarcoma (leiomyosarcoma of retroperitoneum), sebaceous adenocarcinoma, soft tissue sarcoma (leiomyosarcoma of upper arm) and she even developed a sixth primary malignancy (metaplastic carcinoma of hairy scalp). Both patients got children who were also affected with retinoblastoma. Only the fifth primary malignancy of the patient who received radiotherapy for the original ocular disease, developed in the field of radiation. The unilateral patient was still alive and the bilateral patient had died as of the date of censoring.

4. Discussion

To our knowledge, this is the first study which compared the risk of third primary malignancies among retinoblastoma patients to the risk of second malignancies. In this study among Dutch retinoblastoma patients we show that having had a second malignancy strongly increases the risk of a subsequent malignancy. Retinoblastoma patients treated with radiotherapy had elevated risks of third malignancies compared to those treated with surgery alone. Also, overall survival was worse for patients diagnosed with a third malignancy compared with patients only diagnosed with a second malignancy.

Table 4 – Multivariate Cox regression analysis of third malignancy risk, with second malignancy as a time-dependent covariate.

Risk factor	P-value	HR	95% CI
Retinoblastoma type	<0.001		
Non-hereditary[a]		1.0	
Hereditary		5.0	3.2–8.0
Treatment for retinoblastoma	<0.001		
Surgery only[a]		1.0	
Radiotherapy		2.9	1.8–4.8
Radiotherapy and chemotherapy		4.5	2.4–8.4
Chemotherapy only		5.3	0.7–40.3
Missing		1.6	0.4–6.5
Second primary malignancy (time-dependent covariate)	<0.001	7.6	3.9–14.8

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Reference group.

Combined results of previous cohort studies examining second malignancies,[18,19] suggest that the most frequently observed cancers among retinoblastoma patients are soft tissue sarcoma, osteosarcoma, melanoma and brain cancers. However, in this report we found that the majority of the observed second primary malignancies were of epithelial origin (43.4%). In contrast with retinoblastoma patients in the United States, until the early 1950s most patients in the Netherlands were treated with surgery alone. As a consequence, second malignancies in our cohort were observed at older ages (>40 years), and were mainly epithelial cancers. This larger proportion of second malignancies of epithelial origin can also be explained by the very long follow-up due to the historical nature of our cohort.

Studies convincingly show that radiotherapy increases the risk of subsequent malignancies in hereditary retinoblastoma patients.[11,20,21] In the Dutch retinoblastoma cohort almost 60% of the hereditary patients was treated with radiotherapy for retinoblastoma,[22] whereas in the United States studies[23] almost 90% of the retinoblastoma patients were treated with radiation, and between 1937 and 1965 many of those patients received very high radiation doses.[11] This explains why the previous report on third primary malignancies[12] observed 58% ($n = 122$) of all second primary malignancies and 54% of all third primary malignancies within the field of radiation, whereas only 36.7% ($n = 22$) of all second primary malignancies and 9% ($n = 1$) of all third primary malignancies in our study population were found within the field of radiation. Among patients treated with chemotherapy, only one was diagnosed with a second malignancy. Although a non-significantly increased risk of subsequent malignancies was observed, the number of patients who received chemotherapy and their follow-up is still too limited to draw conclusions with respect to the risk associated with chemotherapy.

Unsurprisingly, the SIR of developing any type of a third primary malignancy in survivors of a second primary malignancy after hereditary retinoblastoma were statistically significantly elevated compared to cancer incidence in the general population (SIR, 8.5). The SIR for second primary malignancy after hereditary retinoblastoma in our previous report[7] was 20.4 (95% CI, 15.6–26.1). The SIR found for third primary malignancies was therefore borderline significantly lower than the SIR among all Dutch hereditary retinoblastoma subjects ($P = .06$). Unexpectedly, a significantly increased risk of third primary malignancies among non-hereditary retinoblastoma patients compared to the general population was observed (SIR, 6.0), while in a previous paper[7] the risk of second primary malignancies was not significantly increased among the non-hereditary cases. Probably at least one of the three unilateral retinoblastoma cases without a family history might be a carrier of a *RB1* mutation. Unfortunately, it was not

possible to investigate this further because two of them had already died and the third one refused DNA analysis.

