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Hypertension in long-term survivors of childhood cancer: A nested case-control study

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ABSTRACT

Aim of the study: To examine risk factors for developing hypertension in childhood cancer survivors (CCS).

Methods: We conducted a nested case-control study of risk for hypertension within a cohort of 1362 childhood cancer survivors treated between 1966 and 1996 in the Emma's Children's Hospital/Academic Medical Center in the Netherlands. Detailed information on treatment and several lifestyle factors was collected for 44 cases with hypertension and 123 matched controls. Odds ratios (ORs) for hypertension were calculated by conditional logistic regression analysis.

Results: Body Mass Index (BMI) was the only significant risk factor associated with the occurrence of hypertension (OR 3.95; 95% confidence interval (CI) 1.7–9.1 for BMI $\geqslant$ 25 kg/m^2 compared to BMI < 25 kg/m^2). However, cisplatin, cyclophosphamide and radiotherapy (RT) to the abdominal region were all associated with non-significant risk increases (ORs of 4.3, 2.1, and 1.8, respectively).

Conclusion: Our results show that BMI is the most important risk factor for hypertension following treatment of childhood cancer, emphasising the need for CCS to maintain a normal weight.

1. Introduction

The introduction of more effective treatments for childhood cancer has spectacularly improved survival rates, implying that childhood cancer survivors (CCS) are a rapidly growing group of young adults.[1–3] Unfortunately, improved prognosis has been accompanied by the occurrence of late treatment-related complications, such as second neoplasms, organ dysfunction and psychosocial and cognitive problems.[4–7] Late treatment sequelae will increase the incidence of chronic diseases in survivors and ultimately reduce their life expectancy. Therefore, the need for long-term follow-up of CCS is uniformly recognised.[8–10]

One of the several long-term effects in CCS is hypertension.[4] Nowadays, throughout the world, 1 in every 4 adults suffers from hypertension, a disease that contributes to 49%

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of ischemic heart disease and 62% of strokes worldwide.[11,12] Inadequately controlled hypertension is currently the number one risk factor attributing to death across the globe.[13] Also, in children and young adults hypertension is being diagnosed with increasing frequency, amongst others due to the increasing incidence of obesity.[14] The global obesity epidemic is leading to a shift in the blood pressure (BP) distribution, towards increasing levels in children and adolescents.[12,15] Especially in CCS who have already a high risk for anthracycline-induced heart failure,[16] for radiation-induced heart failure[17] and for cardiac mortality,[7] it is important to focus on potential additional risk factors for heart disease like hypertension.

Very few studies assessed the risks of hypertension in CCS, although both radiotherapy and chemotherapy have been hypothesised to affect blood pressure. In 1989 Kantor and colleagues reported on hypertension in long-term survivors of childhood renal cancers.[18] Recently, Haddy and colleagues found hypertension and prehypertension in survivors of several different childhood cancer diagnosis, especially in Wilms' tumour survivors.[19] As far as we know, it has not been examined in a large number of CCS what aspects of chemotherapy or radiotherapy increase the risk of hypertension. Therefore the aim of this study is to examine risk factors for developing hypertension in the cohort of CCS treated in the Emma's Children's Hospital/Academic Medical Center (EKZ/AMC) in the Netherlands.

2. Patients and methods

2.1. Study population and data collection

In the first part of our investigation we conducted a cohort study comprising 1362 5-year CCS treated in the EKZ/AMC in the Netherlands between 1966 and 1996, of whom 1080 visited our long-term follow-up clinic (PLEK). The methods to identify the CCS cohort have been described extensively elsewhere.[4] The cohort had a complete medical follow-up for 94.3% of the 1362 survivors. The 1080 survivors visiting PLEK were used to select survivors who were diagnosed with hypertension. At each visit to the PLEK, the blood pressure (BP) was routinely measured using standardised hospital equipment, allowing the identification of hypertensive patients. Hypertension was defined as a systolic BP higher or equal to 140 mm Hg and/or a diastolic BP higher or equal to 90 mm Hg, following the guidelines of the National Institute for Public Health and the Environment (RIVM).[20]

