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Original Research

Hypertension in long-term childhood cancer survivors after treatment with potentially nephrotoxic therapy; DCCSS-LATER 2: Renal study

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KEYWORDS
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Abstract ***Purpose:*** To evaluate the prevalence of and risk factors for hypertension in childhood cancer survivors (CCSs) who were treated with potentially nephrotoxic therapies. ***Methods:*** In the Dutch Childhood Cancer Survivor Study LATER cohort part 2 renal study, 1024 CCS ≥5 years after diagnosis, aged ≥18 years at study participation, treated between

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Late effects;
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1963 and 2001 with nephrectomy, abdominal radiotherapy, total body irradiation (TBI), cisplatin, carboplatin, ifosfamide, high-dose cyclophosphamide (≥1 g/m^2 per single dose or ≥10 g/m^2 total) or haematopoietic stem cell transplantation participated and 500 controls from Lifelines. Hypertension was defined as blood pressure (BP) (mmHg) systolic ≥140 and/or diastolic ≥90 or receiving medication for diagnosed hypertension. At the study visit, the CKD-EPI 2012 equation including creatinine and cystatin C was used to estimate the glomerular filtration rate (GFR). Multivariable regression analyses were used.

For ambulatory BP monitoring (ABPM), hypertension was defined as BP daytime: systolic ≥135 and/or diastolic ≥85, night time: systolic ≥120 and/or diastolic ≥70, 24-h: systolic ≥130 and/or diastolic ≥80. Outcomes were masked hypertension (MH), white coat hypertension and abnormal nocturnal dipping (aND).

Results: Median age at cancer diagnosis was 4.7 years (interquartile range, IQR 2.4–9.2), at study 32.5 years (IQR 27.7–38.0) and follow-up 25.5 years (IQR 21.4–30.3). The prevalence of hypertension was comparable in CCS (16.3%) and controls (18.2%). In 12% of CCS and 17.8% of controls, hypertension was undiagnosed. A decreased GFR (<60 ml/min/1.73 m^2) was associated with hypertension in CCS (OR 3.4, 95% CI 1.4–8.5). Risk factors were abdominal radiotherapy ≥20 Gy and TBI. The ABPM-pilot study (n = 77) showed 7.8% MH, 2.6% white coat hypertension and 20.8% aND.

Conclusion: The prevalence of hypertension was comparable among CCS who were treated with potentially nephrotoxic therapies compared to controls, some of which were undiagnosed. Risk factors were abdominal radiotherapy ≥20 Gy and TBI. Hypertension and decreased GFR were associated with CCS. ABPM identified MH and a ND.

1. Introduction

Childhood cancer survival rates have increased significantly over the last decades [1]. As a consequence, childhood cancer survivors (CCSs) are at risk for late effects [2].

One of these conditions is nephrotoxicity [3,4]. Oncological treatments contributing to nephrotoxicity are nephrectomy, abdominal irradiation and chemotherapeutic agents such as ifosfamide, cyclophosphamide, cisplatin and carboplatin [4–10].

Kidney impairment may be caused by or lead to hypertension. Uncontrolled hypertension is a risk factor for cardiovascular disease (CVD) [11]. Some CCS have an increased risk for hypertension compared to the general population or siblings [12–14].

Studies assessing CCS describe the prevalence of high blood pressure (BP) ranging from 0 to 70% depending on the study population, treatments received and follow-up duration [4,12]. Reported risk factors are nephrectomy and radiotherapy involving the kidney [14–17]. However, the literature is inconclusive and extended follow-up studies in large cohorts are sparse. Because the prevalence of hypertension increases with age, timely identification of CCS at risk prior to its onset is important.

Ambulatory blood pressure monitoring (ABPM) is an indispensable adjunct to office BP measurement in the diagnosis and management of hypertension [18]. It better reflects actual BP, and nocturnal BP is the most significant predictor of CVD [19–21]. Studies in various cohorts of CCS using ABPM [15,22–26] reported insufficient nocturnal dipping [23,24,26] or deviant night-time diastolic BP (DBP) [15,22,25]. Unfortunately, these studies included small patient numbers.

In this nationwide cross-sectional cohort study, we evaluated the prevalence of and risk factors for hypertension in CCS treated with potentially nephrotoxic therapy in comparison with matched controls. Second, the association between hypertension and glomerular filtration rate (GFR) was assessed. Last, we aimed to substantiate the added value of ABPM by determining BP profiles.

2. Methods

2.1. Study population

The Dutch Childhood Cancer Survivor Study LATER cohort part 2; clinical visit and questionnaire study includes CCS diagnosed at the age of 0–17 years, treated between 1963 and 2001 in one of the Dutch childhood cancer centres, who survived ≥5 years from diagnosis (Fig. 1). Additional inclusion criteria for this renal substudy were (1) ≥18 years at the time of study, (2) sufficient understanding of the Dutch language to provide informed consent, (3) exposure to potentially nephrotoxic treatment, i.e. (a) nephrectomy, (b) radiotherapy involving the kidney (abdominal, total body irradiation (TBI)), (c)

