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Risk of second malignancies in long-term survivors of childhood cancer

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ABSTRACT

Introduction: Childhood cancer survivors are known to be at increased risk for second malignancies.

Patients and methods: The risk of second malignancies was assessed in 1368 5-year survivors of childhood cancer treated in the Emma Children's Hospital AMC in Amsterdam. The median follow-up time was 16.8 years.

Results: Sixty two malignancies were observed against 5.4 expected, yielding a standardised incidence ratio (SIR) of 11.2 (95% confidence interval: 8.53–14.4; absolute excess risk: 3.2 per 1000 person-years). New observations were the strongly increased risks of meningiomas (SIR = 40) and basal cell carcinomas (SIR = 9). Patients whose treatment involved radiotherapy had a 2-fold increased second cancer risk compared to patients with chemotherapy alone.

Discussion: The relative risk of second malignancies does not decrease till at least 30 years of follow-up. With aging of the survivor cohort this results in a strong increase of the AER, due to the rising background risk of cancer with age.

1. Introduction

Over the last three decades, advances in the treatment of childhood cancer have resulted in substantially improved survival rates. In the late 1960s the 5-year survival of childhood cancer patients in The Netherlands was about 30%, whilst nowadays around 70% of children survive at least for five years.[1] These survival rates are similar to the 5 year-survival reported in other western countries.[2,3] In view of the excellent cure rates in this young population, it is increasingly important to evaluate to which extent the occurrence of late complications affects (the quality of) their long-term survival.[4,5]

Already in 1975, Li *et al.* published data about second malignancies in childhood cancer survivors.[6] Numerous studies, both hospital- and population-based, have reported on the issue of increased risk of second malignancies.[7–12] Overall, these studies report an approximately 6-fold increased risk of second malignancies as compared to the rate in the general population.

In 1996 an outpatient clinic for the assessment of late effects of childhood cancer treatment in the Emma Children's

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Hospital Academic Medical Center (PLEK EKZ/AMC) in Amsterdam was established. Childhood cancer survivors are screened yearly, using standardised protocols, and near complete follow-up has been achieved. In this study we report on long-term second cancer risk in 1368 5-year survivors, treated from the late 1960s onwards, including second cancer risk for second meningiomas and basal cell carcinomas.

2. Patients and methods

2.1. *Identification of study cohort and data collection procedures*

Between 1966 and 1996, 2603 children (aged 0–18 years) were treated for a first primary cancer in the EKZ/AMC. All patients who survived for at least five years after the diagnosis of cancer were included in the study cohort. Five-year survivors were identified using the Childhood Cancer Registry of the EKZ/AMC. This registry was established in 1966 and contains detailed data on all patients admitted to the EKZ/AMC with respect to diagnosis, treatment and follow-up.

In total, 1368 5-year-survivors were identified. More than 78% ($n = 1078$) of them had already visited the PLEK EKZ/AMC when this study started. The Childhood Cancer and PLEK registry of EKZ/AMC provided us with second malignancy data. For the remaining 5-year survivors, we abstracted data from the medical records. Special attempts were made to establish the recent medical status of the patients who were lost to follow-up, by mailing a questionnaire to their general practitioners and treating physicians in other hospitals. Patients who were still lost to follow-up after approaching these physicians were traced by a request to the municipal registries, which fully cover the population of The Netherlands. Patients who were still alive were invited to visit PLEK EKZ/AMC, where information on their medical status could be completed. We finally succeeded in obtaining medical follow-up data up to at least January 2001 for 1258 patients (92.0% of the total cohort). For the remaining patients ($n = 110$), we obtained vital status except for 10 survivors (9 emigrated and 1 medical record was lost).

All second malignancies were confirmed by pathology reports. One second acute myeloid leukaemia occurred almost 20 years after the initial acute myeloid leukaemia. Both initial and relapse slides and immunological data were reviewed and it was confirmed that these leukaemias were distinct entities.

2.2. *Treatment*

Because the treatment of childhood cancer changed considerably over the last decades, a variety of treatment regimens had been used in our study population. Most of the patients were treated according to national or international protocols, such as DCLSG (Dutch Childhood Leukemia Study Group) protocols and SIOP (Société Internationale d' Oncologie Pédiatrique) protocols.

To assess the effects of treatment on the risk of developing a second cancer, we compared mutually exclusive treatment groups, as defined by all treatments received, including recurrence therapy. Two treatment eras (*i.e.* before and after October 1984) were defined for stratified analysis. This cut-off date was chosen because from then onwards prophylactic cranio-spinal radiation in leukaemia patients without central nervous system (CNS) involvement was abolished.

2.3. *Statistical analysis*

A comparison was made between second cancer incidence in the survivors of childhood cancer and cancer incidence in the Dutch population. Time at risk for second malignancy began five years after the initial diagnosis and ended at the date of diagnosis of the second malignancy, date of death, or date of the most recent medical follow-up examination, whichever occurred first. Consequently, 5-year survivors who developed second malignancies in the first five years after diagnosis of the primary cancer ($n = 6$) were excluded from analysis. One patient developed a second malignancy within one year after the first primary cancer and a third primary cancer almost 10 years after diagnosis of the first primary cancer. The second primary malignancy was therefore excluded from analysis, but the third primary cancer was included.

