The Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 kidney analysis examined long-term glomerular dysfunction in childhood cancer survivors

Check for updates

OPEN

Esmee C.M. Kooijmans[1,2], Helena J.H. van der Pal[2], Saskia M.F. Pluijm[2], Margriet van der Heiden-van der Loo[2,3], Leontien C.M. Kremer[2,4,5], Dorine Bresters[2,6], Eline van Dulmen-den Broeder[1], Marry M. van den Heuvel-Eibrink[2,7], Jacqueline J. Loonen[8], Marloes Louwerens[9], Sebastian J.C. Neggers[10], Cécile Ronckers[2], Wim J.E. Tissing[2,11], Andrica C.H. de Vries[2,7], Gertjan J.L. Kaspers[1,2], Margreet A. Veening[1,2,13] and Arend Bökenkamp[12,13]; on behalf of the Dutch LATER study group

[1]*Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands;* [2]*Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands;* [3]*Dutch Childhood Oncology Group, Utrecht, the Netherlands;* [4]*Division of Child Health, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, the Netherlands;* [5]*Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands;* [6]*Department of Pediatric Oncology, Willem Alexander Children's Hospital/Leiden University Medical Center, Leiden, the Netherlands;* [7]*Department of Pediatric Oncology, Sophia Children's Hospital/Erasmus Medical Center, Rotterdam, the Netherlands;* [8]*Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands;* [9]*Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands;* [10]*Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands;* [11]*Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; and* [12]*Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands*

This investigation aimed to evaluate glomerular dysfunction among childhood cancer survivors in comparison with matched controls from the general population. In the Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 kidney analysis, a nationwide cross-sectional cohort study, 1024 survivors five or more years after diagnosis, aged 18 or more years at study, treated between 1963-2001 with nephrectomy, abdominal radiotherapy, total body irradiation, cisplatin, carboplatin, ifosfamide, high-dose cyclophosphamide or hematopoietic stem cell transplantation participated. In addition, 500 age- and sex-matched controls from Lifelines, a prospective population-based cohort study in the Netherlands, participated. At a median age of 32.0 years (interquartile range 26.6-37.4), the glomerular filtration rate was under 60 ml/min/1.73m^2 in 3.7% of survivors and in none of the controls. Ten survivors had kidney failure. Chronic kidney disease according to age-thresholds (glomerular filtration rate respectively under 75 for age under 40, under 60 for ages 40-65, and under 40 for age over 65) was 6.6% in survivors vs. 0.2% in controls. Albuminuria (albumin-to-creatinine ratio over3 mg/mmol) was found in 16.2% of survivors and 1.2% of controls. Risk factors for chronic kidney disease, based on multivariable analyses, were nephrectomy (odds ratio 3.7 (95% Confidence interval 2.1-6.4)), abdominal radiotherapy (1.8 (1.1-2.9)), ifosfamide (2.9 (1.9-4.4)) and cisplatin over 500 mg/m^2 (7.2 (3.4-15.2)). For albuminuria, risk factors were total body irradiation (2.3 (1.2-4.4)), abdominal radiotherapy over 30 Gy (2.6 (1.4- 5.0)) and ifosfamide (1.6 (1.0-2.4)). Hypertension and follow-up 30 or more years increased the risk for glomerular dysfunction. Thus, lifetime monitoring of glomerular function in survivors exposed to these identified high risk factors is warranted.

Kidney International (2022) **102,** 1136–1146; https://doi.org/10.1016/j.kint.2022.05.029

KEYWORDS: childhood cancer survivor; glomerular toxicity; late effects; nephrotoxicity

Correspondence: *Esmee C.M. Kooijmans, Amsterdam UMC, VUmc, PK-1X52, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail: e.kooijmans@amsterdamumc.nl*

[13]MAV and AB shared last authorship.

Received 19 January 2022; revised 14 April 2022; accepted 20 May 2022; published online 27 June 2022

The survival of childhood cancer has increased significantly over the past few decades, resulting in a current 5-year survival of 80% in developed countries.[1,2] With the growing number of childhood cancer survivors (CCS), the concern about long-term adverse effects has increased correspondingly.[3–5]

Nephrotoxicity is one of the known late effects in CCS. Renal dysfunction can be induced by nephrectomy, radiotherapy to

the kidney region, or nephrotoxic chemotherapeutic agents such as ifosfamide, cyclophosphamide, cisplatin, and carboplatin.[6–15]

Glomerular impairment can be assessed by estimation of glomerular filtration rate (eGFR) and the presence of albuminuria.[16] The reported prevalence of renal outcomes among CCS is highly variable because of variation in outcome measures, study population, treatment exposure, and follow-up duration. The prevalence of reduced GFR varies from 0% to 73.7% and proteinuria from 0% to 84% among CCS.[17] Microalbuminuria is an early indicator of kidney disease and has been shown to predict the development of kidney function impairment.[18,19] A low eGFR and albuminuria are independent predictors of all-cause and cardiovascular mortality.[20,21] This emphasizes the need to identify CCS at risk of glomerular dysfunction at an early stage.

To date, long-term follow-up studies investigating nephrotoxicity in large cohorts of CCS are limited, in part, because the survival rates have increased mainly in the last 2 decades. Recently 2 reports have been published on nephrotoxicity in large cohorts of long-term CCS.[22,23] In the general population, GFR also declines during adulthood as part of normal aging.[24–26] By taking into account an age- and sex-matched control group, and investigating glomerular dysfunction comprehensively in a well-characterized cohort of CCS, our study builds on previous literature.

This nationwide cross-sectional cohort study was set out to analyze the prevalence of and risk factors for glomerular dysfunction in a large cohort of very long-term CCS in comparison with matched controls from the general population.

METHODS

Study population

The Dutch Childhood Cancer Survivor Study-LATER cohort (1963–2001) part 2: clinical visit and questionnaire study includes patients with a histologically verified diagnosis of malignancy. Patients were treated before the age of 18 years in one of the 7 Dutch pediatric oncology centers between 1963 and 2001 and have a follow-up of ≥5 years since initial diagnosis. Additional inclusion criteria for this sub-study were as follows: (i) age ≥18 years at the time of study; (ii) sufficient understanding of the Dutch language to provide informed consent; (iii) treatment with (a) nephrectomy (unilateral, partial bilateral), (b) radiotherapy involving 1 or both kidneys in the field (abdominal, total body irradiation [TBI], in nephrectomized patients' radiotherapy in the field of the remnant kidney), (c) chemotherapy with cisplatin, carboplatin, ifosfamide, and/or high-dose (HD) cyclophosphamide, that is, ≥1 g/m^2 per single dose or ≥10 g/m^2 cumulative dose, or (d) allogeneic hematopoietic stem cell transplantation (HSCT). If the cyclophosphamide cumulative dose was <10 g/m^2, CCS were only selected if they had been treated according to the ALL7 and ALL8 protocols[27,28] because that information was complete. Pregnancy at the time of data collection was an exclusion criterion. Patients with a history of kidney transplantation before their study visit were designated as having decreased eGFR or chronic kidney disease (CKD) stage 5. Their laboratory data from study visit were considered as "missing." Three subcohorts have been reported previously.[10,11,29]

Controls

Data from 500 participants of the Lifelines project were provided as controls. Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique 3-generation design of the health and health-related behaviors of 167,729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.[30,31] For controls, the same exclusion criteria as described for CCS were applied, with the addition that they were not allowed to have a history of cancer. The 500 controls were randomly selected from the eligible study cohort. CCS and controls were matched by age and sex using frequency matching, meaning that the ratio between CCS and controls is equal for every unique age-sex combination.