Subsequently, we conducted a case-control study of risk factors for hypertension, nested in the cohort. Case patients were defined as 5-year survivors of childhood cancer who had an increased BP at least three times on a row, measured at three different visits (PLEK visit or visit to general practitioner) and/or used anti-hypertensive drugs. If the patient's BP, either systolic or diastolic was above normal, measurements were repeated once or twice (sometimes even on additional occasions) to confirm or refute the presence of hypertension. The lowest BP determination was recorded. Case patients were not eligible if anti-hypertensive drugs were used for other diagnoses or if the BP was only increased during one of the standard measurement at the follow-up clinic. We excluded 1 case who underwent a kidney transplantation.

In total, 44 cases with hypertension were identified. Each case patient was matched with 3 control subjects from the EKZ/AMC CCS cohort. Control subjects were matched on several characteristics, in order of priority: gender, age at diagnosis of childhood cancer (within 3 years) and date of birth (within 3 years). In addition, cases with Wilms' tumours were matched with controls with Wilms' tumours, because of the known increased risk of high BP as a result of nefrectomy[19]; all other diagnoses combined were matched on non-Wilms' tumours. For controls, the follow-up time without hypertension had to be at least as long as the interval between the childhood cancer diagnosis and hypertension in the case patient. If more than 3 controls were available, we selected the subjects who met the eligibility criteria best. For 35 hypertension cases 3 control subjects were identified and for 9 cases only 2 control subjects could be selected. One control subject was used twice as a control for 2 case patients, with different follow-up intervals. In total 123 matched controls were found for the 44 cases.

For all subjects full medical records were obtained for detailed data abstraction of several characteristics and treatment details of the childhood cancer. Treatment data were collected on radiation fields, types of chemotherapy and types of surgery, both for primary treatment and recurrence treatment. We also collected information on all BP measurements, Body Mass Index (BMI), smoking, premature menopause, medication use and other co-morbidities.

2.2. Statistical analysis

The odds ratios (ORs) of hypertension associated with specific exposures (e.g. radiation or chemotherapy) were estimated by comparing the case patients' exposure histories with those of their matched controls, using conditional logistic regression methods.[21] For each case patient, we considered only the therapies in the period between the primary diagnosis and hypertension; for the corresponding control patients, the analysis took into account only the therapy administered during a period of equal length, starting with the date of diagnosis of childhood cancer. ORs, 95% confidence intervals (CIs) and *P*-values were performed using the statistical software SPSS v15.0.1 for Windows (SPSS Inc., Chicago, IL).

3. Results

Of the total of 1080 cohort members who visited PLEK, 44 had hypertension, according to our criteria (4.1%). Table 1 shows the sex-specific prevalence rates according to different attained age groups. The sex-specific overall prevalence of hypertension in our cohort was 4.3% for men and 3.8% for women aged 0–40 years.

Table 2 provides patient characteristics of the 44 cases and 123 controls included in the nested case-control study. As a result of the matching, case patients and control subjects were similar with regard to childhood cancer diagnosis (Wilms' versus non-Wilms'), gender, follow-up time and age at diagnosis. The median age at childhood cancer diagnosis

Table 1 – Sex- and age-specific prevalence of hypertension in the EKZ/AMC[a] childhood cancer survivors cohort.

Age-category (years)	Observed hypertensive patients		Prevalence of hypertension (%) (95% CI[b])	
	Men	Women	Men	Women
<19	2	3	0.8 (0.1–2.8)	2.8 (0.6–7.9)
20–29	13	13	5.4 (2.9–9.1)	5.8 (3.1–9.7)
30–39	9	3	12.3 (5.8–22.1)	2.0 (0.4–5.8)
40–49	1	0	10.0 (0.3–44.5)	0.0 (0–14.8)
0–49	25	19	4.3 (2.8–6.3)	3.8 (2.3–5.8)

[a] Emma Children's Hospital Academic Medical Center.
[b] Confidence interval.