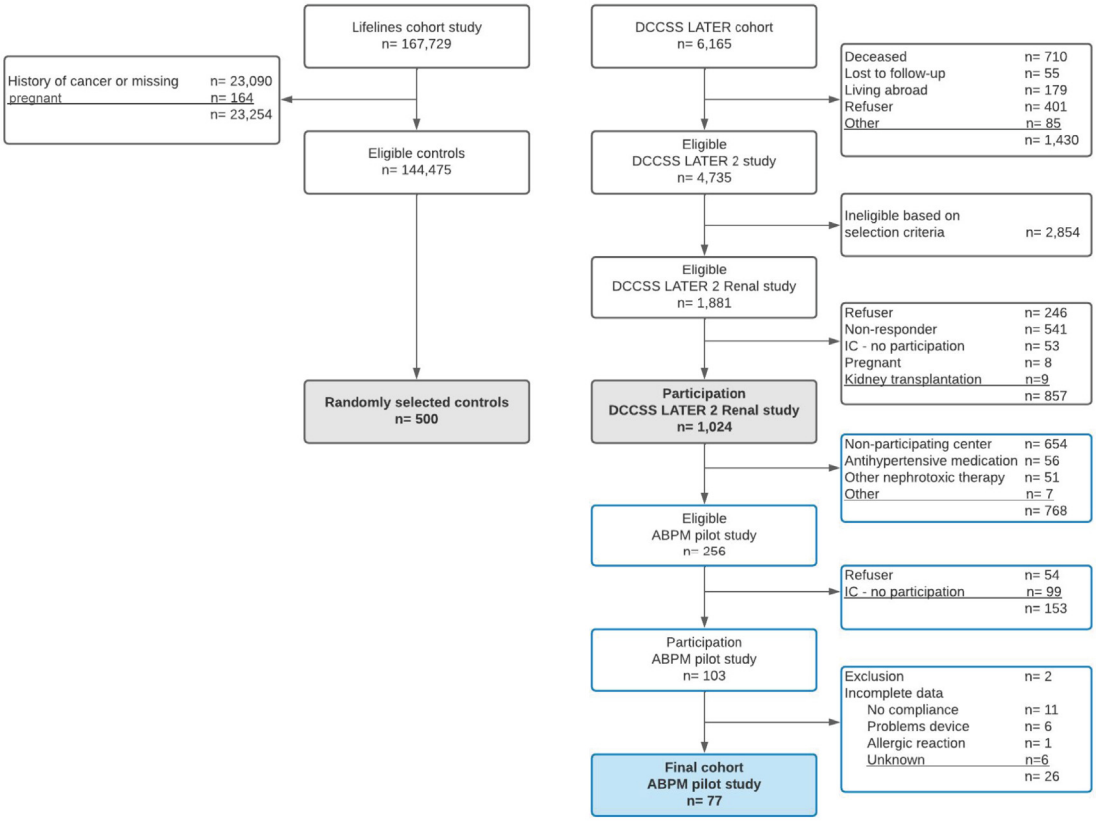

Fig. 1. Flowchart study cohort. Note 1: 53 childhood cancer survivors who had given informed consent did not participate for logistical reasons (i.e. restructuring of oncological follow-up in the Netherlands in the study period). Note 2: 7 childhood cancer survivors were considered ineligible by their physician for the ABPM pilot study for other reasons including expected burden for the patient based on medical history or known other kidney problems such as kidney cysts and dialysis. Note 3: 99 childhood cancer survivors who had given informed consent for the ABPM pilot study but did not participate for logistical reasons (i.e. time-lag in availability of monitors in the participating centres, insufficient number of devices available at time of study visit and late withdrawal of consent). Note 4: 2 childhood cancer survivors who underwent ABPM were excluded afterwards because one patient was found to use antihypertensive medication and the other had no representative data as the measurement was performed during a transatlantic flight with different time zones. Abbreviations: ABPM, ambulatory blood pressure monitoring; DCCSS, Dutch Childhood Cancer Survivor Study; IC, informed consent.

chemotherapy; cisplatin, carboplatin, ifosfamide or high dose (HD)-cyclophosphamide, i.e. $\geq$1 g/m^2 per single dose or $\geq$10 g/m^2 cumulative or (d) allogeneic haematopoietic stem cell transplantation (HSCT). For HD-cyclophosphamide information regarding dose per single dose was incomplete. In total, 1045 CCS had cyclophosphamide cumulative dose <10 g/m^2 and were not eligible based on other nephrotoxic cancer treatments. As not all individual schemes could be checked, we only selected CCS who had been treated with $\geq$1 g/m^2 per single dose according to ALL7 or ALL8 protocol [27,28] (n = 382). In these protocols, the high single doses were well documented and traceable. For the remaining CCS, it was unclear if they received high-dose cyclophosphamide according to our definition, and were therefore not invited (n = 663). Pregnancy during study or kidney transplantation in history were exclusion criteria. Two subsets have been described previously [10,14].

A pilot study with ABPM was performed in 2 participating centres in a subgroup suspected to be at the highest risk of kidney damage [10], i.e. (a) nephrectomy, (b) abdominal radiotherapy or TBI, (c) chemotherapy; cisplatin, ifosfamide. Patients using antihypertensive drugs were excluded from ABPM.

2.2. Controls

Five hundred controls from Lifelines participated. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and

complex genetics [29]. The same selection criteria applied, except those controls were not allowed to have cancer in history. CCS and controls were matched by age and sex using frequency matching.

2.3. Data collection

For all CCS, details on diagnosis and its treatment were collected. Furthermore, at study visit, data on medical history, physical examination and questionnaires were collected, and laboratory testing was performed. Patient weight was measured using an electronic scale (SECA, Hamburg, Germany), and height using a Holtain stadiometer (Holtain Ltd, Crymych, Dyved, Great Britain) and used to calculate body mass index (BMI), defined as weight divided by height squared. This study was approved by the Institutional Review Board of Emma Children's Hospital of the Amsterdam UMC (NL35046.018.11). All participants provided informed consent.

Lifelines provided demographic data and results of questionnaires, physical examinations and laboratory testing. Participants of lifelines provided informed consent for other study groups to use the data. The use of antihypertensive drugs was explored in CCS and controls in a similar manner. Participants were asked if they had specific health outcomes, including hypertension, at the time of the questionnaire. If yes, they were asked if they were currently using medication for high BP. In addition, they were asked to provide an overview of their current medication including the indications.

2.4. BP measurement

Office BP was measured three times on the right arm in a sitting position with 5 min intervals using an automated oscillometric BP measurement (Dinamap Pro 100, GE Healthcare, Little Chalfont, UK) with an appropriate-sized cuff. The mean systolic BP (SBP), DBP and mean arterial pressure (MAP) of the last two measurements were used for statistical analyses.

ABPM was performed using the non-invasive oscillometric Spacelabs Healthcare 90217 device (Snoqualmie, WA, USA). An appropriate-sized cuff was placed on the non-dominant arm and BP was automatically recorded every 15 min during daytime (10 am to 8pm), and every 30 min during night time (midnight to 6 am) [18,30]. In the remaining hours, BP was automatically recorded every 20 min. Patients received a diary to record events that could have influenced ABPM. Recordings with $<70\%$ successful readings were excluded for analysis. Mean daytime, night time and 24-h SBP, DBP and MAP were determined. The average 24-h BP was weighted for the intervals between successive readings. Nocturnal dipping of BP was calculated by subtracting the night time BP from the daytime BP, and then dividing this value by the daytime BP for MAP, SBP and DBP.