Data collection

For all eligible CCS with the exception of those refusing data storage, details of diagnosis and treatment, including cumulative doses, were collected. In addition, at the time of study, participants underwent laboratory testing, a physical examination, and were asked to complete questionnaires regarding medical history, medication, and lifestyle. All participants were seen for the study visit between October 2016 and February 2020. This study was approved by the institutional review board of Emma Children's Hospital of Amsterdam University Medical Centers (NL35046.018.11). Written informed consent was obtained from all participants.

From the controls demographic data and results of questionnaires, medical examination and laboratory testing were provided. Blood samples of CCS and controls were drawn in the morning. At the same time, an early morning urine sample was collected.

Definition of glomerular dysfunction

GFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2012 formula including creatinine and cystatin C.[32] Serum creatinine (μmol/l) was determined using an enzymatic, isotope dilution mass spectrometry traceable method. Cystatin C (mg/l) was measured on a BN ProSpec nephelometer (Siemens Healthcare) until July 2018, thereafter on an Atellica neph 630 system nephelometer (Siemens Healthcare) until December 2019, and last on a Rochel/Hitachi Cobas C 701 analyzer (Cobas). For the controls, a Roche Cobas 6000 (C502) analyzer (Cobas) was used. All are traceable to the international federation of clinical chemistry standard.[33] An eGFR <90 ml/min per 1.73 m^2 was defined as decreased eGFR. In addition, we used eGFR categories as recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline[16]: G1: eGFR ≥90 ml/min per 1.73 m^2, G2: eGFR 60–89 ml/min per 1.73 m^2, G3a: eGFR 45–59 ml/min per 1.73 m^2, G3b: eGFR 30–44 ml/min per 1.73 m^2, G4: eGFR 15–29 ml/min per 1.73 m^2, and G5: eGFR <15 ml/min per 1.73 m^2. Furthermore, CKD according to age-specific thresholds as suggested by Delanaye *et al.*[26] was evaluated: age <40 years, eGFR <75 ml/min per 1.73 m^2; age 40–65 years, eGFR <60 ml/min per 1.73 m^2; and age >65 years, eGFR <40 ml/min per 1.73 m^2.

Last, albuminuria was classified according to the KDIGO 2012 guideline[16]: (i) albumin-to-creatinine ratio <3 mg/mmol normal to mildly increased, (ii) albumin-to-creatinine ratio 3–30 mg/mmol moderately increased (i.e., microalbuminuria), and (iii) albumin-to-creatinine ratio >30 mg/mmol severely increased (i.e., macroalbuminuria). Classifications 2 and 3 were defined as albuminuria.

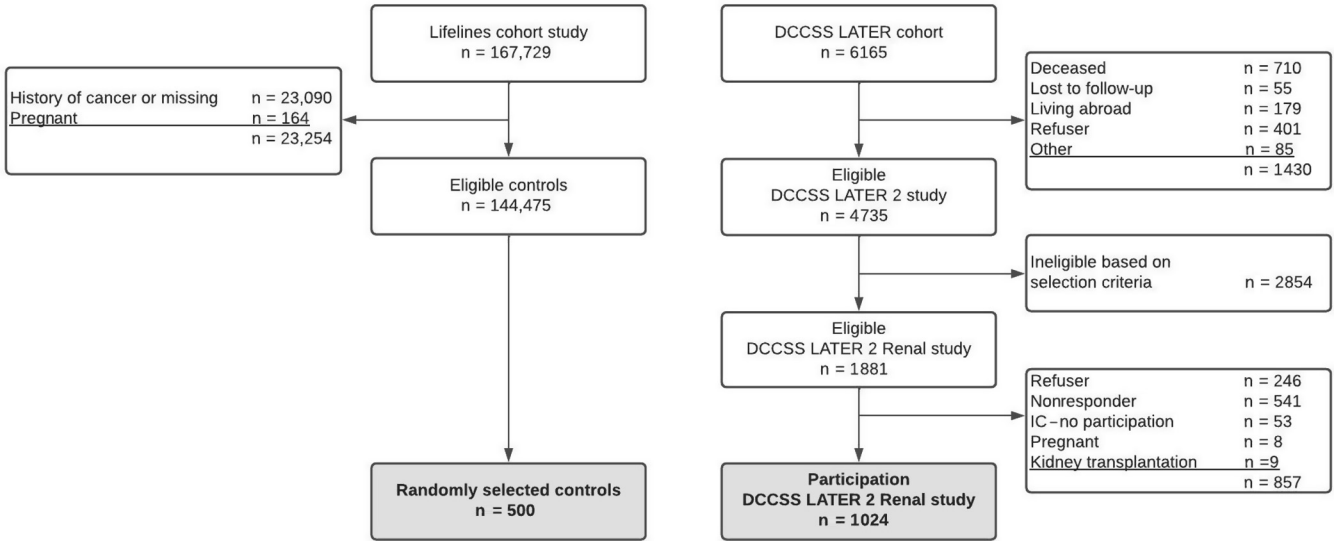

Figure 1 | Flowchart study cohort. DCCSS, Dutch Childhood Cancer Survivor Study; IC, informed consent.

Statistical analyses

Descriptive statistics were used to summarize demographic variables and glomerular outcomes. Continuous outcomes were compared using the independent sample *t* test in case of the normal distribution or the Mann-Whitney *U* test in case of non-normality. χ^2 tests or Fisher exact tests (if the number of cases in 1 cell was less than 5) were performed to compare nominal outcomes. Descriptive statistics are expressed as mean (± standard deviation) for normally distributed continuous variables or as median (interquartile range [IQR]) in case of non-normal distribution.

Risk factors for decreased eGFR and albuminuria were assessed using multivariable logistic regression analyses in 2 ways. First, in comparison to controls, mutually exclusive treatment groups were evaluated, as well as different tumor types. These models were corrected for age at study, sex, hypertension, and diabetes.

Second, the impact of individual agents was assessed among CCS. The following risk factors were investigated (yes/no): cisplatin, carboplatin, ifosfamide, HD cyclophosphamide, abdominal radiotherapy, TBI, nephrectomy, HSCT, and age at diagnosis (per year). Possible confounders included follow-up duration, sex, hypertension, and diabetes. For albuminuria, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker was also assessed as potential confounder. Correlation between variables was assessed using Spearman's rank correlation. In case the correlation coefficient between 2 variables was >0.6, one of the variables was excluded for the final model based on lowest prevalence or clinical consideration. Because TBI and HSCT were strongly correlated (correlation coefficient 0.77), HSCT was not included in the models. This decision was based on clinical judgment. TBI is an important treatment modality often used in the conditioning regimen of HSCT, and the cause of kidney damage in HSCT is often multifactorial,[34] which limits the evaluation of this association.

Confounders that were not significantly associated with the outcome were removed unless they caused a ≥10% change in the odds ratio (OR) of a variable included in the model. We additionally tested hypothesized interactions using interaction terms between hypertension and nephrectomy, hypertension and abdominal radiotherapy, diabetes and nephrectomy, diabetes with abdominal radiotherapy, and diabetes with TBI for both outcomes.

To investigate the association between cumulative doses and glomerular outcomes, treatment agents with at least 10 exposed cases were categorized according to cumulative dose tertiles. Extra multivariable models were created likewise as described above, in which per model 1 dichotomous treatment variable was replaced by cumulative dose tertiles.

Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp.). Two-tailed hypothesis tests were performed, and *P* values <0.05 were considered statistically significant.

RESULTS

Study population

Of 1881 CCS eligible for participation in the Dutch Childhood Cancer Survivor Study-LATER 2 renal study, 1094 (58.2%) gave informed consent. The final study cohort consisted of 1033 participants and 500 controls (Figure 1). In 8 of 9 kidney transplant recipients, kidney failure had been caused by cancer treatment–induced nephrotoxicity. Of 710 deceased patients, 4 were known with chronic kidney failure as a secondary cause of death.