Taking into account the person-years of observation in the childhood cancer survivors' cohort, the expected numbers of second malignancies were computed with the use of age-, sex- and calendar-period-specific cancer incidence rates from the Eindhoven Cancer Registry [15] up to 1990 and from the Netherlands Cancer Registry for the period of 1990–2002.[16–18] Cancer incidence data for the whole country were not available for the total study period. Using a person-year type of analysis, SIRs were determined as the ratio of observed (O) and expected (E) numbers of second malignancies. The confidence limits of SIRs were obtained using exact Poisson probabilities of O numbers.[19] Absolute excess risk (AER) of second cancer was calculated by subtracting the expected number of cases from the number observed, dividing by person-years at risk (expressed per 1000 person-years).

Basal cell carcinomas were not included in the overall second cancer analyses, but a separate analysis of basal cell carcinoma risk was done using reference incidence data from the Southern part of The Netherlands where basal cell carcinomas were registered since 1973. Both benign and malignant meningiomas were included in our analyses since reference data from the general population were available from several regional Cancer Registries.

Patients who developed a third primary malignancy were considered to have had only one second cancer in the analyses of overall second malignancy risk, with time at risk ending at the date of diagnosis of the second primary cancer. To estimate the risk of specific second malignancies, however, a third primary cancer was retained in the analysis. The 16 survivors who developed a basal cell carcinoma as second tumour were included in the person-year calculation till the diagnosis of the basal cell carcinoma, which was not counted as a second malignancy in the analyses of all other second malignancies.

Actuarial risks of second malignancies were compared using the log-rank test developed by Mantel.[20,21] The Cox proportional hazards model was used to quantify the effects of different treatments on second cancer risk, adjusting for variable follow-up periods, and to explore the effect of concom-

Table 1 – Patient characteristics of EKZ AMC childhood cancer survivors cohort

Characteristic	Number of cancer patients N (%)		
	Overall N = 1368	Cases with a SMN[a,b] N = 79	Cases without a SMN[a] N = 1289
Sex			
Male	749 (54.8)	31 (39.2)	718 (55.7)
Female	619 (45.2)	48 (60.8)	571 (44.3)
Primary childhood cancer diagnosis			
Leukaemia	335 (24.5)	17 (21.5)	318 (24.7)
Lymphoma	256 (18.7)	13 (16.5)	243 (18.9)
Wilms tumour	192 (14.0)	10 (12.7)	182 (14.1)
Brain/CNS	109 (8.0)	9 (11.4)	100 (7.8)
Bone	117 (8.6)	7 (8.9)	110 (8.5)
Soft tissue sarcoma	147 (10.7)	11 (13.9)	136 (10.6)
Other	212 (15.5)	12 (15.2)	200 (15.5)
Age at diagnosis of childhood cancer (years)			
0–4	600 (43.9)	33 (41.8)	567 (44.0)
5–9	379 (27.7)	29 (36.7)	350 (27.2)
10–14	309 (22.6)	11 (13.9)	298 (23.1)
15–18	80 (5.8)	6 (7.6)	74 (5.7)
Childhood cancer treatment category			
Surgery alone[c] (±recurrence)	104 (7.6)	7 (8.9)	97 (7.5)
Chemotherapy (±S[d]) only (±recurrence)	656 (48.0)	15 (19.0)	641 (49.7)
Radiotherapy[e] (±S[d]) only (±recurrence)	93 (6.8)	11 (13.9)	82 (6.4)
CT[f]& RT[g] (±S[d]) initial treatment (no recurrence)	336 (24.6)	33 (41.8)	303 (23.5)
CT[f]& RT[g] (±S[d]) including recurrence treatment	179 (13.1)	13 (16.5)	166 (12.9)
Recurrence			
Yes	277 (20.2)	20 (25.3)	257 (19.9)
No	1091 (79.8)	59 (74.7)	1032 (80.1)
Calendar year of childhood cancer diagnosis			
January 1966–January 1979	335 (24.5)	35 (44.3)	300 (23.3)
February 1979–September 1984	365 (26.7)	30 (38.0)	335 (26.0)
October 1984–April 1990	330 (24.1)	5 (6.3)	325 (25.2)
May 1990–December 1995	338 (24.7)	9 (11.4)	329 (25.5)
Survival after diagnosis (years)			
5–9	262 (19.2)	21 (26.6)	241 (18.7)
10–14	302 (22.1)	13 (16.5)	289 (22.4)
15–19	306 (22.4)	17 (21.5)	289 (22.4)
20–24	254 (18.6)	14 (17.7)	240 (18.6)
25–29	160 (11.7)	10 (12.7)	150 (11.6)
⩾30	84 (6.1)	4 (5.1)	80 (6.2)
Attained age at the end of follow-up (years)			
5–14	206 (15.1)	10 (12.7)	196 (15.2)
15–19	225 (16.4)	16 (20.3)	209 (16.2)
20–24	307 (22.4)	18 (22.8)	289 (22.4)
25–29	252 (18.4)	15 (19.0)	237 (18.4)
⩾30	378 (27.6)	20 (25.3)	358 (27.8)
Vital status at the end of follow-up			
Alive	1245 (91.0)	58 (73.4)	1187 (92.1)
Dead	123 (9.0)	21 (26.6)	102 (7.9)

a Second malignant neoplasm.
b Includes 3 MDS cases and 12 benign meningiomas and 16 basal cell carcinomas.
c Including 2 patients who received no treatment at all.
d Surgery.
e Including patients who received external beam radiotherapy or radioactive isotopes (such as meta-iodobenzylguanidine treatment).
f Chemotherapy.
g Radiotherapy.

itant variables on second cancer risk and on the relationship between treatment and second cancer risk.[22]

For all analyses SPSS software was used (SPSS for Windows, Release 11.5, SPSS Inc, Chicago, IL).