2.5. Outcome measures

Office hypertension was considered if participants had measured SBP $>$ 140 mmHg and/or DBP $>$ 90 mmHg or if they were taking medication for previously diagnosed hypertension [18]. Uncontrolled hypertension was defined as if hypertension was present during office measurement despite the use of antihypertensive medication.

For ABPM, hypertension was defined as [18]

- Daytime: systolic $\geq$135 and/or diastolic $\geq$85 mmHg
- Night time: systolic $\geq$120 and/or diastolic $\geq$70 mmHg
- 24-h: systolic $\geq$130 and/or diastolic $\geq$80 mmHg

White coat hypertension (WCH) was defined as hypertensive office readings in the absence of hypertension according to ABPM (daytime, night time and/or 24 h). Masked hypertension (MH) was defined if no hypertensive readings were found during office BP, while hypertension was present during ABPM. Insufficient nocturnal dipping was defined as a $<10\%$ fall of mean daytime BP values [18].

2.6. Kidney function

The CKD-EPI 2012 equation using creatinine and cystatin C was used to estimate GFR in CCS as well as controls [31]. Serum creatinine was measured using an enzymatic, isotope dilution mass spectrometry traceable method. Cystatin C was measured by analysers traceable to the international federation of clinical chemistry standard [32]. Laboratory testing was performed at the time of the study visit. An eGFR $<$60 ml/min/1.73m [2] was defined as decreased, corresponding with the kidney disease: improving global outcomes (KDIGO) 2012 guideline stages 3–5 of GFR categories in CKD [33].

2.7. Statistical analyses

Statistical analyses were carried out in IBM SPSS Statistics 25.0 (IBM Corp., Foster City, CA, USA). P-values $<$0.05 were considered statistically significant. Continuous values were assessed using the independent sample t-test or the Mann–Whitney U test in case of non-normality. For nominal variables, the Chi-Squared Analyses or Fisher exact test was used as appropriate.

The prevalence of hypertension, stratified by sex and age, was compared in CCS and controls. Multivariable logistic regression analyses were used to adjust for confounders including BMI and smoking. The association between GFR and hypertension was analysed by multivariable logistic regression, adjusted for age at study, BMI and smoking. By adding an interaction term

Table 1
Baseline characteristics study cohort.

Characteristics	Underlying cohort	Invited study population	Non-participants[b]	Participants	ABPM pilot study	Controls
	n = 6165	n = 1881	n = 787	n = 1024	n = 77	n = 500
Sex, n (%)						
Male	3433 (55.7)	**1009 (53.6)**	484 (61.5)	**505 (49.3)**	38 (49.4)	241 (48.2)
Female	2731 (44.3)	**872 (46.4)**	303 (38.5)	**519 (50.7)**	39 (50.6)	259 (51.8)
Transgender	1 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Primary childhood cancer (ICCC), n (%)						
Leukaemia, myeloproliferative diseases and myelodysplastic diseases	2094 (34.0)	569 (30.2)	225 (28.6)	317 (31.0)	9 (11.7)	–
Lymphomas and reticuloendothelial neoplasms	1062 (17.2)	150 (8.0)	68 (8.6)	79 (7.7)	5 (6.5)	–
CNS and miscellaneous intracranial and intraspinal neoplasms	844 (13.7)	121 (6.4)	55 (7.0)	62 (6.1)	0 (0)	–
Neuroblastoma and other peripheral nervous cell tumours	324 (5.3)	94 (5.0)	28 (3.6)	65 (6.3)	7 (9.1)	–
Retinoblastoma	33 (0.5)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0)	–
Kidney tumours	596 (9.7)	476 (25.3)	200 (25.4)	254 (24.8)	30 (39.0)	–
Hepatic tumours	52 (0.8)	34 (1.8)	22 (2.8)	12 (1.2)	1 (1.3)	–
Bone tumours	370 (6.0)	148 (7.9)	67 (8.5)	78 (7.6)	8 (10.4)	–
Soft tissue and other extraosseous sarcomas	450 (7.3)	168 (8.9)	72 (9.1)	92 (9.0)	14 (18.2)	–
Germ cell tumours, trophoblastic tumours and neoplasms of gonads	232 (3.8)	99 (5.3)	41 (5.2)	52 (5.1)	3 (3.9)	–
Other malignant epithelial neoplasms and malignant melanomas	102 (1.7)	18 (1.0)	8 (1.0)	10 (1.0)	0 (0)	–
Other and unspecified malignant neoplasms	6 (0.1)	2 (0.1)	0 (0)	2 (0.2)	0 (0)	–
Age at diagnosis (yr), n (%)[c]						
0–4	2727 (45.3)	994 (52.9)	417 (53.1)	537 (52.4)	44 (57.1)	–
5–9	1628 (27.1)	476 (25.3)	198 (25.2)	265 (25.9)	22 (28.6)	–
10–14	1285 (21.4)	312 (16.6)	128 (16.3)	171 (16.7)	9 (11.7)	–
15–17	376 (6.3)	98 (5.2)	43 (5.5)	51 (5.0)	2 (2.6)	–
Treatment period, n (%)						
1963–1969	119 (1.9)	20 (1.1)	6 (0.8)	14 (1.4)	1 (1.3)	–
1970–1979	978 (15.9)	130 (6.9)	54 (6.9)	72 (7.0)	5 (6.5)	–
1980–1989	1931 (31.3)	477 (25.4)	184 (23.4)	272 (26.6)	29 (37.7)	–
1990–1999	2541 (41.2)	1093 (58.1)	479 (60.9)	576 (56.3)	38 (49.4)	–
2000–2001	596 (9.7)	161 (8.6)	64 (8.1)	90 (8.8)	4 (5.2)	–
Age at participation/invitation (yr), n (%)[d]						
<18	49 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
18–30	1313 (32.9)	640 (39.1)	205 (37.8)	381 (37.2)	26 (33.8)	182 (36.4)
30–40	1511 (37.9)	709 (43.3)	244 (45.1)	446 (43.6)	36 (46.8)	216 (43.2)
>40	1118 (28.0)	286 (17.5)	92 (17.0)	197 (19.2)	15 (19.5)	102 (20.4)
Follow-up time since childhood cancer diagnosis (yr), n (%)						
10–20	981 (15.9)	328 (17.4)	133 (16.9)	186 (18.2)	12 (15.6)	–
20–30	1931 (31.3)	1078 (57.3)	469 (59.6)	569 (55.6)	35 (45.5)	–
30–40	1393 (22.6)	351 (18.7)	136 (17.3)	197 (19.2)	25 (32.5)	–
40–50	460 (7.5)	112 (6.0)	48 (6.1)	61 (6.0)	4 (5.2)	–
50–60	46 (0.7)	12 (0.6)	1 (0.1)	11 (1.1)	1 (1.3)	–
Surgery, n (%)[a]						
No	2912 (47.2)	694 (36.9)	281 (35.7)	385 (37.6)	15 (19.5)	–
Yes	3185 (51.7)	1182 (62.8)	503 (63.9)	637 (62.2)	62 (80.5)	–
Missing	68 (1.1)	5 (0.3)	3 (0.4)	2 (0.2)	0 (0)	–