Most of the participants were diagnosed with leukemia (30.7%) or Wilms tumor (25.4%) (Table 1). Potentially, nephrotoxic cancer therapies often used were ifosfamide (29.1%), HD cyclophosphamide (27.0%), and nephrectomy (26.3%). The distribution of nephrotoxic agents per decade is shown in Supplementary Figure S1. Study participants diagnosed before 1980 were in large part treated with nephrectomy and abdominal radiotherapy. The median age at diagnosis was 4.7 years (IQR: 1.3–8.1 years), the median age at study was 32.0 years (IQR: 26.6–37.4 years), and the median follow-up duration was 25.6 years (IQR: 21.1–30.1 years). The median age of controls was 32.6 years (IQR: 27.4–37.8 years). The distribution of birth weight categories was comparable among CCS and controls. Diabetes was more prevalent in CCS (3.7%) than controls (0.8%), $P = 0.001$. In addition, angiotensin-converting enzyme inhibitors or

Table 1 | Baseline characteristics study cohort

Characteristics	Underlying cohort n = 6165	Invited study population n = 1881	Nonparticipants[e] n = 787	Participants n = 1033	Controls n = 500
Sex, n (%)					
Male	3433 (55.7)	**1009 (53.6)**	484 (61.5)	**507 (49.1)**	241 (48.2)
Female	2731 (44.3)	**872 (46.4)**	303 (38.5)	**526 (50.9)**	259 (51.8)
Transgender	1 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)
Primary childhood cancer (ICCC), n (%)					
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	2094 (34.0)	569 (30.2)	225 (28.6)	317 (30.7)	—
Lymphomas and reticuloendothelial neoplasms	1062 (17.2)	150 (8.0)	68 (8.6)	79 (7.6)	—
CNS and miscellaneous intracranial and intraspinal neoplasms	844 (13.7)	121 (6.4)	55 (7.0)	62 (6.0)	—
Neuroblastoma and other peripheral nervous cell tumors	324 (5.3)	94 (5.0)	28 (3.6)	65 (6.3)	—
Retinoblastoma	33 (0.5)	2 (0.1)	1 (0.1)	1 (0.1)	—
Renal tumors	596 (9.7)	476 (25.3)	200 (25.4)	262 (25.4)	—
Hepatic tumors	52 (0.8)	34 (1.8)	22 (2.8)	12 (1.2)	—
Bone tumors	370 (6.0)	148 (7.9)	67 (8.5)	78 (7.6)	—
Soft tissue and other extraosseous sarcomas	450 (7.3)	168 (8.9)	72 (9.1)	92 (8.9)	—
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	232 (3.8)	99 (5.3)	41 (5.2)	52 (5.1)	—
Other malignant epithelial neoplasms and malignant melanomas	102 (1.7)	18 (1.0)	8 (1.0)	10 (1.0)	—
Other and unspecified malignant neoplasms	6 (0.1)	2 (0.1)	0 (0)	2 (0.2)	—
Age at diagnosis, yr, n (%)[a]					
0–4	2727 (45.3)	994 (52.9)	417 (53.1)	543 (52.6)	—
5–9	1628 (27.1)	476 (25.3)	198 (25.2)	268 (25.9)	—
10–14	1285 (21.4)	312 (16.6)	128 (16.3)	171 (16.6)	—
15–17	376 (6.3)	98 (5.2)	43 (5.5)	51 (4.9)	—
Treatment period, n (%)					
1963–1969	119 (1.9)	20 (1.1)	6 (0.8)	14 (1.4)	—
1970–1979	978 (15.9)	130 (6.9)	54 (6.9)	74 (7.2)	—
1980–1989	1931 (31.3)	477 (25.4)	184 (23.4)	276 (26.7)	—
1990–1999	2541 (41.2)	1093 (58.1)	479 (60.9)	577 (55.9)	—
2000–2001	596 (9.7)	161 (8.6)	64 (8.1)	92 (8.9)	—
Age at participation/invitation, yr, n (%)[b]					
<18	49 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
18–30	1313 (32.9)	640 (39.1)	205 (37.8)	383 (37.1)	182 (36.4)
30–40	1511 (37.9)	709 (43.3)	244 (45.1)	451 (43.7)	216 (43.2)
>40	1118 (28.0)	286 (17.5)	92 (17.0)	199 (19.3)	102 (20.4)
Follow-up time since childhood cancer diagnosis, yr, n (%)					
10–20	981 (15.9)	328 (17.4)	133 (16.9)	188 (18.2)	—
20–30	1931 (31.3)	1078 (57.3)	469 (59.6)	571 (55.3)	—
30–40	1393 (22.6)	351 (18.7)	136 (17.3)	201 (19.5)	—
40–50	460 (7.5)	112 (6.0)	48 (6.1)	62 (6.0)	—
50–60	46 (0.7)	12 (0.6)	1 (0.1)	11 (1.1)	—
Surgery, n (%)[c]					
No	2912 (47.2)	694 (36.9)	281 (35.7)	385 (37.3)	—
Yes	3185 (51.7)	1182 (62.8)	503 (63.9)	646 (62.5)	—
Missing	68 (1.1)	5 (0.3)	3 (0.4)	2 (0.2)	—
Radiotherapy, n (%)[c]					
No	3608 (58.5)	**1177 (62.6)**	533 (67.7)	**602 (58.3)**	—
Yes	2527 (41.0)	**703 (37.4)**	254 (32.3)	**430 (41.6)**	—
Missing	30 (0.5)	1 (0.05)	0 (0)	1 (0.1)	—

(*Continued on following page*)

Table 1 | (Continued) **Baseline characteristics study cohort**

Characteristics	Underlying cohort n = 6165	Invited study population n = 1881	Nonparticipants[e] n = 787	Participants n = 1033	Controls n = 500
Chemotherapy, n (%)[c]					
No	1123 (18.2)	35 (1.9)	15 (1.9)	20 (1.9)	—
Yes	5005 (81.2)	1845 (98.1)	771 (98.0)	1013 (98.1)	—
Missing	37 (0.6)	1 (0.05)	1 (0.1)	0 (0)	—
Stem cell transplantation/reinfusion, n (%)[a,c]					
No	5532 (89.7)	1624 (86.4)	698 (88.8)	872 (84.4)	—
Autologous transplant	155 (2.5)	90 (4.8)	34 (4.3)	56 (5.4)	—
Allogeneic HSCT	231 (3.7)	153 (8.1)	51 (6.5)	95 (9.2)	—
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)	—
Surgery only	575 (9.3)	17 (0.9)	8 (1.0)	9 (0.9)	—
Chemotherapy only (± surgery)	2967 (48.1)	1160 (61.7)	525 (66.7)	593 (57.4)	—
Radiotherapy only (± surgery)	484 (7.9)	18 (1.0)	7 (0.9)	11 (1.1)	—
Chemotherapy and radiotherapy (± surgery)	2030 (32.9)	684 (36.4)	246 (31.3)	419 (40.6)	—
Missing	48 (0.8)	2 (0.1)	1 (0.1)	1 (0.1)	—
Potentially nephrotoxic cancer treatment, n (%)[c]					
Nephrectomy	622 (10.1)	492 (26.2)	207 (26.3)	272 (26.3)	—
Unilateral	605 (97.3)	478 (97.2)	204 (98.6)	261 (96.0)	—
Bilateral partial	17 (2.7)	14 (2.9)	3 (1.5)	11 (4.0)	—
Radiotherapy renal area	467 (7.6)	273 (14.5)	90 (11.4)	177 (17.4)	—
Total body irradiation	221 (3.6)	143 (7.6)	52 (6.6)	85 (8.3)	—
Ifosfamide	714 (11.6)	524 (27.9)	206 (26.2)	301 (29.1)	—
HD cyclophosphamide	833 (13.5)	504 (26.8)	208 (26.4)	278 (27.0)	—
Cisplatin	457 (7.4)	328 (17.4)	142 (18.0)	176 (17.0)	—
Carboplatin	422 (6.9)	284 (15.1)	125 (15.9)	152 (14.7)	—
Allogeneic HSCT	231 (3.8)	153 (8.1)	51 (6.5)	95 (9.3)	—
Birth weight, n (%)					
Low birth weight (<2.5 kg)	—	—	—	33 (3.2)	20 (4.0)
Normal birth weight (2.5–4 kg)	—	—	—	656 (63.5)	320 (64.0)
Macrosomia (>4 kg)	—	—	—	100 (9.7)	48 (9.6)
Missing				244 (23.6)	112 (22.4)
Hypertension, n (%)[d]					
No	—	—	—	841 (83.0)	409 (81.8)
Yes	—	—	—	172 (17.0)	91 (18.2)
Missing				20 (2.0)	0 (0)
Diabetes, n (%)					
No	—	—	—	**913 (96.3)**	**496 (99.2)**
Yes	—	—	—	**35 (3.7)**	**4 (0.8)**
Missing				85 (5.5)	0 (0)
Current use ACEi-ARB, n (%)					
No	—	—	—	**958 (92.7)**	**495 (99.0)**
Yes	—	—	—	**75 (7.3)**	**5 (1.0)**