The smaller SIR among hereditary retinoblastoma subjects with a third primary malignancy compared to a second one is in contrast with our result from the time-dependent multivariable analysis. We observed that retinoblastoma patients who developed a second primary malignancy have a 7-fold greater risk of a subsequent malignancy compared to the risk of a second primary malignancy after retinoblastoma. This difference can be explained by differences in the time at risk for a second or subsequent malignancy. Time at risk for a second primary malignancy starts at the date of diagnosis of retinoblastoma, whereas time at risk for a third primary malignancy starts at the date of diagnosis of a second primary malignancy. Furthermore, in the present study most third primary malignancies were observed at ages when cancer normally occurs in the general population, which is in contrast with most observed second primary malignancies.

Radiotherapy used for the treatment of retinoblastoma further increased the risk of a third primary malignancy with almost 3-fold. As is generally known, hereditary retinoblastoma patients carry a mutation in the *RB1* gene and, consequently, are genetically predisposed by the nature of their genotype to develop other malignancies.[19] Other studies have indicated that the *RB1* gene is associated with a number of other common cancers,[24–28] and the *RB1*-encoded protein (pRb) is well known as a general cell cycle regulator, and this activity is critical for pRb-mediated tumour suppression.[24] Furthermore, studies have demonstrated that children exposed to radiation have high risks of radiation-related malignancies, and these risks persist for decades following exposure.[29] However, it is unknown which mechanisms underlie development of a subsequent primary malignancy, and why some hereditary retinoblastoma patients develop subsequent primary malignancies, whereas others do not.

In a previous report on third primary malignancies[12] the investigators reported 5- and 10-years survival rates after diagnosis of the second primary malignancy and the third primary malignancy. The data showed a trend towards higher 5- and 10-years survival rates from third primary malignancies. In contrast to these findings, our results indicate an overall poor survival for retinoblastoma patients diagnosed with a third malignancy compared with retinoblastoma patients diagnosed with a second malignancy only. The results from the study by Abramson and colleagues[12] might be influenced by treatment for retinoblastoma and the type of second and third malignancy. It is known that sarcomas in the head and neck region are difficult to treat, and therefore often lethal.[30] Abramson and collegues[12] reported 14 brain cancers as a second malignancy with very poor survival. It might be that these brain cancers were mainly pineoblastomas, because they are known to have a poor prognosis.[31]

Our study has some limitations. The numbers of third primary malignancies were small. Due to the historical nature of our database no medical files on the subsequent malignancies were available for 59 patients. These malignancies could only be confirmed through the death certificates from Statistics Netherlands. Also, there might be some potential misclassification of non-hereditary patients due to incomplete chromosomal or DNA analysis. Furthermore, non-hereditary patients with a second and a third primary malignancy who subsequently died might have been misclassified more frequently because no blood sample was available to analyse their DNA. Of all hereditary patients, 45% was confirmed by DNA analysis. Of all other hereditary patients DNA analysis could not be performed, because they died before DNA testing was available or refused to donate blood for DNA testing. These patients were defined as hereditary because they had bilateral disease and/or had a positive family history of retinoblastoma.

In conclusion, our study shows that after a second primary malignancy the risk of a subsequent malignancy was increased more than 7-fold. This risk further increases 3-fold when patients were treated with radiotherapy for their retinoblastoma. Furthermore, overall survival was significantly worse among retinoblastoma patients diagnosed with a third primary malignancy compared with patients diagnosed with a second primary malignancy only. Unfortunately, it is unclear which mechanisms underlie development of a subsequent primary malignancy, and why some hereditary retinoblastoma patients develop subsequent primary malignancies, whereas others do not. Therefore, we conclude that treating physicians should be aware of the fact that survivors of retinoblastoma who already have developed a second malignancy have an even higher risk of subsequent malignancies than retinoblastoma survivors without a second malignancy. Also, whenever possible ionising radiation should be avoided in the treatment of retinoblastoma itself as well as in the treatment for the subsequent malignancies.

Conflict of interest statement

None declared.

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