3. Results

Table 1 provides patient characteristics of the 1368 5-year childhood cancer survivors according to the occurrence of second malignancy. Most of the survivors received chemotherapy alone (48%). Combination therapy was given to 37.6% of the patients. The median age at diagnosis was 5.9 years. Median follow-up time was 16.8 years, but 244 patients (17.8%) were followed for more than 25 years. Nine percent (n = 123) of patients had died at the end of follow-up.

In the entire cohort, 79 second and seven subsequent malignancies were observed 5 years or more after the diagnosis of the primary childhood cancer. This includes 12 benign meningioma cases, three cases of myelodysplastic syndrome and 16 basal cell carcinomas. The second malignancies occurred on average 17.1 years after diagnosis of the primary neoplasm. Of all survivors with a second malignancy, almost 27% had died at the end of follow-up, in most cases due to the second or subsequent malignancy.

Table 2 – Risk of second malignancies in 5-year survivors of childhood cancer, according to the type of second malignancy and the type of first primary childhood cancer

	Observed cases[a]	Expected cases	SIR[b]	95% CI[c]	Absolute excess risk[d]
Second malignancy					
All second malignancies (incl. benign meningiomas)[e]	60	5.37	11.2	8.53–14.4	3.20
All second malignancies (excl. benign meningiomas)	48	5.08	9.45	6.97–12.5	2.51
Solid tumours[f]	51	4.20	12.1	9.05–16.0	2.74
Solid tumours including third primary tumours[g]	56	4.20	13.3	10.1–17.3	3.03
Bone	5	0.18	28.1	9.14–65.7	0.28
Connective tissue	10	0.21	48.6	23.3–89.4	0.57
Breast	3	0.50	5.98	1.23–17.5	0.15
Ovary	2	0.12	16.1	1.95–58.2	0.11
Brain	4	0.37	10.8	2.93–27.6	0.21
CNS[h]	13	0.32	40.1	21.4–68.6	0.74
Meningioma	12	0.29	41.2	21.3–71.9	0.69
Thyroid[i]	6	0.16	38.7	14.2–84.2	0.34
Basal cell carcinoma[j]	18	2.01	8.95	5.30–14.1	0.94
Leukaemia and lymphoma[k]	9	1.16	7.76	3.55–14.7	0.46
Leukaemia	4	0.36	11.1	3.02–28.3	0.21
Leukaemia and MDS[l]	7	0.36	19.4	7.79–39.9	0.39
Non-Hodgkin lymphoma	4	0.32	12.7	3.45–32.4	0.22
Primary childhood cancer					
Acute lymphoblastic leukaemia[m]	10	0.88	11.3	5.42–20.8	2.71
Lymphoma[n]	9	1.15	7.82	3.58–14.9	2.40
Wilms tumours[o]	6	0.64	9.42	3.46–20.5	2.07
Brain/CNS tumours[p]	7	0.40	17.4	6.98–35.8	5.36
Bone tumours	6	0.65	9.22	3.38–20.1	3.72
Soft-tissue sarcomas	9	0.71	12.6	5.76–23.9	3.98

a At least 2 observed cases per category are represented in table.
b Standardised incidence ratio.
c Confidence interval.
d Per 1000 person-years.
e 12 benign meningioma cases are included in the analysis; expected rate is based on the incidence of benign CNS tumours. 3 MDS cases and 16 basal cell carcinoma cases are excluded, since incidence rates in population are not available.
f Includes, other than the specific sites denoted below, 12 benign meningiomas, and 2 malignant orbita tumours, 2 melanomas, 1 abdominal adenosarcoma, 1 cervical carcinoma, 1 carcinoma sinus maxillaris, 1 carcinoma colon and 1 carcinoma of tongue.
g Includes also 5 third primary cancers (2 lung carcinomas, 1 meningioma, 1 thyroid carcinoma and 1 rectal carcinoma).
h Includes 12 second benign meningiomas.
i Including 1 third malignant thyroid carcinoma.
j Expected rate of basal cell carcinoma was calculated using the incidence rates of the Eindhoven Cancer Registries; observed number includes 2 third primary basal cell carcinomas.
k 2 ALL, 1 AML, 1 CML, 4 Non-Hodgkin lymphomas, 1 Hodgkin's lymphoma.
l Includes 3 second myelodysplastic syndromes; MDS only included in this subgroup.
m Includes 6 second benign meningiomas.
n Includes 1 benign meningioma.
o Includes 1 benign meningioma.
p Includes 3 benign meningiomas.

3.1. *Risk of second malignancy in comparison with the general population*

Table 2 shows the SIRs of second malignancies, according to the type of second malignancy and the type of first primary childhood cancer. Overall, including meningioma, the risk of second malignancy was 11.2-fold (95% confidence interval (CI): 8.53–14.4) increased in comparison with cancer risk in the general population. The SIR for the analysis that excludes meningioma (as is commonly done in the literature[10,11,23]) was slightly lower (SIR = 9.45). Compared with the general population, our 5-year survivors of childhood cancer experienced an excess of almost 3.2 secondary malignancies per 1000 person-years. High relative and absolute excess risks were observed for second solid tumours (SIR = 12.1; AER = 2.74 per 1000 person-years), especially for connective tissue tumours and CNS tumours, which showed the largest SIRs (48.6 and 40.1, respectively) and AERs (0.57 and 0.74 per 1000 person-years, respectively).