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; HD, high-dose; HSCT, hematopoietic stem cell transplantation; ICCC, International Classification of Childhood Cancer.
[a]Missing for survivors refusing registration, n = 149.
[b]Missing for survivors refusing participation, n = 2174.
[c]For primary cancer and recurrences.
[d]Hypertension defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or taking medication for previously diagnosed hypertension.
[e]Nonparticipants include refusers and nonresponders. Childhood cancer survivors with informed consent without participation (n = 53) or being pregnant (n = 8) were not included in this table because they were willing to participate.
Bold data indicate $P < 0.05$.

Table 2 | Glomerular function in childhood cancer survivors compared with matched controls

Glomerular function parameter	Childhood cancer survivors Mean (SD)/N (%)	Controls Mean (SD)/N (%)	*P* value
Mean eGFR	101.6 (18.8)	103.6 (12.3)	0.02
eGFR <90 ml/min per 1.73 m^2	226/943 (24.0)	71/500 (14.2)	<0.001
GFR category			<0.001
G1	717/943 (76.0)	429/500 (85.8)	
G2	191/943 (20.3)	71/500 (14.2)	
G3	21/943 (2.2)	0/500 (0)	
G4	4/943 (0.4)	0/500 (0)	
G5	10/943 (1.1)	0/500 (0)	
Albuminuria (ACR ≥ 3)	152/929 (16.4)	6/500 (1.2)	<0.001
ACR (mg/mmol)			<0.001
<3	777/929 (83.6)	494/500 (98.8)	
3–30	142/929 (15.3)	5/500 (1.0)	
>30	10/929 (1.1)	1/500 (0.2)	

ACR, albumin:creatinine ratio; eGFR, estimated glomerular function rate.

angiotensin receptor blocker was more frequently used in CCS (7.3%) as compared with controls (1.0%), $P < 0.001$.

Prevalence of glomerular dysfunction

The prevalence rates of the KDIGO 2012 eGFR and albuminuria categories are presented in Table 2 and Figure 2.[16] CCS had more often a GFR of <90 ml/min per 1.73 m^2 compared with controls. In total 226 CCS (24.0%) and 71 controls (14.2%) had an eGFR <90 ml/min per 1.73 m^2. Stage 3–5 CKD was present in 35 CCS (3.7%), with 1.1% having end-stage kidney disease, but not in controls. The modified CKD definition adapted to age showed CKD in 62 of 943 CCS (6.6%) and 1 of 500 controls (0.2%), $P < 0.001$. At an age >40 years, the mean eGFR for CCS became significantly lower when compared with controls (Figure 3). Albuminuria was more prevalent in CCS (16.4%) than controls (1.2%), $P < 0.001$. Of these, 10 CCS (1.1%) and 1 control (0.2%) had macroalbuminuria.

When comparing risk categories for CKD outcomes based on combined eGFR and albuminuria measurement, higher risks of concurrent complications were estimated in CCS (Figure 2). Moreover, low risk was estimated in at least 70.8% CCS and 98.8% controls, moderately increased risk in at least 13.1% CCS and 1% controls, high risk in at least 1.6% CCS and 0.2% controls, and very high risk in 1.7% CCS and 0% controls.

Risk factors for glomerular dysfunction

Risk factors in CCS compared with controls. In relation to controls, the odds for reduced eGFR were especially increased for CCS treated with nephrectomy only (OR: 2.9, 95% confidence interval [CI]: 1.7–4.9), ifosfamide only (OR: 2.4, 95% CI: 1.3–4.2), cisplatin only (OR: 2.4, 95% CI: 1.3–4.5), nephrectomy combined with abdominal radiotherapy (OR: 3.1, 95% CI: 1.8–5.3), and the combination of ifosfamide with carboplatin (OR: 4.0, 95% CI: 1.9–8.3) (Figure 4, Supplementary Table S1). Moreover, survivors of solid tumors, including neuroblastoma, renal tumors, bone tumors, and soft tissue sarcomas, showed increased odds for decreased eGFR in comparison with controls (Figure 5, Supplementary Table S2).

The prevalence of albuminuria was increased for almost all treatment groups and tumor types (Supplementary Tables S1 and S2). As a consequence of the low prevalence in the control group, no multivariable analyses could be performed

CCS (n = 986)			KDIGO 2012 albuminuria categories		
eGFR (ml/min per 1.73 m^2)	KDIGO 2012 eGFR category	Missing albuminuria	A1 (<3 mg/mmol)	A2 (3–30 mg/mmol)	A3 (>30 mg/mmol)
Missing eGFR			38 (3.9%)	5 (0.5%)	0 (0%)
≥90	G1	34 (3.4%)	588 (59.6%)	91 (9.2%)	4 (0.4%)
60–89	G2	10 (1.0%)	143 (14.5%)	38 (3.9%)	0 (0%)
45–59	G3a	1 (0.1%)	6 (0.6%)	5 (0.5%)	3 (0.3%)
30–44	G3b	0 (0%)	2 (0.2%)	3 (0.3%)	1 (0.1%)
15–29	G4	2 (0.2%)	0 (0%)	0 (0%)	2 (0.2%)
<15	G5	10 (1.0%)	0 (0%)	0 (0%)	0 (0%)

Controls (n = 500)		KDIGO 2012 albuminuria categories		
eGFR (ml/min per 1.73 m^2)	KDIGO 2012 eGFR category	A1 (<3 mg/mmol)	A2 (3–30 mg/mmol)	A3 (>30 mg/mmol)
≥90	G1	424 (84.8%)	5 (1.0%)	0 (0%)
60–89	G2	70 (14.0%)	0 (0%)	1 (0.2%)
45–59	G3a	0 (0%)	0 (0%)	0 (0%)
30–44	G3b	0 (0%)	0 (0%)	0 (0%)
15–29	G4	0 (0%)	0 (0%)	0 (0%)
<15	G5	0 (0%)	0 (0%)	0 (0%)

Estimated risk of concurrent complications and future outcomes of CKD based on the combination of eGFR and albuminuria categories according to the KDIGO 2012 Clinical Practice Guideline.[16]

Green indicates low risk. Yellow indicates moderately increased risk. Orange indicates high risk. Red indicates very high risk.

Figure 2 | Distribution of Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline[16] estimated glomerular filtration rate (eGFR) and albuminuria categories in childhood cancer survivors and controls. A, albuminuria stage; CCS, childhood cancer survivors; CKD, chronic kidney disease.