was 7.7 years, the median follow-up time 20.4 years and the median attained age at date of hypertension diagnosis (cases) or cut-off date (controls) was 28.0 years, all comparable for cases and controls. Twenty-eight percent of the cases and controls were Wilms' tumour survivors. Slightly more cases were found in lymphoma survivors, while controls were more frequently diagnosed with leukaemia or brain tumours. The main treatment groups, like surgery, radiotherapy (RT) and chemotherapy (CT), were quite equally distributed among cases and controls. Slightly more cases received CT only, RT only or received CT and RT combined including recurrence treatment. In the case group more recurrences occurred (23% versus 13%, respectively). The BMI differed substantially between both study groups, with 52% of the cases having a BMI of more than 25 kg/m^2 versus 28% of the controls. In the 18–24 years age group more than 66% of our female cases and 50% of our male cases had a BMI higher than 25 kg/m^2, compared with 11% of our female and 35% of our male controls. Only 4 survivors (3 cases and 1 control) had a BMI higher than 35 kg/m^2.

Table 3 shows the prevalence of other relevant health problems. Only a few subjects had co-morbidities. Hypothyroidism occurred almost twice as often in control patients compared to case patients. Only one cardiovascular event was diagnosed in the case group versus 5 in controls; only 1 case experienced renal insufficiency and 3 cases had hyperlipidemia, both compared to none of the controls. There were no differences in prevalence of other co-morbidities between cases and controls.

Table 4 shows the results of two different conditional logistic regression analyses. In the first model, which included only treatment variables, no significant associations emerged. However, the OR associated with cisplatin was 2.5 (95% CI: 0.44–13.9). The second model with BMI included showed that the OR for BMI $\geqslant$ 25 kg/m^2 was strongly increased compared to BMI < 25 kg/m^2 (OR 3.95; 95% CI: 1.71–9.09). Including BMI to the regression model slightly increased the ORs for CT variables, especially for cisplatin, indicating that the association between cisplatin and hypertension cannot be explained by an effect of cisplatin on an increase of BMI. Although BMI was the only significant variable associated with the occurrence of hypertension, cisplatin, cyclophosphamide, ifosfamide and RT to the abdominal region were all associated with non-significant risk increases (ORs of 4.3, 2.1, 1.3 and 1.8, respectively).

Carboplatin was not given to any of the cases and controls in our study. Anthracyclines did not show an increased OR in any of the models examined; therefore we combined anthracyclines with the other chemotherapeutic agents (excluding cisplatin, cyclophosphamide and ifosfamide).

We also performed an analysis stratified by follow-up time (Table 5). More than 56% of the hypertension cases occurred after 20 years of follow-up. Abdominal radiotherapy seemed to be stronger associated with the risk of hypertension after more than 20 years of follow-up (OR = 2.3; 95% CI: 0.60–8.55). The associations with cyclophosphamide and other chemotherapy did not change during follow-up. Due to very few cisplatin and ifosfamide cases in the long-term follow-up subgroup (early treatment era), we could not examine the effects of these chemotherapeutic agents on the very long-term risk of hypertension. However, the model restricted to the first 20 years of follow-up showed an OR for cisplatin of 5.5 (95% CI: 0.7–41.1). In the models stratified according to follow-up interval, BMI remained the only risk factor significantly affecting the risk of hypertension.

Smoking was not associated with the occurrence of hypertension (OR 0.86; 95% CI: 0.26–2.90), and did not confound the associations with other variables. For women we also had information on premature menopause, which might affect hypertension risk. Only three of the 73 women experienced premature menopause, which is probably an underestimation because in this young population most women used oral contraceptives (and postmenopausal status would not became apparent). In women an almost 12-fold significantly increased risk of hypertension associated with cisplatin use was observed (OR 11.8; 95% CI: 1.03–136). The OR for developing hypertension was 2.35 for women with a premature menopause in comparison with women who did not reach a premature menopause (95% CI: 0.11–50.7; data not shown).