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Underlying cohort	Invited study population	Non-participants[b]	Participants	ABPM pilot study	Controls
	n = 6165	n = 1881	n = 787	n = 1024	n = 77	n = 500
Radiotherapy, n (%)[a]						
No	3608 (58.5)	**1177 (62.6)**	533 (67.7)	**596 (58.2)**	45 (58.4)	–
Yes	2527 (41.0)	**703 (37.4)**	254 (32.3)	**427 (41.7)**	31 (41.6)	–
Missing	30 (0.5)	**1 (0.05)**	0 (0)	**1 (0.1)**	0 (0)	–
Chemotherapy, n (%)[a]						
No	1123 (18.2)	35 (1.9)	15 (1.9)	20 (2.0)	0 (0)	–
Yes	5005 (81.2)	1845 (98.1)	771 (98.0)	1004 (98.0)	77 (100)	–
Missing	37 (0.6)	1 (0.05)	1 (0.1)	0 (0)	0 (0)	–
Haematopoietic stem cell transplantation, n (%)[a,c]						
No	5532 (89.7)	1624 (86.4)	698 (88.8)	863 (84.3)	69 (98.6)	–
Autologous stem cell transplant	155 (2.5)	90 (4.8)	34 (4.3)	56 (5.5)	5 (6.5)	–
Allogenic stem cell transplant	231 (3.7)	153 (8.1)	51 (6.5)	95 (9.3)	3 (3.9)	–
Missing	98 (1.6)	13 (0.7)	3 (0.4)	10 (1.0)		–
Therapy, n (%)						
No treatment	61 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Surgery only	575 (9.3)	17 (0.9)	8 (1.0)	9 (0.9)	0 (0)	–
Chemotherapy only (± surgery)	2967 (48.1)	1160 (61.7)	525 (66.7)	587 (57.3)	45 (58.4)	–
Radiotherapy only (± surgery)	484 (7.9)	18 (1.0)	7 (0.9)	11 (1.1)	0 (0)	–
Chemotherapy and radiotherapy (± surgery)	2030 (32.9)	684 (36.4)	246 (31.3)	416 (40.6)	32 (41.6)	–
Missing	48 (0.8)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0)	–
Potentially nephrotoxic cancer treatment, n (%)[a]						
Nephrectomy	622 (10.1)	492 (26.2)	207 (26.3)	264 (25.8)	31 (40.3)	–
Unilateral	605 (97.3)	478 (97.2)	204 (98.6)	255 (96.6)	75 (97.4)	–
Bilateral partial	17 (2.7)	14 (2.9)	3 (1.5)	9 (3.4)	2 (2.6)	–
Radiotherapy, kidney area	467 (7.6)	273 (14.5)	90 (11.4)	175 (17.1)	15 (19.5)	–
Total body irradiation	221 (3.6)	143 (7.6)	52 (6.6)	85 (8.3)	4 (5.2)	–
Ifosfamide	714 (11.6)	524 (27.9)	206 (26.2)	300 (29.3)	32 (41.6)	–
HD-cyclophosphamide	833 (13.5)	504 (26.8)	208 (26.4)	278 (27.1)	6 (7.8)	–
Cisplatin	457 (7.4)	328 (17.4)	142 (18.0)	175 (17.1)	14 (18.2)	–
Carboplatin	422 (6.9)	284 (15.1)	125 (15.9)	151 (14.7)	14 (18.2)	–
Hematopoietic stem cell transplantation	231 (3.8)	153 (8.1)	51 (6.5)	95 (9.3)	3 (3.9)	–
BMI (kg/m^2)						
<25	–	–	–	**629 (61.4)**	56 (72.7)	**274 (54.8)**
25–30	–	–	–	**284 (27.7)**	20 (26.0)	**169 (33.8)**
>30	–	–	–	**92 (9.0)**	1 (1.3)	**57 (11.4)**
Missing	–	–	–	19 (1.9)	0 (0)	0 (0)
Smoking, ever for >1 year, n (%)						
No	–	–	–	**619 (60.4)**	43 (55.8)	**251 (50.2)**
Yes	–	–	–	**271 (26.5)**	23 (29.9)	**231 (46.2)**
Missing	–	–	–	134 (13.1)	11 (14.3)	18 (3.6)
Office blood pressure (mmHg), mean ± SD						
Systolic blood pressure	–	–	–	**122.16 ± 14.70**	120.47 ± 13.11	**126.35 ± 14.12**
Diastolic blood pressure	–	–	–	**75.09 ± 9.98**	74.28 ± 8.03	**72.59 ± 8.84**

Antihypertensive medication regardless of indication, n (%)						
No	–	–	–	**914 (89.3)**	0 (0)	**488 (97.6)**
Yes	–	–	–	**110 (10.7)**	0 (0)	**12 (2.4)**
Medication for hypertension, n (%)						
No	–	–	–	**959 (93.7)**	0 (0)	**493 (98.6)**
Yes	–	–	–	**65 (6.3)**	0 (0)	**7 (1.4)**
Office hypertension, n (%)						
No	–	–	–	837 (81.7)	70 (90.9)	409 (81.8)
Yes	–	–	–	167 (16.3)	7 (9.1)	91 (18.2)
Missing	–	–	–	20 (2.0)	0 (0)	0 (0)
Uncontrolled hypertension, n (%)						
No	–	–	–	984 (96.1)	–	495 (99.0)
Yes	–	–	–	19 (1.9)	–	5 (1.0)
Missing	–	–	–	21 (2.1)	–	0 (0)

Abbreviations: BMI, body mass index; HD, high dose; n, number; yr, year.
Bold = p-value <0.05.
[a] For primary cancer and recurrences.
[b] Non-participants includes refusers and non-responders. CCS with informed consent without participation (n = 53), being pregnant (n = 8) or a history of kidney transplantation (n = 9) were not included in this table because they were willing to participate.
[c] Missing for survivors refusing registration, n = 149.
[d] Missing for survivors refusing participation, n = 2174.