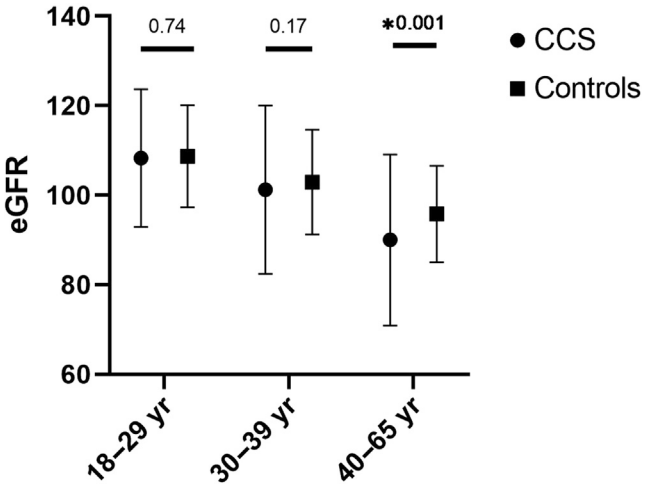

Figure 3 | Boxplots of mean estimated glomerular filtration rate in childhood cancer survivors compared to controls per age group at time of study. CCS, childhood cancer survivors; eGFR, estimated glomerular function rate.

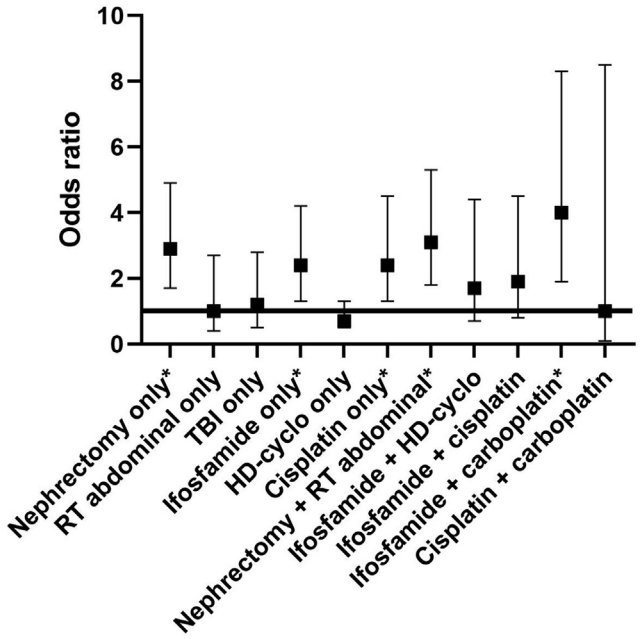

Figure 4 | Multivariable logistic regression analyses for decreased estimated glomerular filtration rate including mutually exclusive treatment groups. The figure displays the odds ratios in childhood cancer survivors (CCS) as compared with controls. Exact values of the odds ratios are listed in Supplementary Table S1. The square represents the odds ratio, and the vertical lines represent the 95% confidence interval. The horizontal line represents the value 1 (no difference between CCS and controls). Model corrected for age at study, sex, hypertension, and diabetes. Carboplatin only was not added in this figure because no odds ratio could be calculated because of low patient numbers. *$P < 0.05$. HD-cyclo, high-dose cyclophosphamide; RT, radiotherapy; TBI, total body irradiation.

to estimate ORs for mutually exclusive treatment groups and tumor types.

Risk factors among CCS. Risk factors for decreased eGFR and albuminuria among CCS are shown in Table 3. Treatment risk factors significantly associated with eGFR <90 ml/min per 1.73 m^2 were nephrectomy (OR: 3.7, 95% CI: 2.1–6.4), abdominal radiotherapy (OR: 1.8, 95% CI: 1.1–2.9), and ifosfamide (OR: 2.9, 95% CI: 1.9–4.4). Ifosfamide increased the odds for a decreased eGFR dose dependently: OR: 1.2 (95% CI: 0.6–2.5) for ≤12 g/m^2, OR: 3.2 (95% CI: 1.8–5.8) for 12–42 g/m^2, and OR: 6.4 (95% CI: 3.4–12.2) for >42 g/m^2 (P_{trend} = 0.006). Exposure to a cisplatin cumulative dose of ≥500 mg/m^2 was also a risk factor (OR: 7.2, 95% CI: 3.4–15.2).

The odds for albuminuria were significantly increased by TBI (OR: 2.3, 95% CI: 1.2–4.4) and ifosfamide exposure (OR: 1.6, 95% CI: 1.0–2.4). For ifosfamide this only holds for cumulative doses >12 g/m^2. Abdominal radiotherapy was not associated with albuminuria when analyzed as dichotomous variable, but showed an increased OR for a cumulative dose of >30 Gy (OR: 2.6, 95% CI: 1.4–5.0).

Other significant risk factors for decreased eGFR included an older age at diagnosis (OR: 1.1 per year, 95% CI: 1.06–1.2), a follow-up duration ≥30 years (OR: 2.7, 95% CI: 1.6–4.8), and hypertension (OR: 2.5, 95% CI: 1.6–3.9). Hypertension was a risk factor for albuminuria as well (OR: 1.9, 95% CI: 1.2–3.1).

No interaction between hypertension and nephrectomy, hypertension and abdominal radiotherapy, diabetes and nephrectomy, diabetes with abdominal radiotherapy, and diabetes with TBI for both decreased eGFR and albuminuria was observed (data not shown).

DISCUSSION

This study in a well-characterized large cohort with median 25-year follow-up showed that CCS treated with potentially nephrotoxic therapy are at increased risk for glomerular dysfunction compared with age- and sex-matched controls, especially at an age >40 years.

The prevalence of stage 3–5 CKD according to the KDIGO 2012 classification[16] was 3.7% among CCS, with 1.1% having end-stage kidney disease, and 0% in controls. This prevalence is higher compared with other recent large cohort studies in CCS that reported a prevalence of 1.7%–2.8%.[10,11,22,23] This might result from the differences in selection criteria, as we included only CCS exposed to potentially nephrotoxic therapy. It is therefore important to borne in mind that our results are only generalizable to CCS treated with potentially nephrotoxic therapies, and not to the total CCS population. This is the first study in CCS that also used the new CKD classification incorporating age-specific GFR decline.[26] The new definition better correlates with mortality risks.[26] In our CCS population, this resulted in a higher prevalence of CKD: 6.6% versus 3.7%. The new definition has the advantage to earlier identify CKD in younger persons. We support using this definition as earlier identification might prevent further deterioration by timely intervention.

Risk factors for CKD in the current study were nephrectomy, abdominal radiotherapy, ifosfamide (especially >12 g/m^2), and cisplatin >500 mg/m^2. Nephrectomy and

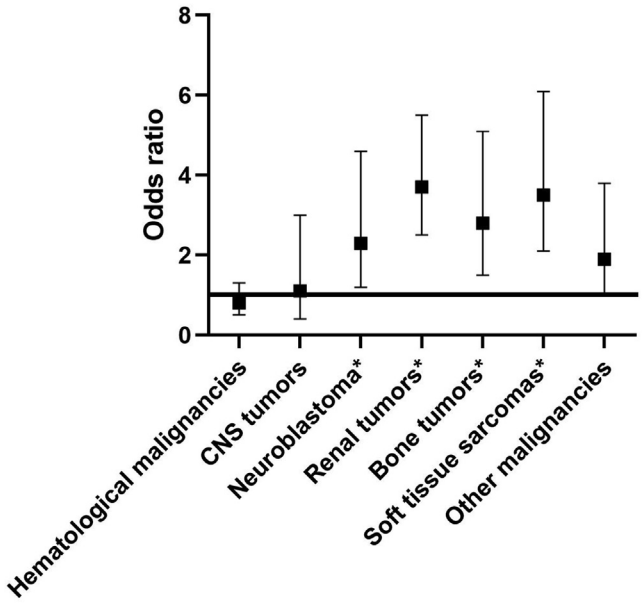

Figure 5 | Multivariable logistic regression analyses for decreased estimated glomerular filtration rate including tumor types. The figure displays the odds ratios in childhood cancer survivors (CCS) as compared with controls. Exact values of the odds ratios are listed in Supplementary Table S2. The square represents the odds ratio, and the vertical lines represent the 95% confidence interval. The horizontal line represents the value 1 (no difference between CCS and controls). Model corrected for age at study, sex, hypertension, and diabetes. *$P < 0.05$. CNS, central nervous system.