4. Discussion

Our nested case-control study shows that BMI is the most important risk factor for hypertension in this population of childhood cancer survivors, with a median attained age of 28 years. Survivors with a BMI of more than 25 kg/m^2 had a 4-fold significantly increased risk of hypertension compared with the survivors with a BMI lower than 25 kg/m^2. Cisplatin, cyclophosphamide, and abdominal radiotherapy seemed to be associated with increased risks, but no significant results were found, possibly due to limited power of our study.

As far as we know, this is the first study that investigates treatment-related risk factors for hypertension in a large

Table 2 – Patient characteristics.

Characteristic	Number of cancer patients, N (%)		
	Case patients ($n = 44$) N (%)	Control subjects ($n = 123$) N (%)	Total ($n = 167$) N (%)
Sex			
Male	25 (56.8)	69 (56.1)	94 (56.3)
Female	19 (43.2)	54 (43.9)	73 (43.7)
Primary childhood cancer diagnosis			
Leukaemia	4 (9.1)	22 (17.9)	26 (15.6)
Lymphoma	16 (36.4)	28 (22.8)	44 (26.3)
Wilms' tumour	12 (27.3)	35 (28.5)	47 (28.1)
Brain/CNS	3 (6.8)	15 (12.2)	18 (10.8)
Bone	2 (4.5)	7 (5.7)	9 (5.4)
Soft tissue sarcoma	4 (9.1)	12 (9.8)	16 (9.6)
Other	3 (6.8)	4 (3.3)	7 (4.2)
Age at diagnosis of childhood cancer (years)			
<5.0	13 (29.5)	42 (34.1)	55 (32.9)
5.0–9.9	16 (36.4)	35 (28.5)	51 (30.5)
10.0–14.9	12 (27.3)	39 (31.7)	51 (30.5)
15.0–17.9	3 (6.8)	7 (5.7)	10 (6.0)
Attained age at diagnosis of hypertension (cases) or cut-off date (controls) (years)			
5.0–14.9	1 (2.3)	2 (1.6)	3 (1.8)
15.0–19.9	4 (9.1)	12 (9.8)	16 (9.6)
20.0–24.9	11 (25.0)	30 (24.4)	41 (24.6)
25.0–29.9	15 (34.1)	40 (32.5)	55 (32.9)
30.0–34.9	7 (15.9)	21 (17.1)	28 (16.8)
⩾35.0	6 (13.6)	18 (14.6)	24 (14.4)
Calendar year of diagnosis childhood cancer			
December 1968–January 1979	24 (54.5)	68 (55.3)	92 (55.1)
February 1979–September 1984	12 (27.3)	36 (29.3)	48 (28.7)
October 1984–April 1990	6 (13.6)	14 (11.4)	20 (12.0)
May 1990–December 1993	2 (4.5)	5 (4.1)	7 (4.2)
Surgery			
Yes	29 (65.9)	76 (61.8)	105 (62.9)
Nefrectomy	12 (27.3)	35 (28.5)	47 (28.1)
No	15 (34.1)	47 (38.2)	62 (37.1)
Chemotherapy			
Yes	40 (90.9)	106 (86.2)	146 (87.4)
No	4 (9.1)	17 (13.8)	21 (12.6)
Radiotherapy			
Yes	27 (61.4)	75 (61.0)	102 (61.1)
No	17 (38.6)	48 (39.0)	65 (38.9)
Childhood cancer treatment category			
Surgery alone (±recurrence)	0 (0)	7 (5.7)	7 (4.2)
Chemotherapy (±S[a]) only (±recurrence)	17 (38.6)	41 (33.3)	58 (34.7)
Radiotherapy (±S[a]) only (± recurrence)	4 (9.1)	10 (8.1)	14 (8.4)
CT[b] & RT[c] (±S[a]) initial treatment (no recurrence)	17 (38.6)	51 (41.5)	68 (40.7)
CT[b] & RT[c] (±S[a]) including recurrence treatment	6 (13.6)	14 (11.4)	20 (12.0)
Recurrence			
Yes	10 (22.7)	16 (13.0)	26 (15.6)
No	34 (77.3)	107 (87.0)	141 (84.4)
Body Mass Index (kg/m^2)			
<20	2 (4.5)	16 (13.0)	18 (10.8)
20.0–24.9	16 (36.4)	63 (51.2)	79 (47.3)
25.0–29.9	14 (31.8)	25 (20.3)	39 (23.4)
30.0–34.9	6 (13.6)	8 (6.5)	14 (8.4)
⩾35.0	3 (6.8)	1 (0.8)	4 (2.4)