(cohort*decreased GFR), we tested to determine if the association between decreased GFR and hypertension differed for CCS and controls. Because the interaction term was significant, stratified analyses were performed. To evaluate the odds for hypertension of different diagnosis groups compared to controls, multivariable logistic regression analyses were performed adjusted for age, gender, BMI and smoking.

In addition, multivariable logistic regression analyses were used to assess risk factors for hypertension in CCS. The following risk factors were assessed: exposure to cisplatin, carboplatin, ifosfamide, HD-cyclophosphamide, abdominal radiotherapy, TBI, nephrectomy and HSCT. Possible confounders included age at diagnosis, follow-up duration, sex, BMI and smoking. A second model was performed to assess the association of cumulative doses, categorised as dose tertiles when at least 10 CCS were exposed. Correlation between variables was assessed using Spearman's rank correlation and considered relevant in case >0.6. Due to the strong correlation between TBI and HSCT (correlation coefficient 0.77), HSCT was not included.

3. Results

3.1. Study sample

The study sample consisted of 1024 CCS (Fig. 1). With respect to the invited study population, participants were slightly more likely to be female and been treated with radiotherapy, although exposure to abdominal radiotherapy and TBI were not significantly different (Table 1). The majority of the final study group was diagnosed with leukaemia (31.0%) or Wilms tumour (24.8%). CCS were mostly exposed to ifosfamide (29.3%), HD-cyclophosphamide (27.1%) or nephrectomy (25.8%). The median age at diagnosis was 4.7 years (interquartile range [IQR] 2.4–9.2), at study 32.5 years (IQR 27.7–38.0), and median follow-up was 25.5 years (IQR 21.4–30.3). Obesity (BMI ≥30) and smoking were less common in CCS compared to controls (respectively, 9% versus 11.4%, p = 0.01, and 26.5% versus 46.2%, p < 0.001).

3.1.1. ABPM-pilot study

The ABPM-pilot study included 77 participants (Fig. 1). It consisted mainly of survivors treated with nephrectomy (40.3%) and ifosfamide (41.6%). The most frequent diagnoses were Wilms tumours (39.0%) and soft tissue sarcoma (18.2%) (Table 1).

3.2. Hypertension in CCS and controls

The overall prevalence of office hypertension was comparable between CCS (16.3%) and controls (18.2%) (p = 0.45) (Table 1). Of the CCS, 121 (12.1%) had hypertension during office measurement and 65 (6.3%)

were receiving medication for known hypertension. Of the controls, 89 (17.8%) had hypertension during office measurement and 7 (1.4%) were using medication. Uncontrolled hypertension was uncommon in both CCS (1.9%) and controls (1.0%). Stratified analyses showed that male CCS aged 18–29 years had lower odds for hypertension compared to controls (OR 0.4, 95% CI 0.2–0.8) (Table 2). For the other groups, no significant differences were found. Also, for the diagnosis groups, no differences were observed (Table 3).

A decreased eGFR (<60 ml/min/1.73m [2]) was associated with hypertension in CCS (OR 3.4, 95% CI 1.4–8.5). Out of 26 CCS with eGFR <60 ml/min/1.73m [2], 14 (53.8%) had hypertension of whom 5 (35.8%) controlled with medication, 2 (14.2%) uncontrolled and 7 (50%) being untreated. None of the controls had eGFR <60 ml/min/1.73m [2].

3.3. Risk factors

Risk factors for hypertension were abdominal radiotherapy (OR 2.2, 95% CI 1.3–4.0) and TBI (OR 3.0, 95% CI 1.6–5.8) (Table 4, Supplementary Table 1). For abdominal radiotherapy, this only holds for cumulative dose ≥20 Gy. Other risk factors included older age at diagnosis, longer follow-up duration, obesity and male sex.

3.4. ABPM-pilot study

Mean office BP was 120/74 (±13/±8) mmHg, and mean 24-h BP was 112/69 (±9/±6) mmHg (Table 5). In the 77 participants of the ABPM-pilot study, hypertension was more often identified with ABPM (14.3%) than with office measurement (9.1%), p < 0.001. Moreover, 7 (9.1%) CCS had daytime hypertension, 8 (10.4%) night time hypertension and 6 (7.8%) 24-h hypertension. Six (7.8%) CCS had MH and 2 (2.6%) WCH. Insufficient nocturnal dipping was detected in 16 (20.8%) participants.

Demographic statistics showed no differences in outcomes for the four therapies (i.e. nephrectomy, abdominal radiotherapy or TBI, ifosfamide and cisplatin). However, CCS treated with nephrectomy had higher mean 24-h ABPM values compared to CCS without nephrectomy. CCS treated with abdominal radiotherapy or TBI had higher 24-h DBP and 24-h MAP than those not radiated.

Table 3
Multivariable logistic regression analysis for hypertension including diagnosis groups.

	Hypertension	
	Prevalence[a]	OR (95% CI) Multivariable
Controls	91/500 (18.2)	1.0 (ref)
Haematological malignancies	57/389 (14.7)	0.9 (0.6–1.3)
CNS tumours	4/55 (7.3)	0.4 (0.1–1.2)
Neuroblastoma	10/65 (15.4)	1.2 (0.5–2.5)
Kidney tumours	53/249 (21.3)	1.1 (0.7–1.7)
Bone tumours	13/78 (14.1)	0.8 (0.4–1.6)
Soft tissue sarcomas	13/92 (14.1)	0.7 (0.3–1.4)
Other malignancies	17/76 (22.4)	1.5 (0.7–2.9)

Model corrected for age at study, sex, BMI and smoking status (ever for >1 years).
Numbers do not always add up to the total because of missing values.
Abbreviations: 95% CI, 95% confidence interval; CNS, central nervous system; OR, odds ratio; ref, reference.
Bold = p-value < 0.05.
[a] Values are the number of participants with a positive test result/total number of participants tested (percentage).