Calculation of the standardised incidence ratio (SIR) for meningiomas and basal cell carcinomas is often not possible because reference rates from population-based registries are usually not available. For second meningiomas (malignant, borderline and benign) and basal cell carcinomas, the SIRs were 41.2 and 8.95, respectively, and the highest AER was observed for basal cell carcinoma (0.94 per 1000 person-years). Radiation was a strong risk factor for both basal cell carcinomas and meningiomas, with all meningiomas and 94% of the basal cell carcinomas occurring after radiotherapy. The majority of the basal cell carcinomas (94%) and meningiomas (75%) were diagnosed after 15 years of follow-up and one third of both diagnoses occurred even after 25 years (data not shown).

Table 3 – Risk of developing a second malignancy[a] (overall and solid tumours) in 5-year survivors of childhood cancer, according to several patient and treatment characteristics

	All second malignancies			Second solid tumours		
	O[b]	SIR[c] (95% CI[d])	AER[e]	O[2]	SIR[3] (95% CI[4])	AER[5]
Gender						
Male	27	9.89 (6.52–14.4)	2.64	23	11.3 (7.17–17.0)	2.28
Female	33	12.5 (8.61–17.6)	3.84	28	12.9 (8.60–18.7)	3.26
Age at diagnosis (years)						
<6	26	12.9 (8.43–18.9)	2.70	24	16.3 (10.5–24.3)	2.54
⩾6	34	10.1 (7.02–14.2)	3.73	27	9.90 (6.52–14.4)	2.95
Treatment era						
<01-10-1984	48	11.5 (8.45–15.2)	3.64	40	11.9 (8.49–16.2)	3.04
⩾01-10-1984	12	10.2 (5.25–17.7)	2.14	11	13.2 (6.60–23.6)	2.01
Treatment category						
CT[f] only (±recurrence)	13	6.78 (3.61–11.6)	1.57	8	5.60 (2.42–11.0)	0.93
RT[g] only (±recurrence)	10	15.4 (7.41–28.4)	6.35	9	16.5 (7.56–31.4)	5.74
CT[4] and RT[5] (±S[h]) initial treatment (no recurrence)	22	12.4 (7.78–18.8)	3.85	22	15.6 (9.78–23.6)	3.92
CT[4] and RT[5] (±S[h]) including recurrence treatment	9	15.7 (7.17–29.8)	4.40	9	20.1 (9.18–38.1)	4.46
Surgery only (±recurrence)	6	13.1 (4.81–28.5)	3.94	3	8.2 (1.68–23.9)	1.87
Recurrence						
Yes	13	13.4 (7.13–22.9)	3.88	11	14.4 (7.18–25.7)	3.30
No	47	10.7 (7.85–14.2)	3.05	40	11.6 (8.32–15.9)	2.61
Follow-up interval (years)						
5–9	20	19.2 (11.7–29.6)	3.03	17	24.2 (14.1–38.8)	2.60
10–14	11	9.14 (4.56–16.4)	2.05	9	20.2 (4.65–19.3)	1.70
15–19	10	8.31 (3.98–15.3)	2.73	9	9.47 (4.33–18.0)	2.50
20–24	10	9.59 (4.60–17.6)	4.87	8	9.07 (3.91–17.9)	3.87
⩾25	9	10.3 (4.69–19.5)	8.24	8	10.3 (4.44–20.2)	7.33
Attained age (years)						
5–14	10	17.7 (8.49–32.6)	1.97	9	25.5 (11.7–48.5)	1.81
15–19	16	18.9 (10.8–30.7)	3.69	12	21.0 (10.9–36.7)	2.78
20–24	13	11.4 (6.05–19.4)	3.10	13	15.4 (8.22–26.4)	3.17
25–29	7	6.13 (2.47–12.6)	2.35	6	6.35 (2.33–13.8)	2.03
⩾30	14	8.37 (4.58–14.0)	6.56	11	7.39 (3.69–13.2)	5.06

a Including 12 meningiomas.
b Observed number of cases.
c Standardised incidence ratio.
d Confidence interval.
e Absolute excess risk per 1000 person-years.
f Chemotherapy.
g Radiotherapy.
h Surgery.

3.2. *Risk of second malignancies according to patient and treatment characteristics*

Table 3 shows risks of second malignancies according to several patient and treatment characteristics. Of all treatments, radiotherapy alone and combined modality therapy, including treatment for recurrence, were associated with the highest SIRs (15.4 and 15.7, respectively). However, radiotherapy alone was associated with the highest AER (6.35 per 1000 person-years) and therefore contributed most to the excess second cancer risk, due to the fact that since survivors who received radiotherapy alone were oldest at the end of follow-up. Treatment with chemotherapy alone was associated with a significantly lower SIR (6.78) than all treatment categories involving radiotherapy (SIR of 13.7). The SIR was highest in the 5–9 year follow-up interval (SIR = 19.2) and stabilised at 9-fold increased risk after 10 years of follow-up without a further decrease till at least 30 years of follow-up. However, the AER especially increased after 25 years of follow-up, related to the increasing background incidence of cancer with a longer follow-up. Remarkably, both the SIR and AER decreased with attained age till survivors had reached the age of 30 years, but slightly increased for older ages (SIR $\geqslant$ 30 years = 8.37; AER = 6.56).

The SIRs and AERs of second *solid* malignancy according to patient and treatment characteristics showed very similar patterns as observed for the risk of all second malignancies combined (Table 3). The SIRs for basal cell carcinoma and meningioma increased with longer follow-up, resulting in SIRs of 12.8 and 212, respectively, for the follow-up interval of more than 25 years (data not shown).