(continued on next page)

Table 2 – *continued*

Characteristic	Number of cancer patients, N (%)		
	Case patients (n = 44) N (%)	Control subjects (n = 123) N (%)	Total (n = 167) N (%)
Missing	3 (6.8)	10 (8.1)	13 (7.8)
Smoking			
Yes	5 (11.4)	15 (12.2)	20 (12.0)
No	39 (88.6)	104 (84.6)	143 (85.6)
Missing	0	4 (3.3)	4 (2.4)
Premature menopause (73 women)			
Yes	1 (5.3)	2 (3.7)	3 (4.1)
No	18 (94.7)	52 (96.3)	70 (95.9)
Interval between primary childhood cancer and diagnosis of hypertension (years)			
5.0–9.9	9 (20.5)	NA	NA
10.0–14.9	1 (2.3)	NA	NA
15.0–19.9	9 (20.5)	NA	NA
20.0–24.9	12 (27.3)	NA	NA
25.0–29.9	12 (27.3)	NA	NA
⩾30.0	1 (2.3)	NA	NA

[a] Surgery.
[b] Chemotherapy.
[c] Radiotherapy.

Table 3 – Prevalence of relevant health problems other than hypertension.

Adverse events	Number of cancer patients, N (%)		
	Case patients (n = 44) N (%)	Control subjects (n = 123) N (%)	Total (n = 167) N (%)
Cardiovascular disease[a]			
Yes	1 (2.3)	5 (4.1)	6 (3.6)
No	43 (97.7)	118 (95.9)	161 (96.4)
Hyperthyroidism[b]			
Yes	0 (0)	1 (0.8)	1 (0.6)
No	44 (100)	122 (99.2)	166 (99.4)
Hypothyroidism[c]			
Yes	2 (4.5)	9 (7.3)	11 (6.6)
No	42 (95.5)	114 (92.7)	156 (93.4)
Decreased ejection fraction[d]			
Yes	0 (0)	2 (1.6)	2 (1.2)
No	44 (100)	121 (98.4)	165 (98.8)
Renal insufficiency[e]			
Yes	1 (2.3)	0 (0)	1 (0.6)
No	43 (97.7)	123 (100)	166 (99.4)
Hyperlipidemia[f]			
Yes	3 (6.8)	0 (0)	3 (1.8)
No	41 (93.2)	123 (100)	164 (98.2)
Diabetes mellitus[g]			
Yes	0 (0)	0 (0)	0 (0)
No	44 (100)	123 (100)	167 (100)

[a] Clinical cardiac or cardiovascular events (cardiomyopathy, arrhythmia, septal defects, peripheral arterial vascular disease).
[b] TSH < 0.4 mU/l and FT4 > 23 pmol/l (TSH = thyroid stimulating hormone).
[c] TSH ⩾ 5 mE/l and free T4 < 9 pmol/l or use of thyroxine (TSH = thyroid stimulating hormone).
[d] LVEF < 50% (LVEF = left ventricular ejection fraction).
[e] Glomerular filtration rate < 60 ml/min.
[f] TC/HDL ratio > 5, LDL cholesterol > 4.5 mmol/l or use lipid lowering medication (TC = total cholesterol, HDL = high density lipoprotein, and LDL = low density lipoprotein).
[g] Fasting blood glucose ⩾ 7.0 mmol/l and glycohemoglobin A1c (HbA1c) ⩾ 6.5% or use of oral antidiabetic medication or use of insulin.

Table 4 – Treatment-specific risk factors for hypertension.