4. Discussion

This cross-sectional cohort study in long-term CCS treated with potentially nephrotoxic therapy showed a prevalence of hypertension in CCS comparable to that of controls and lower odds for hypertension in male survivors aged 18–29 years. Undiagnosed hypertensive BP was found in 12% of CCS and 17.8% of controls.

Based on previous large cohort studies and identified cancer-treatment related risk factors in our study, we expected a higher prevalence and increased odds for hypertension in CCS compared to controls [12,14]. Several factors might have contributed to our findings.

Table 2
Multivariable logistic regression analyses for hypertension in childhood cancer survivors compared to matched controls.

	Male				Female			
	CCS[a]	Controls[a]	OR (95% CI) uncorrected[b]	OR (95% CI) MV model[b,c]	CCS[a]	Controls[a]	OR (95% CI) uncorrected[b]	OR (95% CI) MV model[b,c]
Age group (years)								
18-29	17/178 (9.6)	17/84 (20.2)	**0.4 (0.2–0.9)**	**0.4 (0.2–0.8)**	13/193 (6.7)	3/98 (3.1)	2.3 (0.6–8.2)	2.2 (0.6–8.5)
30-39	42/228 (18.4)	30/114 (26.3)	0.6 (0.4–1.1)	0.7 (0.4–1.3)	26/208 (12.5)	9/102 (8.8)	1.5 (0.7–3.3)	1.8 (0.7–4.3)
40-65	35/91 (38.5)	16/43 (37.2)	1.1 (0.5–2.2)	1.2 (0.5–2.7)	34/106 (32.1)	16/59 (27.1)	1.3 (0.6–2.6)	1.7 (0.7–3.6)

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; MV, multivariable; OR, odds ratio.
Bold = p-value < 0.05.
[a] Values are the number of participants with hypertension/total number of participants tested (percentage).
[b] Reference group controls.
[c] Models correct for BMI and smoking (ever for >1 year).

First, when comparing the prevalence in our control group to that reported in the general Dutch population, it is similar for females and males aged ≥40 years. However, for males aged 30–40 years, the prevalence is higher in our controls (26%) than the overall Dutch population (17%), and for males aged 18–30 years, no information is available [34]. Prevalence in young male controls might have been overestimated and been influenced by a confounder we are not aware of. We looked into potential familial relationships in our

Table 4
Multivariable logistic regression analyses for hypertension in childhood cancer survivors including treatment.

	Prevalence of hypertension[a] 167/1004 (16.3)	OR (95% CI) Univariable	OR (95% CI) Multivariable Model 1	OR (95% CI) Multivariable Model 2	p-trend[b]
Nephrectomy					
No	113/745 (15.2)	**1.0 (ref)**	1.0 (ref)	1.0 (ref)	
Yes	54/259 (20.8)	**1.5 (1.03–2.1)**	0.9 (0.5–1.7)	0.9 (0.5–1.9)	
Abdominal RT					
No	114/816 (14.0)	**1.0 (ref)**	**1.0 (ref)**		
Yes	52/173 (30.1)	**2.6 (1.8–3.9)**	**2.2 (1.3–4.0)**		
Model 2: dose, Gy					
None	114/816 (14.0)			1.0 (ref)	0.41
<20	8/47 (17.0)			1.5 (0.5–4.0)	
20–30	21/54 (38.9)			**2.8 (1.3–6.1)**	
>30	22/70 (31.4)			**2.3 (1.1–4.6)**	
TBI					
No	143/904 (15.8)	**1.0 (ref)**	**1.0 (ref)**	**1.0 (ref)**	
Yes	23/85 (27.1)	**2.0 (1.2–3.3)**	**3.0 (1.6–5.8)**	**3.6 (1.8–7.2)**	
Ifosfamide					
No	126/706 (17.8)	1.0 (ref)	1.0 (ref)		
Yes	41/298 (13.8)	0.7 (0.5–1.1)	0.9 (0.6–1.4)		
Model 2: dose, mg/m^2					
None	126/706 (17.8)			1.0 (ref)	0.63
≤12,000	12/98 (12.2)			0.6 (0.3–1.4)	
12,0001–42,000	13/98 (13.3)			1.0 (0.5–2.1)	
>42,000	16/100 (16.0)			1.3 (0.6–2.7)	
HD-cyclo					
No	127/732 (17.3)	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Yes	38/270 (14.1)	0.8 (0.5–1.2)	1.3 (0.7–2.2)	1.4 (0.8–2.6)	
Cisplatin					
No	139/832 (16.7)	1.0 (ref)	1.0 (ref)		
Yes	28/172 (16.3)	1.0 (0.6–1.5)	1.4 (0.7–2.5)		
Model 2: dose mg/m^2					
None	139/832 (16.7)			1.0 (ref)	0.57
≤300	9/58 (15.5)			1.4 (0.5–3.6)	
301–500	9/58 (15.5)			1.2 (0.5–3.0)	
>500	9/55 (16.4)			1.7 (0.7–4.2)	
Carboplatin					
No	155/858 (18.1)	1.0 (ref)	1.0 (ref)		
Yes	12/146 (8.2)	0.4 (0.2–0.8)	1.0 (0.4–2.1)		
Model 2: dose, mg/m^2					
None	155/858 (18.1)			1.0 (ref)	0.99
≤1500	3/50 (6.0)			0.4 (0.05–3.1)	
1501–2800	5/47 (10.6)			1.1 (0.3–3.4)	
>2800	4/47 (8.5)			1.4 (0.4–4.5)	
HSCT					
No	146/901 (16.2)	1.0 (ref)	NA	NA	
Yes	20/93 (21.5)	1.4 (0.8–2.4)			
Sex					
Male	94/497 (18.9)	1.0 (ref)	**1.0 (ref)**	**1.0 (ref)**	
Female	73/507 (14.4)	0.7 (0.5–1.0)	**0.6 (0.4–0.9)**	**0.6 (0.4–0.9)**	
Age at diagnosis (per year)	–	**1.1 (1.02–1.1)**	**1.1 (1.03–1.13)**	**1.1 (1.02–1.12)**	
Follow-up duration (per 5 year)	–	**1.5 (1.3–1.7)**	**1.5 (1.3–1.8)**	**1.5 (1.3–1.8)**	
BMI					
<25	77/626 (12.3)	**1.0 (ref)**	**1.0 (ref)**	**1.0 (ref)**	