3.3. *Actuarial risk of second malignancy and impact on survival*

The cumulative risks of developing a second malignancy in 5-year survivors of childhood cancer were 1.6%, 4.4% and 11.1% at 10-, 20- and 30 years of follow-up, respectively (data not shown). Those developing a second cancer had a significantly worse survival compared to those who did not (logrank = 36.9; p-value < 0.001). The 20-year actuarial risk of death in survivors who developed a second malignant neoplasm was 31.7% versus 9.0% in survivors who did not. Fig. 1 illustrates the impact of second malignancies on overall survival. The actuarial 25-year survival improved from 88.6% to 90.7% after censoring second cancer death, although the difference between the curves was not statistically significant (p-value = 0.23). Fig. 2 illustrates that treatment era did not affect the actuarial risk of second malignancy (p-value = 0.54). The treatment-specific actuarial risk of developing a second cancer as a function of attained age is given in Fig. 3. At age 35 the risks were 5.8% for patients treated with CT only and 10.8% for patients whose treatment involved radiotherapy (p-value = 0.01).

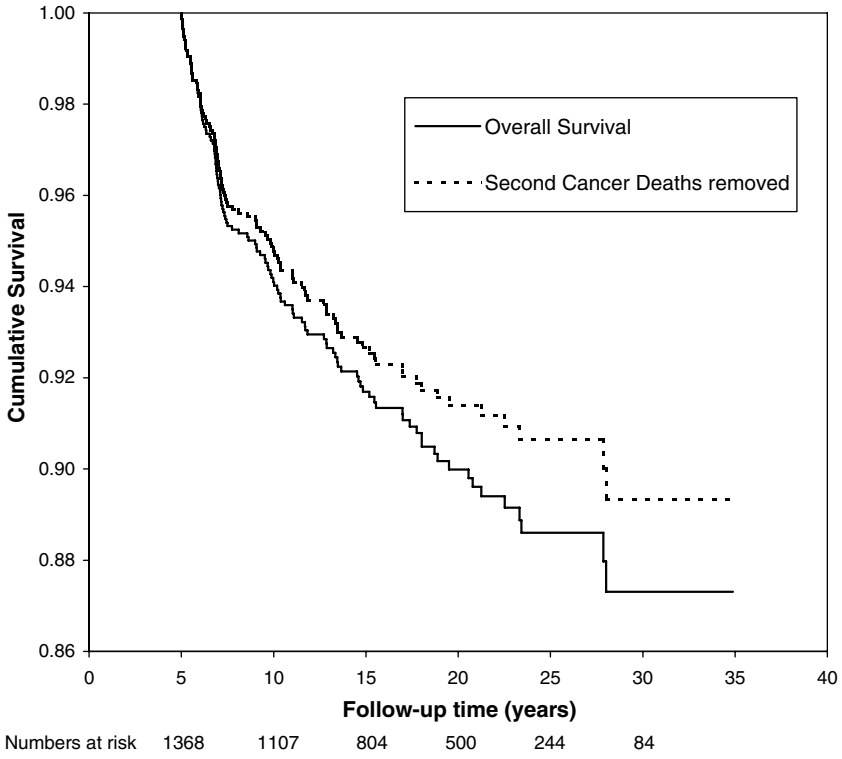
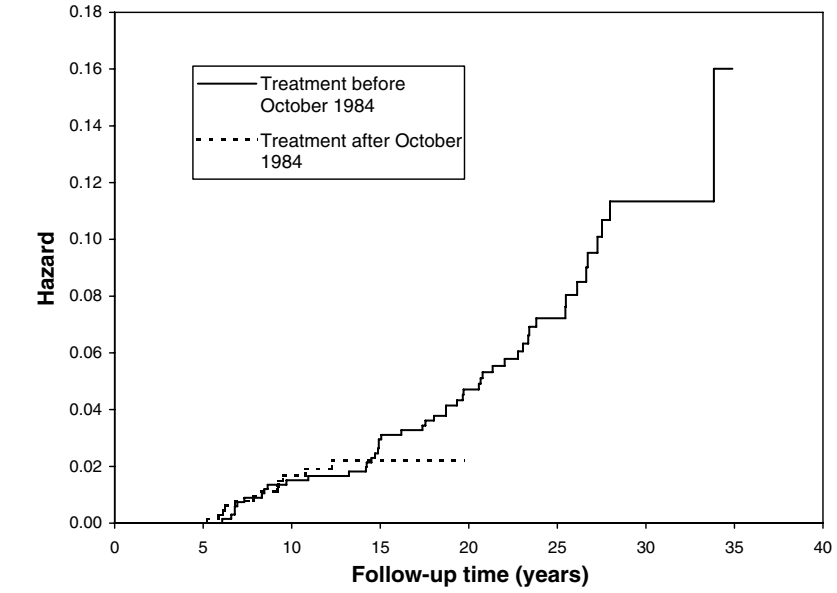
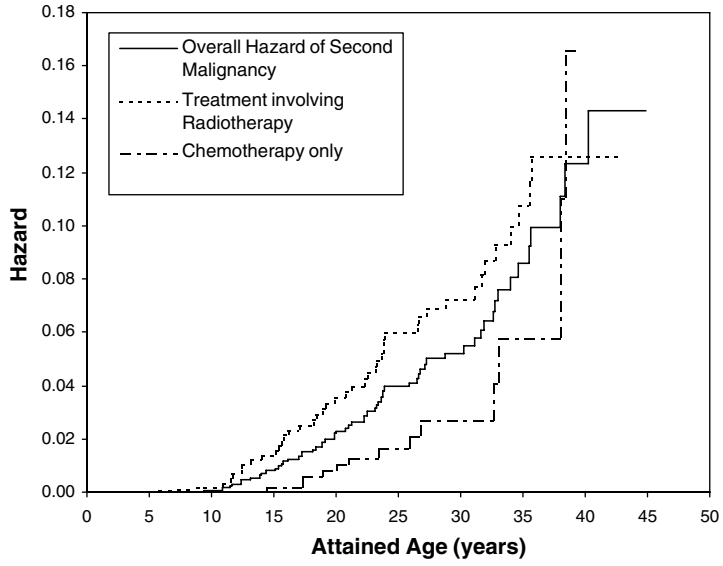