	Case patients	Control subjects	Adjusted analysis[a]	
	N (%)	N (%)	OR (95% CI)	P-value
Model 1				
Treatment factors	44 (100)	123 (100)		
Cisplatin (yes versus no)	3 (6.8)	4 (3.3)	2.48 (0.44–13.93)	0.303
Cyclophosphamide (yes versus no)	12 (27.3)	26 (21.1)	1.68 (0.65–4.32)	0.282
Ifosfamide (yes versus no)	3 (6.8)	6 (4.9)	1.71 (0.33–8.84)	0.521
CT other (incl anthracyclines) (yes versus no)	35 (79.5)	99 (80.5)	1.03 (0.36–2.96)	0.957
RT Abdominal region (yes versus no)	16 (36.4)	38 (30.9)	1.52 (0.56–4.10)	0.410
RT cranium (yes versus no)	12 (27.3)	34 (27.6)	0.95 (0.40–2.28)	0.915
Model 2				
Treatment factors incl Body Mass Index	44 (100)	123 (100)		
Cisplatin (yes versus no)	3 (6.8)	4 (3.3)	4.32 (0.64–29.01)	0.132
Cyclophosphamide (yes versus no)	12 (27.3)	26 (21.1)	2.06 (0.73–5.78)	0.172
Ifosfamide (yes versus no)	3 (6.8)	6 (4.9)	1.33 (0.22–8.03)	0.756
CT other (incl anthracyclines) (yes versus no)	35 (79.5)	99 (80.5)	0.88 (0.28–2.82)	0.836
RT abdominal region (yes versus no)	16 (36.4)	38 (30.9)	1.79 (0.60–5.34)	0.295
RT cranium (yes versus no)	12 (27.3)	34 (27.6)	0.88 (0.36–2.14)	0.776
Body Mass Index (<25)	18 (40.9)	79 (64.2)	1.00	
Body Mass Index (⩾25 versus <25)	23 (52.3)	34 (27.6)	3.95 (1.71–9.09)	0.001
BMI unknown (versus <25)	3 (6.8)	10 (8.1)	1.91 (0.30–12.40)	0.497

[a] The odds ratio for every treatment factor is adjusted for all other treatment factors in this multivariate analysis.

Table 5 – Treatment-specific risk factors for hypertension according to follow-up interval.

	Case patients	Control subjects	Adjusted analysis[a]	
	N (%)	N (%)	OR (95% CI)	P-value
Model 1				
Follow-up ⩾ 20 years	25 (100)	69 (100)		
Cisplatin (yes versus no)	0	0	–	–
Cyclophosphamide (yes versus no)	6 (24.0)	12 (17.4)	2.03 (0.42–9.90)	0.382
Ifosfamide (yes versus no)	0	1 (1.4)	–	–
CT other (incl anthracyclines) (yes versus no)	20 (80.0)	56 (81.2)	0.72 (0.09–6.06)	0.762
RT abdominal region (yes versus no)	13 (52.0)	29 (42.0)	2.26 (0.60–8.55)	0.228
RT cranium (yes versus no)	7 (28.0)	18 (26.1)	1.13 (0.29–4.45)	0.859
Body Mass Index (<25)	10 (40.0)	41 (59.4)	1.00	
Body Mass Index (⩾25 versus <25)	15 (60.0)	24 (34.8)	2.98 (1.02–8.76)	0.047
BMI unknown (versus <25)	0	4 (5.8)	–	–
Model 2				
Follow-up < 20 years	19 (100)	54 (100)		
Cisplatin (yes versus no)	3 (15.8)	4 (7.4)	5.47 (0.73–41.11)	0.099
Cyclophosphamide (yes versus no)	6 (31.6)	14 (25.9)	1.82 (0.43–7.72)	0.419
Ifosfamide (yes versus no)	3 (15.8)	5 (9.3)	1.31 (0.13–12.73)	0.818
CT other (incl anthracyclines) (yes versus no)	15 (78.9)	43 (79.6)	0.88 (0.16–4.89)	0.882
RT abdominal region (yes versus no)	3 (15.8)	9 (16.7)	0.97 (0.11–8.92)	0.980
RT cranium (yes versus no)	5 (26.3)	16 (29.6)	0.58 (0.14–2.37)	0.447
Body Mass Index (<25)	8 (42.1)	38 (70.4)	1.00	
Body Mass Index (⩾25 versus <25)	8 (42.1)	10 (18.5)	6.89 (1.35–35.07)	0.020
BMI unknown (versus <25)	3 (15.8)	6 (11.1)	8.57 (0.38–192.41)	0.176