(*continued on next page*)

Table 4 (*continued*)

	Prevalence of hypertension[a] 167/1004 (16.3)	OR (95% CI) Univariable	OR (95% CI) Multivariable Model 1	OR (95% CI) Multivariable Model 2	p-trend[b]
25–30	68/283 (24.0)	**2.3 (1.6–3.2)**	**2.4 (1.6–3.7)**	**2.4 (1.6–3.7)**	
>30	20/92 (21.7)	**2.0 (1.1–3.4)**	**2.4 (1.3–4.6)**	**2.5 (1.3–4.7)**	
Smoking ever >1 year					
No	102/605 (16.9)	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Yes	50/268 (18.7)	1.1 (0.8–1.6)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	

All factors have been adjusted for simultaneously. Model 2 was similar to model 1, except that the dichotomous treatment modalities have been substituted by cumulative doses if applicable.
Numbers do not always add up to the total because of missing values.
Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; Gy, gray; HD, high-dose; HSCT, hematopoietic stem cell transplantation; NA, not applicable; OR, odds ratio; ref, reference; RT, radiotherapy; TBI, total body irradiation.
Bold = p-value < 0.05.
[a] Number of participants with hypertension/number available for the outcome (%).
[b] Test for trend in continuous dose variable among exposed CCS.

controls which might have influenced our results. Indeed, two pairs of siblings were included in the control cohort, yet none of them had arterial hypertension. Second, obesity and smoking were less common in CCS compared to controls. We adjusted for these factors, but a generally healthier lifestyle in CCS might have positively influenced BP. Third, we used a strict definition of hypertension including office BP measurement and medication for previously diagnosed hypertension. Antihypertensive agents are often prescribed for other indications as well in CCS including proteinuria, arrhythmias and cardiomyopathy [35]. Despite the other indication, a BP-lowering effect can be expected and we cannot exclude that these patients would have become hypertensive when no medication was taken. Lastly, maybe the impact of former oncologic treatment manifests later during follow-up since hypertension is more common with advancing age and our study population was relatively young [36].

Nevertheless, the observed association between hypertension and decreased GFR in our cohort of CCS being in early to mid-adulthood is alarming, especially since hypertension has been shown to be a relevant risk factor for CVD [37] and chronic kidney disease (CKD) in CCS [38,39]. Although CCSs are invited for surveillance programs, still 12% had undiagnosed hypertension. Of note, hypertension was uncontrolled or not yet treated in the majority of CCS with stage 3–5 CKD. Lifestyle counselling together with screening and treatment of modifiable risk factors such as hypertension are of utmost importance in this population at risk of CKD. In addition, GFR monitoring in CCS at risk for hypertension based on their oncological treatment is essential.

In line with some other studies, exposure to abdominal radiotherapy [14,16] and TBI [17] were associated with hypertension. For abdominal radiotherapy, the odds were increased for cumulative doses ≥20 Gy. It should, however, be noted that our analyses are based on prescribed cumulative radiation dose rather than estimated absorbed radiation dose. Green *et al.* recently observed a significant association of lower radiotherapy doses to a higher volume of the kidney with CKD, while there was no statistical impact of higher doses ≥15 Gy to a smaller volume of the kidney [38]. For future studies, it would be of interest to investigate the association of kidney dosimetry with hypertension.

Gibson *et al.* only identified nephrectomy as a risk factor for hypertension. Nephrectomy also increased the odds of hypertension in our cohort in univariate analysis, but this was not confirmed in the multivariable model. This may be related to differences in the studied populations including follow-up time, age at evaluation and treatment exposures. Our study population consisted of CCS treated with potentially nephrotoxic therapy, while Gibson *et al.* included a wider range of treatment exposures. Therefore, our results are not generalisable to the complete CCS population but are restricted to those treated with potentially nephrotoxic therapy. Our study also identified other known risk factors for hypertension in CCS [12,14,17,40] and the general population [18], including obesity, male sex, older age at diagnosis and longer follow-up.

In our ABPM-pilot study, MH was observed in 7.8% and WCH in 2.6%. In other CCS studies, MH was seen in 0% [23] up to 34% of Wilms tumour survivors [26]. Comparison of our findings is difficult because these studies were mainly performed on children and cohorts are heterogeneous. In the general population, MH is found in approximately 10% [41] and WCH up to 30–40% [18], the latter especially in older people. We found insufficient nocturnal dipping in 20.8% of CCS. Reported prevalence in other CCS cohorts ranged from 26 to 52% [23–26]. The high prevalence in our study and others is worrisome since non-dipping has been associated with cardiovascular mortality in patients with CKD [42]. Despite the benefits, ABPM has some disadvantages as well. ABPM can be uncomfortable, which was also seen in our study as 10.6% had incomplete measurements. Another disadvantage is the limited availability. ABPM should be considered in the surveillance of CCS treated with radiotherapy, nephrectomy or CCS

Table 5
Results of the ABPM pilot study.