Fig. 1 – Impact of second malignancy on overall survival in 5-year survivors of childhood cancer. In the upper curve (second cancer death removed) all second cancer deaths were considered to be lost to follow-up at time of death (censored). This shows the impact of second cancer death in comparison with the overall survival. Both curves were stopped when less then 10 patients were at risk.



Numbers at risk							
	700	634	599	492	244	84	Treatment before October 1984
	668	473	205				Treatment after October 1984

Fig. 2 – Hazard function of developing second malignancy according to treatment era. Both curves were stopped when less then 10 patients were at risk.



Numbers at risk									
	1368	1322	1162	937	630	378	157	51	Overall Hazard of Second Malignancy
	608	589	533	452	348	237	108	36	Treatment involving Radiotherapy
	656	633	542	414	230	110	35		Chemotherapy only

Fig. 3 – Cumulative hazard of second malignancy as a function of attained age, specified for 2 specific treatment categories, in 5-year survivors of childhood cancer. Survivors treated with surgery only are excluded in both treatment specific hazard curves. All curves were stopped when less then 10 patients were at risk.

3.4. *Prognostic factors for second cancer development: Cox model analysis*

In the Cox model analysis (Table 4), prognostic factors for second cancer development were examined within the patient group, as opposed to the person-year analysis (Tables 2 and 3) in which risk is compared to that in the general population. For all second malignant neoplasms combined, radiotherapy was associated with significantly elevated second cancer risk in comparison with no radiotherapy (Hazard Ratio (HR) 1.84). When focusing on second solid tumours, radiotherapy showed an even stronger risk increase (HR 3.39). Female

Table 4 – Multivariate Cox regression analysis of potential risk factors for second (solid) malignancy in childhood cancer survivors

Risk factor	Hazard ratio (95% CI[a])[b]			
	All second malignancies[c] (n = 60)	All solid second tumours[c] (n = 51)	Basal Cell Carcinomas (n = 16)	Meningiomas (n = 12)
Gender (female versus male)	1.35 (0.81–2.25)	1.33 (0.76–2.31)	3.26 (1.05–10.1)	0.37 (0.10–1.37)
Age at diagnosis (per year)[d]	1.02 (0.96–1.07)	1.00 (0.94–1.06)	1.00 (0.88–1.13)	1.03 (0.90–1.18)
Treatment era (after October 1984 versus before October 1984)	1.01 (0.48–2.11)	1.36 (0.62–2.97)	1.57 (0.16–15.2)	1.46 (0.16–13.7)
Radiotherapy (yes versus no)	1.84 (1.04–3.27)	3.39 (1.68–6.84)	8.42 (1.05–67.3)	X[e]
Chemotherapy (yes versus no)	0.63 (0.35–1.13)	0.72 (0.37–1.40)	4.79 (0.62–37.0)	2.74 (0.34–21.8)

a Confidence interval.
b Two survivors (no second cancer cases) with unknown treatment are excluded for Cox analysis.
c Including 12 meningiomas, excluded are 3 MDS cases and 16 Basal Cell Carcinomas.
d Age at diagnosis is a continuous variable.
e Hazard ratio could not be calculated since all 12 meningiomas received radiotherapy.

survivors and those who received radiotherapy had a significantly increased risk of basal cell carcinoma (HR 3.26 and 8.42, respectively).

4. Discussion

In this study of Dutch childhood cancer survivors, with long-term and complete follow-up, the overall second cancer risk was about 11-fold higher than in the population at large. The absolute excess risk of solid tumours was much larger than that of leukaemia and lymphoma (2.74 versus 0.46 cases per 1000 person-years). Soft tissue sarcoma, CNS tumours and meningioma contributed most to the excess risk of second solid cancers. Basal cell carcinomas accounted for an even larger excess (0.94 per 1000 person-years). Radiotherapy was the main risk factor for new primary malignancies. Even more than 25 years after diagnosis of the initial childhood cancer, there still was a significantly increased 10-fold risk of developing a second malignancy, resulting in 8.2 excess cases per 1000 person-years. While the SIR decreased till survivors attained the age of 25–30 years, it appeared to stabilise in those survivors who had reached the oldest age group ($\geqslant$30 years). This suggests that excess second cancer risk may persist through life.

Table 5 gives an overview of the design and outcome of the largest and most recent studies about second malignant neoplasms following childhood cancer. We only included studies in which most types of childhood cancer were included in the original study. Compared to the other studies, the overall SIR in our study is higher, *i.e.* 9.5 versus around 6 in other studies.[8,10–12,21] The wide range in second cancer risk estimates reported for various cohorts may be related to a population- versus hospital-based approach, which may reflect differences between study cohorts with respect to the upper age limit allowed for the diagnosis of childhood cancer, the calendar years of diagnosis, duration and completeness of follow-up, the attained age of the cohort, the distribution of childhood cancer diagnoses, and/ or the intensity of treatment.