[a] The odds ratio for every treatment factor is adjusted for all other treatment factors in this multivariate analysis.

cohort of childhood cancer survivors treated for all kind of cancer diagnoses occurring during childhood in a broad treatment era (1966–1996). The strength of our study includes the long-term and complete follow-up of the CCS. Next, the medical assessment of all cohort members at the PLEK of the EKZ/AMC enabled us to use a strict definition of hypertension (systolic BP higher or equal to 140 mm Hg and/or a diastolic BP higher or equal to 90 mm Hg, measured three times on a row at three different visits). In most studies BP is measured by one duplex BP measurement within 5 or 10 min. The added value of several measurements on different occasion makes it possible to distinguish between incidental high blood pressure and persisting hypertension (structural high blood pressure). Due to our definition of hypertension for adults we possibly underestimated the risk of hypertension. However, only 13 patients were younger than 18 years (of whom only

3 below 15 years) at the end of follow-up. Four of them were cases with BP values above the 140/90 cut off for adults and thus also above levels for age-matched peers in the population. The other 9 persons (controls) had blood pressure values below normal for their age.

In our large cohort of CCS there were still relatively few hypertensive patients, probably due to our strict definition of hypertension and the young age of the patients (median: 27.8 years). Compared with the median attained age of the total CCS cohort, which is 24.4 years,[4] hypertension seemed to occur at the very long-term. With longer follow-up and a higher attained age of the survivors the risk of treatment-related hypertension may increase.

Unfortunately, it was not possible to compare the prevalence of hypertension in our cohort with the general population. Hypertension was assessed in several Dutch cohorts of young adults, and in most studies the definition of systolic BP $\geqslant$ 140 mm Hg and/or a diastolic BP $\geqslant$ 90 mm Hg was used. However, none of these studies required a measurement three times on a row at three different visits. Due to our stricter definition we would underestimate the prevalence ratio of hypertension compared with the available reference groups.

Overweight and obesity are known risk factors for hypertension in the general population. Findings from the US National Health and Nutrition Examination Survey, 1999–2004, including adults aged 18 years and older, showed an increase in the prevalence of hypertension with increasing overweight and obesity (18.1% for normal weight to 52.3% for obesity).[22] In our study, high BMI was the only significant risk factor for hypertension. In another study, in Acute Lymphoblastic Leukaemia survivors, an increased risk of obesity and hypertension at least several years after the completion of treatment was found, especially in survivors treated with high doses of corticosteroids.[23] In long-term CCS, Haddy and colleagues reported hypertension or prehypertension in 28% of patients.[19] This is a very high prevalence compared with our study, partly explained by the fact that Haddy and colleagues also included patients with prehypertension, whereas we did not include prehypertension. The different distribution of childhood cancer diagnoses in both studies may also have played a role. Thirty-seven percent of patients were obese or overweight. Seventy percent (7 of 10) of Wilms' tumour patients had hypertension or prehypertension, and 4 of 10 (40%) were obese or overweight. No associations with treatment were examined in this study. Another explanation of the high prevalence in these studies can be the generally higher prevalence of obesity in the population of the US in comparison with the Netherlands.

The percentage of survivors with a BMI $\geqslant$ 25 kg/m^2 (overweight) is, especially in the youngest cases aged 18–24 years, relatively high, compared to the Dutch general population in the Netherlands, where 15% of women and 19% of men aged 18–24 years were overweight (http://www.cbs.nl). In the 25–34 years age group both female and male cases showed an almost double prevalence of overweight persons compared to the general population, but the percentage of overweight persons in the male control group is slightly lower and in the female control group only slightly higher than the general population.