Characteristics	All participants	Nephrectomy			Abdominal RT & TBI[a]			Ifosfamide			Cisplatin		
	N = 77	No (n = 46)	Yes (n = 31)	p- value	No (n = 57)	Yes (n = 19)	p-value	No (n = 45)	Yes (n = 32)	p-value	No (n = 63)	Yes (n = 14)	p-value
Office BP values (mmHg), mean ± SD													
Systolic BP	120.47 ± 13.11	118.4 ± 12.2	123.6 ± 14.0	0.09	119.0 ± 11.0	126.5 ± 15.9	0.07	121.6 ± 12.8	118.9 ± 13.5	0.37	120.7 ± 13.5	119.6 ± 11.7	0.78
Diastolic BP	74.28 ± 8.03	73.1 ± 8.9	76.1 ± 6.3	0.11	73.9 ± 8.0	76.3 ± 6.9	0.25	74.6 ± 7.5	73.8 ± 8.8	0.65	75.0 ± 7.2	71.1 ± 10.8	0.11
MAP	89.68 ± 8.93	88.2 ± 9.3	91.9 ± 8.1	0.07	89.0 ± 8.2	93.0 ± 9.1	0.07	90.3 ± 8.3	88.8 ± 9.8	0.48	90.2 ± 8.6	87.3 ± 10.3	0.27
24-h ABPM values (mmHg), mean ± SD													
Daytime systolic BP	119.06 ± 10.64	**117.0 ± 10.4**	**122.2 ± 10.4**	**0.03**	118.5 ± 9.5	122.3 ± 11.6	0.17	120.6 ± 10.4	116.9 ± 10.7	0.13	119.3 ± 10.8	118.2 ± 10.0	0.74
Daytime diastolic BP	75.30 ± 7.34	74.1 ± 7.8	77.1 ± 6.3	0.08	74.7 ± 7.4	77.8 ± 6.4	0.11	75.8 ± 6.5	74.7 ± 8.4	0.52	75.4 ± 7.1	74.8 ± 8.8	0.78
Daytime MAP	89.89 ± 7.80	**88.4 ± 8.0**	**92.1 ± 7.1**	**0.04**	89.3 ± 7.3	92.6 ± 7.7	0.10	90.7 ± 7.3	88.7 ± 8.4	0.28	90.0 ± 7.7	89.3 ± 8.4	0.74
Night time systolic BP	102.32 ± 9.69	**99.9 ± 8.9**	**105.9 ± 9.8**	**0.01**	102.0 ± 8.9	104.4 ± 11.0	0.35	103.9 ± 10.9	100.1 ± 7.3	0.07	103.0 ± 10.0	99.5 ± 7.8	0.23
Night time diastolic BP	59.66 ± 7.39	**58.2 ± 7.5**	**61.8 ± 6.8**	**0.03**	55.9 ± 6.9	62.4 ± 8.2	0.07	60.4 ± 7.8	58.7 ± 678	0.33	60.1 ± 7.5	57.6 ± 6.6	0.24
Nighttime MAP	73.88 ± 7.54	**72.1 ± 7.3**	**76.5 ± 7.2**	**0.01**	73.3 ± 6.8	76.4 ± 8.9	0.11	74.9 ± 8.4	72.5 ± 5.9	0.18	74.4 ± 7.8	71.5 ± 6.0	0.20
24 h systolic BP	112.71 ± 9.32	**110.5 ± 8.8**	**115.9 ± 9.3**	**0.01**	112.2 ± 8.0	115.6 ± 11.0	0.23	114.0 ± 9.7	110.8 ± 8.5	0.14	113.0 ± 9.6	111.4 ± 7.9	0.55
24 h diastolic BP	69.40 ± 6.83	**68.0 ± 7.1**	**71.5 ± 5.9**	**0.03**	**68.6 ± 6.5**	**72.4 ± 6.7**	**0.04**	69.9 ± 6.3	68.7 ± 7.5	0.44	69.6 ± 6.8	68.6 ± 7.0	0.62
24 h MAP	83.84 ± 6.91	**82.2 ± 6.7**	**86.3 ± 6.5**	**0.01**	**83.2 ± 6.1**	**86.8 ± 7.9**	**0.04**	84.6 ± 7.0	82.7 ± 6.7	0.24	84.1 ± 7.1	82.8 ± 6.3	0.55
Deviant values, n (%)													
Office hypertension	7 (9.1)	3 (6.5)	4 (12.9)	0.43	3 (5.3)	4 (21.1)	0.06	4 (8.9)	3 (9.4)	1.00	6 (9.5)	1 (7.1)	1.00
ABPM hypertension	11 (14.3)	5 (10.9)	6 (19.4)	0.33	7 (12.3)	4 (21.1)	0.45	8 (17.8)	3 (9.4)	0.35	9 (14.3)	2 (14.3)	1.00
Masked hypertension	6 (7.8)	3 (6.5)	3 (9.7)	0.68	5 (8.8)	1 (5.3)	1.00	5 (11.1)	1 (3.1)	0.39	4 (6.3)	2 (14.3)	0.30
White coat hypertension	2 (2.6)	1 (2.2)	1 (3.2)	1.00	1 (1.8)	1 (5.3)	0.44	1 (2.2)	1 (3.1)	1.00	1 (1.6)	1 (7.1)	0.33
Insufficient nocturnal dipping	16 (20.8)	10 (21.7)	6 (19.4)	0.80	12 (21.1)	3 (15.8)	0.75	9 (20.0)	7 (21.9)	0.84	14 (22.2)	2 (14.3)	0.72

Abbreviations24-h, 24 h; ABPM, ambulatory blood pressure measurement; BP, blood pressure; MAP, mean arterial pressure; RT, radiotherapy; SD, standard deviation; TBI, total body irradiation.
Bold = p-value < 0.05.
[a] Missing for n = 1.

having CKD. However, our pilot study was performed in a selected group and limited in its ability to determine which subgroups most benefit from ABPM. More research in larger cohorts is needed.

The complete nationwide Dutch Childhood Cancer Survivor Study-LATER cohort is unique in its kind since diagnosis and cumulative doses of treatment are very well registered. Other strengths were the prolonged follow-up duration and taking into account matched controls. Although the ABPM-pilot study was completed in 30% of eligible CCSs, it is the largest to date and provided new insights. Office BP was measured carefully including multiple readings, but it was assessed at one-time point rather than separate measures over the course of multiple visits due to the cross-sectional design [18]. Since we only included CCS treated according to the ALL7 or ALL8 protocol for high single doses of cyclophosphamide, selection bias cannot be excluded.

In conclusion, after a median of 25 of years follow-up, CCS treated with potentially nephrotoxic therapy have a prevalence of hypertension comparable to that of matched controls. Yet, hypertension is associated with stages 3–5 CKD in this relatively young population of CCS. CCS exposed to abdominal radiotherapy $\geq$20 Gy or TBI are at risk of hypertension. ABPM should be considered in the surveillance of CCS.

Authors contribution

Ek: Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation; HvdP: Data acquisition, Manuscript preparation, Data analysis and interpretation, Statistical analysis; EvD; Data acquisition; MvdHL: Data acquisition, Quality control of data and algorithms; JL: Data acquisition, Quality control of data and algorithms; LK: Data acquisition, Quality control of data and algorithms; ML: Data acquisition; SB: Data acquisition; MP: Data acquisition; WT: Data acquisition; Adv: Data acquisition; SP: Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis; AB: Data analysis and interpretation, Statistical analysis, Manuscript preparation; MV: Data analysis and interpretation, Statistical analysis, Manuscript preparation; All authors: Study concepts, Study design, Manuscript editing, Manuscript review.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.038.

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