As compared with the other cohorts, our study includes more recent years of childhood cancer diagnosis (Table 5). The more recent treatment era encompassed by our study implies that we included more patients with a follow-up of less than 10 years. This may have resulted in a higher SIR in our cohort since second malignancy risk in our study was increased to a much greater extent in the follow-up interval shortly after diagnosis (5–9 year) than in later follow-up intervals.

Complete follow-up and valid ascertainment of second malignancies through pathology reports are critical aspects in the methodology of second cancer research.[24] Overestimation of second cancer risk occurs when follow-up in the original treatment centre is more complete for survivors who develop a second malignancy than for those who remain healthy. This is likely to happen, because patients who remain healthy tend to lose contact with clinical follow-up, whereas those with second malignancies return to clinical follow-up because of their new cancer. In view of this potential for bias, it is of concern that completeness of follow-up till a specific date is rarely reported in second cancer studies. The medical follow-up in our study was complete till 2001 for 92% of the cohort and higher compared with other studies (Table 5).

The median age at diagnosis was comparable in all mentioned studies. Our follow-up time of almost 17 years after primary childhood cancer is slightly higher than in the CCSS and UK/France cohort, but much higher than in the Nordic Countries Cohort and the UK population-based cohort (Table 5). Since radiotherapy is a major determinant of second cancer risk,[10,25,26] the lower proportion of irradiated patients in our study certainly cannot explain the higher SIR observed in our study. The high SIR in our cohort is most likely due to differences in treatment over the years in comparison with other cohorts and the more recently included treatment era.

Both the SIR and the AER in our study decreased with higher attained age, but the risks appeared to stabilise at 25–30 years, with a suggestion of a slight increase in the oldest age group. So the increased second cancer risk in childhood cancer survivors may persist through life. De Vathaire *et al.* also presented second cancer risks for different attained age categories and reported that the interval of 10–19 years of age experienced the highest SIR (SIR = 20), comparable with our results[10].

Table 5 – Summary of design and results of studies on second cancer risk in childhood cancer survivors

Study cohort	CCSS USA	Nordic countries	United Kingdom/ France	United Kingdom	PLEK The Netherlands
Author	Neglia *et al.*[11]	Olsen *et al.*[23]	De Vathaire *et al.*[10]	Jenkinson *et al.*[12]	Cardous-Ubbink *et al.*
Year of publication	2001	1993	1991[a]	2004[b]	2006
Data collection source	25 institutions in USA and Canada; Self administered questionnaire; SMN pathology reports checked	Population-based cancer registries of five Nordic countries	8 hospitals in UK and France	Population-based National Register for Childhood Tumours	One single hospital-based cohort; data from medical records, general practitioners and other specialists
Survivors cohort	5-year Survivors	All patients	3-year Survivors	3-year Survivors	5-year Survivors
Number of patients	13.581	30.880	4.400	16.541 (15.452 non-retinoblastoma cohort)	1.368
Calendar years of diagnosis	1970–1986	1943–1987	<1985	1926–1987	1966–1996
Age range at diagnosis	<21 years	<20 years	<17 years	<15 years	<18 years
Diagnoses included	All primary cancer sites	All primary cancer sites	No primary, secondary or subsequent leukaemias; no retinoblastoma for British Centres	All primary cancer sites Part analysis: non-retinoblastoma cohort	All primary cancer sites
	CNS 13.1% Bone 8.4% Lymphoma 20.9% Wilms' 8.6% Leukaemia 33.7% Soft tissue 8.7% Neuroblastoma 6.6%	CNS 21.3% Bone 6.2% Lymphoma 12.0% Wilms' 4.7% Leukaemia 27.9% Soft tissue 6.6% Other 21.4%	CNS 16.4% Bone 6.6% Lymphoma 18.9% Wilms' 18.6% Leukaemia 0.0% Soft tissue 13.4% Other 16.2%	Brain/CNS 24.2% Bone 3.9% Hodgkin's disease 7.8% Wilms' 7.8% ALL 24.1% Soft tissue 6.6% Other 25.6%	Brain/CNS 8.0% Bone 8.6% Lymphoma 18.7% Wilms' 14.0% Leukaemia 24.5% Soft tissue 10.7% Other 15.5%
Second Malignancies included	All second malignancies; Non-melanoma skin cancers, meningiomas, other non-malignant CNS tumours excluded	All second malignancies; benign tumours of brain and intracranial meninges and papillomas of the urinary tract included; basal cell carcinomas only included in Danish data	All second malignancies; non-melanoma skin cancers excluded	All second malignancies; non-melanoma skin cancers excluded	All second malignancies; myelodysplastic syndromes and basal cell carcinomas excluded; separate analysis for bcc

(*Continued on next page*)