ifosfamide are well-known risk factors for glomerular toxicity in CCS.[10,11,22,23,29,35,36] Abdominal radiotherapy was not previously identified as a risk factor in Dutch subcohorts,[10,11,29] but our findings in this large cohort support other reports in CCS.[22,23,35] The contribution of platinum compounds to CKD is not always evident.[17,23,35] Our results clearly show an association of a cisplatin cumulative dose of >500 mg/m^2 with CKD. Carboplatin, a second-generation platinum compound, is supposed to be less nephrotoxic than cisplatin as it is not transformed into toxic metabolites by renal tubule cells.[37] Indeed, single-agent carboplatin did not increase the risk for glomerular dysfunction. Paradoxically, we found that carboplatin combined with ifosfamide was associated with glomerular toxicity, whereas the combination of cisplatin with ifosfamide was not. A prior study investigating acute nephrotoxicity also reported increased risk by HD regimens including carboplatin and ifosfamide compared with standard dose cisplatin with ifosfamide.[38] Last, an increased risk of CKD was observed after combined nephrectomy and abdominal radiotherapy. An important modifiable risk factor included hypertension. Striving for normal blood pressure in this risk population is extremely important.

A more intensive kidney function follow-up should be considered in CCS with >30 years of follow-up because in that time period CKD risk increased. The increased odds for glomerular dysfunction after a longer follow-up period may be because the impact of former treatment increased over time. Moreover, it has been described that a reduced nephron number initially results in compensatory enlargement of remnant nephrons, indicating glomerular hyperfiltration.[39] However, in the long run, this results in glomerulosclerosis and ongoing GFR decline.[40] Another explanation could be the evolution of cancer therapy and improvement of supportive care over the past few decades, resulting in less glomerular dysfunction for CCS treated in more recent decades compared with those treated >30 years ago. Our study participants diagnosed before 1980 consisted mainly of Wilms tumor survivors treated with nephrectomy and abdominal radiotherapy, probably because of the low survival rates for other malignancies in that time. For malignancies with good prognosis, the indication and total dose of radiotherapy have been significantly reduced[41] and chemotherapy regimens have been evolved. Improvements in supportive care for the kidneys include the use of rasburicase for tumor lysis syndrome,[42] prehydration before administration of nephrotoxic chemotherapy agents,[43-45] and it is suggested that magnesium supplementation during treatment with cisplatin positively influences creatinine levels.[43,46] More recently, novel cancer therapies have been introduced such as targeted biological agents, immune checkpoint inhibitors, and chimeric antigen receptor T-cell treatment. This comes with new kidney-related toxicities, and their toxic effects in the long term are not yet known.[47] To better predict risk over time, more longitudinal studies are needed. Mulder *et al.*[29] investigated predictors over time and reported a worse GFR, but a similar deterioration rate in CCS with potentially nephrotoxic treatment compared with CCS not treated with those modalities. However, this study included only few CCS with >30 years of follow-up.

Albuminuria was seen in 16.4% of CCS and 1.2% of controls. The prevalence in our study population is the highest to date compared with other large CCS cohorts where proteinuria was observed in 4.8%–14.5%.[10,22,48] This can be a result of more exposure to nephrotoxic agents in our cohort, as well as the longer follow-up period or differences in measurement tools. The high prevalence is worrisome, because even a mildly increased albumin-to-creatinine ratio is associated with a faster GFR decline.[19] TBI, abdominal radiotherapy >30 Gy, and ifosfamide were associated with albuminuria. The association of TBI and HD ifosfamide with abnormal urinalysis was also observed by Ramirez *et al.*[48] in a cohort of 773 CCS. A novel finding of this study includes exposure to HD-abdominal radiotherapy (>30 Gy) as a risk factor for proteinuria. Transient proteinuria as a consequence of increased capillary permeability is a common feature of radiation nephropathy,[13] but our study suggests that endothelial damage might persist. Recently, Green *et al.*[22] reported nephrectomy as a risk factor for proteinuria in a cohort of 2753 CCS. This finding was not confirmed in our cohort.

Next to 3 previous Dutch studies in subcohorts,[10,11,29] there have been 2 recent studies regarding nephrotoxicity in long-term CCS.[22,23] Corresponding strengths are the large sample size, long follow-up period, and detailed treatment

Table 3 | Multivariable logistic regression analyses for glomerular dysfunction in childhood cancer survivors including treatment

Risk factor	Decreased eGFR (n = 226/943)			Albuminuria (n = 152/929)		
Model 1	**Prevalence[a]**	**OR (95% CI) multivariable**		**Prevalence[a]**	**OR (95% CI) multivariable**	
Nephrectomy						
No	129/691 (18.7)	**1.0 (ref)**		105/689 (15.2)	1.0 (ref)	
Yes	97/252 (38.5)	**3.7 (2.1–6.4)**		47/240 (19.6)	1.1 (0.6–1.9)	
Abdominal RT						
No	147/763 (19.3)	**1.0 (ref)**		109/751 (14.5)	1.0 (ref)	
Yes	76/165 (46.1)	**1.8 (1.1–2.9)**		40/163 (24.5)	1.6 (0.96–2.8)	
TBI						
No	208/847 (24.6)	1.0 (ref)		128/834 (15.3)	**1.0 (ref)**	
Yes	15/81 (18.5)	0.8 (0.4–1.6)		21/80 (26.3)	**2.3 (1.2–4.4)**	
Ifosfamide						
No	144/661 (21.8)	**1.0 (ref)**		97/649 (14.9)	**1.0 (ref)**	
Yes	82/282 (29.1)	**2.9 (1.9–4.4)**		55/280 (19.6)	**1.6 (1.01–2.4)**	
HD cyclo						
No	192/688 (27.9)	1.0 (ref)		127/687 (18.5)	1.0 (ref)	
Yes	32/253 (12.6)	1.0 (0.6–1.7)		25/240 (10.4)	0.8 (0.4–1.4)	
Cisplatin						
No	187/790 (23.7)	1.0 (ref)		128/769 (16.6)	1.0 (ref)	
Yes	39/153 (25.5)	1.6 (0.9–2.6)		24/160 (15.0)	1.1 (0.6–1.9)	
Carboplatin						
No	200/802 (24.9)	1.0 (ref)		128/791 (16.2)	1.0 (ref)	
Yes	26/141 (18.4)	1.1 (0.6–2.0)		24/138 (17.4)	1.5 (0.8–2.6)	
HSCT						
No	208/847 (24.6)	N/A		130/832 (15.6)	N/A	
Yes	15/87 (17.2)			21/88 (23.9)		
Sex						
Male	100/467 (21.4)	1.0 (ref)		78/458 (17.0)	1.0 (ref)	
Female	126/476 (26.5)	1.3 (0.9–1.9)		74/471 (15.7)	1.0 (0.6–1.4)	
Age at diagnosis (per year)	—	**1.1 (1.06–1.2)**		—	1.0 (0.9–1.03)	
FU duration, yr						
10–19	31/160 (19.4)	1.0 (ref)		27/169 (16.0)	1.0 (ref)	
20–29	87/525 (16.6)	1.0 (0.6–1.6)		66/506 (13.0)	0.8 (0.4–1.4)	
≥30	108/258 (41.9)	**2.7 (1.6–4.8)**		59/254 (23.2)	1.3 (0.7–2.4)	
Hypertension						
No	156/778 (20.1)	**1.0 (ref)**		108/770 (14.0)	**1.0 (ref)**	
Yes	70/161 (43.5)	**2.5 (1.6–3.9)**		44/154 (28.6)	**1.9 (1.2–3.1)**	
Diabetes						
No	202/834 (24.2)	1.0 (ref)		131/821 (16.0)	1.0 (ref)	
Yes	11/34 (32.4)	0.7 (0.3–1.8)		9/31 (29.0)	1.3 (0.6–3.1)	
ACEi-ARB						
No	—	—		135/866 (15.6)	1.0 (ref)	
Yes	—	—		17/63 (27.0)	1.2 (0.6–2.4)	
Model 2[b]	**Prevalence[a]**	**OR (95% CI) multivariable**	**P_{trend}[c]**	**Prevalence[a]**	**OR (95% CI) multivariable**	**P_{trend}[c]**
Abdominal RT: dose, Gy						
None	147/763 (19.3)	1.0 (ref)		109/751 (14.5)	1.0 (ref)	
<20	20/46 (43.5)	**2.5 (1.2–5.1)**		8/45 (17.8)	1.2 (0.5–2.9)	
20–30	20/52 (38.5)	1.0 (0.5–2.0)		9/50 (18.0)	0.9 (0.3–2.1)	
>30	34/65 (52.3)	**2.1 (1.1–3.8)**	0.44	23/66 (34.8)	**2.6 (1.4–5.0)**	**0.001**
Model 3[b]	**Prevalence[a]**	**OR (95% CI) multivariable**	**P_{trend}[c]**	**Prevalence[a]**	**OR (95% CI) multivariable**	**P_{trend}[c]**
Ifosfamide: dose, mg/m^2						
None	144/661 (21.8)	1.0 (ref)		97/649 (14.9)	1.0 (ref)	
≤12,000	14/95 (14.7)	1.2 (0.6–2.5)		10/94 (10.6)	0.6 (0.2–1.3)	
12,0001–42,000	31/96 (32.3)	**3.2 (1.8–5.8)**		19/91 (20.9)	**1.9 (1.01–3.6)**	
>42,000	37/89 (41.6)	**6.4 (3.4–12.2)**	**0.006**	26/93 (28.0)	**3.3 (1.7–6.2)**	0.11
Model 4[b]	**Prevalence[a]**	**OR (95% CI) multivariable**	**P_{trend}[c]**	**Prevalence[a]**	**OR (95% CI) multivariable**	**P_{trend}[c]**
Cisplatin: dose, mg/m^2						
None	187/790 (23.7)	1.0 (ref)		128/769 (16.6)	1.0 (ref)	
≤300	6/53 (11.3)	0.3 (0.1–0.9)		8/54 (14.8)	1.1 (0.4–2.6)	
301–500	7/49 (14.3)	1.0 (0.4–2.5)		6/54 (11.1)	0.7 (0.3–2.0)	
>500	26/50 (52.0)	**7.2 (3.4–15.2)**	0.15	10/51 (19.6)	1.5 (0.7–3.6)	0.76