Risk factors for increasing prevalence of overweight and obesity in the general population are increasing food intake and decreasing physical activity. It would be interesting to examine whether our childhood cancer survivors differ from the general population on these lifestyle factors, or that their tendency to become overweight changed due to the treatments received. Therefore, we examined whether treatment-related factors associated with an increased BMI, might underlie the association we observed between BMI and hypertension. Obesity in childhood cancer survivors has been attributed to the effects of cranial radiation.[24] Cranial irradiation can influence the hypothalamic-pituitary axis and as a consequence result in deficiencies in one or more hormone systems. In our study no cases and 6 controls (of who 5 received cranial radiation) experienced growth hormone deficiency and were treated with growth hormone; due to these limited numbers no formal analysis was possible.

Therefore, we added cranial radiation to the regression model, but the OR for BMI did not change, implying that cranial radiotherapy does not influence BMI in our cohort.

Cisplatin is nephrotoxic and can induce, to a greater or lesser degree, impairment in glomerular function and hypomagnesaemia. Several studies show an association between the use of cisplatin in vascular toxicity, including hypertension.[25] Pietilä and colleagues found hypertension in 15.4% of childhood brain tumour survivors.[26] Elevated blood pressure was observed especially after exposure to both cisplatin and cranial irradiation. In our study cisplatin was associated with a non-significantly increased risk of hypertension, but cranial radiation was not related to the risk. Strikingly, after adjusting for BMI (Table 4) the OR for cisplatin increased from 2.5 to 4.3. So, the effect of cisplatin on hypertension may be underestimated if BMI is not taken into account. The analysis among female survivors suggests that women are possibly more sensitive to cisplatin than men. However, only one man received cisplatin, so we had insufficient power to examine this issue to draw conclusions from this. In future, larger studies of hypertension risk in childhood cancer survivors would be informative to collect detailed data about doses and number of cisplatin-based cycles and conduct analysis stratified by sex and follow-up time.

Cyclophosphamide and ifosfamide are nephrotoxic as well. There is, however, no evidence that these agents increase the risk of hypertension. Because we found non-significantly increased risks of hypertension, larger studies should address the role of these agents.

Radiation therapy is a cause of cardiovascular morbidity and mortality. This is due to the significant degree of atherosclerosis seen in the vessels in the vicinity of the area being irradiated.[27,28] Radiation-induced peripheral arterial disease is increasingly being recognised. Radiation-induced renal arterial stenosis is, however, rare. A major complication of renal arterial stenosis is hypertension. Also radiation nephropathy can lead to hypertension, amongst others through the involvement of the renin angiotensin system (RAS).[29] In CCS hypertension is seen as well following radiotherapy. In a study by Paulino and colleagues in Wilms' tumour survivors treated with radiotherapy, 3 out of 55 patients developed hypertension.[30]

Limitations of our study are the relatively low number of cases and we could not compare the prevalence of hypertension in our CCS cohort with a reference group. A nationwide collaboration between all paediatric oncology centres (LATER-initiative) in the Netherlands, will provide larger numbers of survivors for future studies. A well-defined control group (e.g. siblings) will be of much value for comparison with the prevalence in childhood cancer studies. Future studies should preferably also collect data on other risk factors, such as a family history of hypertension, physical activity and diet. For future research it should be interesting to also consider examining what case and control baseline BMIs were at time of cancer diagnosis, and to determine if cases were significantly more overweight at baseline compared with controls. A finding of similar BMI between the 2 groups at baseline would then suggest that cancer therapy and/or associated subsequent lifestyle changes may influence the development of both excess weight gain and accompanying hypertension at least in a susceptible subgroup of cancer survivors. This finding would have different implications for counselling patients/families, as well as implications for next research steps to further investigate these late effects. Another recommendation for future research is to collect high-quality CT and RT dose information as well, to make it possible to make more detailed analysis.

In conclusion, BMI was the most important risk factor for hypertension in our case-control study. Childhood cancer survivors already experience an increased risk of treatment-related cardiovascular disease. Therefore, it is very important to reduce the prevalence of cardiovascular risk factors such as hypertension. Consequently, childhood cancer survivors should be explained the importance of maintaining a normal weight.

Conflict of interest statement

None declared.

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