Table 5 – *continued*

Study cohort	CCSS USA	Nordic countries	United Kingdom/ France	United Kingdom	PLEK The Netherlands
Author	Neglia *et al.*[11]	Olsen *et al.*[23]	De Vathaire *et al.*[10]	Jenkinson *et al.*[12]	Cardous-Ubbink *et al.*
Year of publication	2001	1993	1991[a]	2004[b]	2006
Expected rates from:	National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER)	Appropriate rates of cancer in the general population	Danish Cancer Registry	National Cancer Registration System	The Netherlands Cancer Registry and Eindhoven Cancer Registry
Median age at diagnosis	6 years		6.0 years	5.8 years	5.9 years
Median follow-up time	15.4 years	6.0 years	15 years	Mean: 10.0 years	16.8 years
Median attained age	23 years				24.1 years
% Complete follow-up	67%	high due to national registration	88%	98%	91.9% medical follow-up till at least 1-1-2001
% Survivors who received radiotherapy	68.1%		70.7%		44.4%
% Survivors who received chemotherapy	Alkylating agents 52.9% Anthracyclines 40.9% Epipodophyllotoxins 9.3% Platinum agents 5.9%		67.0%		85.6 %
SIR overall	6.38 (5.7–7.1) 7.47 (6.61–8.40) solid malignancies	3.6 (3.1–4.1)	9.2 (7.6–11) solid malignancies	6.2 (5.5–7.1)	11.2 incl. meningioma 9.45 excl. meningioma 12.1 solid malignancies
AER overall	1.88 per 1.000	0.95 per 1.000	1.88 per 1.000 (solid)	1.2 per 1.000	3.20 per 1.000
Cumulative risk at 20-years follow-up	3.2%	2.6% 45-year risk: 12.8%	25-year risk: 4.9% (solid) 30-year risk: 7.7% (solid)	3.1% 25-year risk: 4.2%	4.4%

SIRs and AERs during Follow-up	SIRs all intervals (5–9/10–14/15–19/20–24/25–29) increased (data not shown)											
			SIR	AER	Solid SMN	SIR	AER		SIR	AER		SIR	AER
		0	3.5	4	3–9:	16	1.6	3–9	10.2	1.1	5–9:	19.2	3.0
		1–2	5.7	8	10–19:	11	2.1	10–19	5.7	1.0	10–14	9.1	2.1
		3–4	6.1	9	20–29:	6	2.7	20–29	3.5	1.5	15–19	8.3	2.7
		5–9	5.4	9	⩾30:	2	1.6	⩾30	2.4	2.0	20–24	9.6	4.9
		10–14	4.2	11							⩾25	10.3	8.2
		15–19	3.2	12									
		20–29	2.4	15									
		30–44	2.0	28									

SIR attained age		Solid	SMN	SIR AER					SIR	AER
		3–9	7	0.7				5–14	17.7	2.0
		10–19	20	2.1				15–19	18.9	3.7
		20–29	8	2.2				20–24	11.4	3.1
		⩾30	4	3.1				25–29	6.1	2.4
								⩾30	8.4	6.6
SIR treatment groups		Solid SMN	SIR	AER			SIR		SIR	AER
		Surgery	1.5	0.3		No RT CT	3.3	Surgery	13.1	3.9
		RT only	5.6	1.5		RT alone	6.0	RT only	15.4	6.4
		CT only	7.6	1.0		CT alone	7.4	CT only	6.8	1.2
		RT + CT	19	3.0		RT + CT	12.5	RT+CT no recur.	12.4	3.9
								RT + CT + rec.	15.7	4.4
Risk factors multivariate analysis	- Female gender	- SIR men ⩾ SIR woman		No multivariate analysis is done			- Both chemotherapy and radiotherapy	Significantly increased risk:		
	- Younger age at diagnosis	- Higher RR in recent treatment era					- Younger age at diagnosis	- RT alone (HR = 2.9)		
	- Primary Hodgkin/ soft tissue sarcoma						- Recent treatment era	- SOLID: All 3 RT groups (HR3.6–4.7)		
	- Increased exposure anthracyclines/ epipodophyllotoxins									

a Lymphoma are included in the solid tumours.
b Part of the patients overlaps with study of De Vathaire *et al.*

Radiotherapy appears to be the strongest risk factor for developing second cancers; however, chemotherapy only was also associated with a significantly increased risk (SIR of 6.8). Even survivors who received surgery only for the first childhood cancer experienced an increased second cancer risk (SIR = 13).

A special characteristic of our study is the assessment of SIRs for basal cell carcinomas and meningiomas. Only a few studies provided risk estimates for basal cell carcinomas or meningiomas, mostly based on comparisons within the study group instead of the general population.[23,27] As far as we know, our study is the first one showing a SIR for basal cell carcinomas. However, the risk for basal cell carcinoma may have been slightly overestimated due to screening bias, since the majority of our population was screened at PLEK.

A disadvantage of our study is the limited size of the survivor group in our hospital-based cohort. A future nationwide collaborative study will comprise larger numbers of survivors and will therefore allow more detailed analyses. Due to the limited size of this heterogeneous survivor group, we were not able to analyse specific radiotherapy fields and doses or types and doses of specific chemotherapeutic agents.

It should be kept in mind that a substantial proportion of second haematological malignancies already occurred within five years after initial childhood cancer diagnosis (20% in our series). Because our study (and most others) excluded the first five years after diagnosis of the primary childhood cancer, part of the second haematological malignancies was missed and so relative and absolute risks for haematological malignancies cannot be extrapolated to the overall risk of second malignancy after a childhood cancer diagnosis.

In conclusion, it is of major concern that the SIR is not decreasing in the patients with the most prolonged follow-up interval and highest attained age categories. With the increasing background rates of cancer with aging of the survivor cohort, the AER will substantially increase even if the SIR remains constant over time. Lifelong follow-up of childhood cancer survivors is important to see whether increased second cancer risk will persist for life. Unfortunately, screening for most cancers occurring in young adulthood is not effective. Therefore, the search for new treatment regimens with lower second cancer risks and equal level of therapeutic effectiveness is crucial.

Conflict of interest statement

None declared.

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