Table 3 | (Continued)

Risk factor	Decreased eGFR (n = 226/943)			Albuminuria (n = 152/929)		
Model 5[b]	Prevalence[a]	OR (95% CI) multivariable	P_{trend}[c]	Prevalence[a]	OR (95% CI) multivariable	P_{trend}[c]
Carboplatin: dose, mg/m^2						
None	200/802 (24.9)	1.0 (ref)		128/791 (16.2)	1.0 (ref)	
≤1500	8/49 (16.3)	1.1 (0.5–2.6)		9/48 (18.8)	1.5 (0.6–3.6)	
1501–2800	9/47 (19.1)	1.1 (0.5–3.0)		6/41 (14.6)	1.5 (0.6–3.9)	
>2800	9/42 (21.4)	1.3 (0.9–1.9)	0.90	9/46 (19.6)	1.4 (0.6–3.4)	0.10

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; FU, follow-up; Gy, gray; HD-cyclo, high-dose cyclophosphamide; HSCT, hematopoietic stem cell transplantation; N/A, not applicable; OR, odds ratio; ref, reference; RT, radiotherapy; TBI, total body irradiation.
[a]Values are the number of participants with a positive test result/total number of participants tested (percentage).
[b]Models 2–5 were similar to model 1, except that per model 1 dichotomous treatment modality has been substituted by categories of cumulative doses. The other variables are not shown for models 2–5 for clarity.
[c]Test for trend in continuous dose variable among exposed childhood cancer survivors.
Bold data indicate $P < 0.05$.
All factors in model 1 have been adjusted for simultaneously. Numbers do not always add up to the total because of missing values.

information. In those studies, the control population included siblings,[23] CCS without nephrotoxic therapy,[10,11,29] or no controls were included.[22] An important strength of our study is the matched control group. We could therefore more accurately account for a physiological GFR decline. In addition, in our study, eGFR and albuminuria were evaluated more rigorously, by taking into account both creatinine and cystatin for eGFR and using quantitative measurement in an early morning sample for albuminuria, as recommended by the KDIGO guideline.[16] However, a limitation of our study is that we were not able to evaluate the effect of nephrotoxic supportive care drugs used in pediatric cancer care and acute kidney injury episodes to long-term kidney dysfunction. Second, we did not adjust for predisposition syndromes (in Wilms tumor survivors) associated with an elevated risk for kidney failure (e.g., Denys-Drash syndrome or WAGR syndrome).[49] Third, although there were no differences in nephrotoxic treatment exposures between participants and the eligible cohort, selection bias cannot be completely ruled out as 54% of eligible CCS participated. Last, even after a long follow-up period nephrotoxicity may arise, as is demonstrated by Dieffenbach *et al.*,[23] who found a new association of HD anthracylines with kidney failure. Unfortunately, we could not assess the effects of anthracyclines or other cancer treatment that were not part of our selection criteria.

To conclude, CCS are at increased risk for glomerular dysfunction compared with matched controls, particularly at an age >40 years. In CCS exposed to potentially nephrotoxic treatment and at a median age of 32 years, 3.7% had stage 3–5 CKD, 1.1% end-stage kidney disease, 6.6% had CKD according to age thresholds, and 16.2% had albuminuria. Risk factors for CKD included nephrectomy, abdominal radiotherapy, ifosfamide and cisplatin >500 mg/m^2, the combination of nephrectomy with abdominal radiotherapy or ifosfamide with carboplatin, and the risk increased after ≥30 years of follow-up. In addition, CCS exposed to TBI, abdominal radiotherapy >30 Gy, or ifosfamide are at increased risk for albuminuria. Hypertension remains the most important modifiable risk factor for glomerular dysfunction. The results of this study emphasize the need for lifelong monitoring of glomerular function among CCS with identified high-risk factors and minimizing nephrotoxic exposures.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank the other members of the Dutch LATER consortium (Birgitta Versluys, Martha Grootenhuis, Flora van Leeuwen, Lideke van der Steeg, Geert Janssens, Hanneke van Santen, Jaap den Hartogh, Lilian Batenburg, Hanneke de Ridder, Nynke Hollema, Lennart Teunissen, Anke Schellekens) and all physicians, research nurses, data managers, and participating patients, parents, and siblings. This study was supported by KWF Dutch Cancer Society (grant number 7889). In addition, the authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants. The Lifelines initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen (UMCG), Groningen University and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen).

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Figure S1. Distribution of nephrotoxic cancer therapies per decade among study participants.

Table S1. Multivariable logistic regression analyses for glomerular dysfunction including mutually exclusive treatment groups.

Table S2. Multivariable logistic regression analyses for glomerular dysfunction including different tumor types.

REFERENCES

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66:271–289.
2. Erdmann F, Frederiksen LE, Bonaventure A, et al. Childhood cancer: Survival, treatment modalities, late effects and improvements over time. *Cancer Epidemiol*. 2021;71(Pt B):101733.
3. Geenen MM C-UM, Kremer LC, van den Bos C, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA*. 2007;297:2705–2715.

4. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572–1582.
5. Wasilewski-Masker K, Mertens AC, Patterson B, Meacham LR. Severity of health conditions identified in a pediatric cancer survivor program. *Pediatr Blood Cancer*. 2010;54:976–982.
6. Skinner R, Parry A, Price L, et al. Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose. *Pediatr Blood Cancer*. 2010;54:983–989.
7. Oberlin O, Fawaz O, Rey A, et al. Long-term evaluation of Ifosfamide-related nephrotoxicity in children. *J Clin Oncol*. 2009;27:5350–5355.
8. English MW, Skinner R, Pearson AD, et al. Dose-related nephrotoxicity of carboplatin in children. *Br J Cancer*. 1999;81:336–341.
9. Brock PR, Koliouskas DE, Barratt TM, et al. Partial reversibility of cisplatin nephrotoxicity in children. *J Pediatr*. 1991;118(Pt 1):531–534.
10. Knijnenburg SL, Jaspers MW, van der Pal HJ, et al. Renal dysfunction and elevated blood pressure in long-term childhood cancer survivors. *Clin J Am Soc Nephrol*. 2012;7:1416–1427.
11. Dekkers IA, Blijdorp K, Cransberg K, et al. Long-term nephrotoxicity in adult survivors of childhood cancer. *Clin J Am Soc Nephrol*. 2013;8:922–929.
12. Frisk P, Bratteby LE, Carlson K, Lonnerholm G. Renal function after autologous bone marrow transplantation in children: a long-term prospective study. *Bone Marrow Transplant*. 2002;29:129–136.
13. Breitz H. Clinical aspects of radiation nephropathy. *Cancer Biother Radiopharm*. 2004;19:359–362.
14. Schell M, Cochat P, Hadj-Aïssa A, et al. Renal function following unilateral nephrectomy for neuroblastoma and Wilms' tumour. *Pediatr Nephrol*. 1995;9:579–582.
15. de Graaf SS, van Gent H, Reitsma-Bierens WC, et al. Renal function after unilateral nephrectomy for Wilms' tumour: the influence of radiation therapy. *Eur J Cancer*. 1996;32A:465–469.
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150.
17. Kooijmans EC, Bökenkamp A, Tjahjadi NS, et al. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. *Cochrane Database Syst Rev*. 2019;3:Cd008944.
18. Gansevoort RT, Nauta FL, Bakker SJ. Albuminuria: all you need to predict outcomes in chronic kidney disease? *Curr Opin Nephrol Hypertens*. 2010;19:513–518.
19. Melsom T, Solbu MD, Schei J, et al. Mild albuminuria is a risk factor for faster GFR decline in the nondiabetic population. *Kidney Int Rep*. 2018;3:817–824.
20. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
21. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79:1341–1352.
22. Green DM, Wang M, Krasin M, et al. Kidney function after treatment for childhood cancer: a report from the St. Jude Lifetime Cohort Study. *J Am Soc Nephrol*. 2021;2:983–993.
23. Dieffenbach BV, Liu Q, Murphy AJ, et al. Late-onset kidney failure in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Eur J Cancer*. 2021;155:216–226.
24. Eriksen BO, Stefansson VT, Jenssen TG, et al. Blood pressure and age-related GFR decline in the general population. *BMC Nephrol*. 2017;18:77.
25. Christensson A, Elmstahl S. Estimation of the age-dependent decline of glomerular filtration rate from formulas based on creatinine and cystatin C in the general elderly population. *Nephron Clin Pract*. 2011;117:c40–c50.
26. Delanaye P, Jager KJ, Bökenkamp A, et al. CKD: a call for an age-adapted definition. *J Am Soc Nephrol*. 2019;30:1785–1805.
27. Kamps WA, Bökkerink JP, Hählen K, et al. Intensive treatment of children with acute lymphoblastic leukemia according to ALL-BFM-86 without cranial radiotherapy: results of Dutch Childhood Leukemia Study Group Protocol ALL-7 (1988-1991). *Blood*. 1999;94:1226–1236.
28. Kamps WA, Bökkerink JP, Hakvoort-Cammel FG, et al. BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: results of DCLSG protocol ALL-8 (1991-1996). *Leukemia*. 2002;16:1099–1111.
29. Mulder RL, Knijnenburg SL, Geskus RB, et al. Glomerular function time trends in long-term survivors of childhood cancer: a longitudinal study. *Cancer Epidemiol Biomarkers Prev*. 2013;22:1736–1746.
30. Scholtens S, Smidt N, Swertz MA, et al. Cohort profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2015;44:1172–1180.
31. Klijs B, Scholtens S, Mandemakers JJ, et al. Representativeness of the LifeLines cohort study. *PloS One*. 2015;10:e0137203.
32. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29.
33. Grubb A, Blirup-Jensen S, Lindstrom V, et al. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010;48:1619–1621.
34. Renaghan AD, Jaimes EA, Malyszko J, et al. Acute kidney injury and CKD associated with hematopoietic stem cell transplantation. *Clin J Am Soc Nephrol*. 2020;15:289–297.
35. Dietz AC, Seidel K, Leisenring WM, et al. Solid organ transplantation after treatment for childhood cancer: a retrospective cohort analysis from the Childhood Cancer Survivor Study. *Lancet Oncol*. 2019;20:1420–1431.
36. Mudi A, Levy CS, Geel JA, Poole JE. Paediatric cancer survivors demonstrate a high rate of subclinical renal dysfunction. *Pediatr Blood Cancer*. 2016;63:2026–2032.
37. Ciarimboli G, Ludwig T, Lang D, et al. Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. *Am J Pathol*. 2005;167:1477–1484.
38. Hartmann JT, Fels LM, Franzke A, et al. Comparative study of the acute nephrotoxicity from standard dose cisplatin +/- ifosfamide and high-dose chemotherapy with carboplatin and ifosfamide. *Anticancer Res*. 2000;20:3767–3773.
39. Hostetter TH, Olson JL, Rennke HG, et al. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol*. 1981;241:F85–F93.
40. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int*. 1996;49:1774–1777.
41. Breneman JC, Donaldson SS, Constine L, et al. The Children's Oncology Group Radiation Oncology Discipline: 15 years of contributions to the treatment of childhood cancer. *Int J Radiat Oncol Biol Phys*. 2018;101:860–874.
42. Rahmani B, Patel S, Seyam O, et al. Current understanding of tumor lysis syndrome. *Hematol Oncol*. 2019;37:537–547.
43. Crona DJ, Faso A, Nishijima TF, et al. A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. *Oncologist*. 2017;22:609–619.
44. Howard SC, McCormick J, Pui CH, et al. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21:1471–1482.
45. Eaton A, Egelund T, Ng J. Comparison of rapid hydration and standard hydration prior to ifosfamide administration in pediatric patients: a safety and efficacy study. *J Pediatr Pharmacol Ther*. 2020;25:246–250.
46. Matsui M, Saito Y, Yamaoka S, et al. Kidney-protective effect of magnesium supplementation in cisplatin-containing chemotherapy for pediatric cancer: a retrospective study. *J Pediatr Hematol Oncol*. 2018;40:379–381.
47. Sury K, Perazella MA. The nephrotoxicity of new immunotherapies. *Expert Rev Clin Pharmacol*. 2019;12:513–521.
48. Ramirez MD, Mertens AC, Esiashvili N, et al. Yield of urinalysis screening in pediatric cancer survivors. *Pediatr Blood Cancer*. 2016;63:893–900.
49. Breslow NE, Takashima JR, Ritchey ML, et al. Renal failure in the Denys-Drash and Wilms' tumor-aniridia syndromes. *Cancer Res*. 2000;60:4030–4032.