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Original Research

Long-term risk of renal and urinary tract diseases in childhood cancer survivors: A population-based cohort study

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Abstract ***Background:*** Childhood cancer has been associated with long-term risk of urinary tract diseases, but risk patterns remain to be comprehensively investigated. We analysed the lifetime risk of urinary tract diseases in survivors of childhood cancer in the Nordic countries. ***Methods:*** We identified 32,519 one-year survivors of childhood cancer diagnosed since the 1940s and 1950s in the five Nordic cancer registries and selected 211,156 population comparisons of a corresponding age, sex, and country of residence from the national population registries. To obtain information on all first-time hospitalizations for a urinary tract disease, we linked all study subjects to the national hospital registry of each country. Relative risks (RRs) and absolute excess risks (AERs) and associated 95% confidence intervals (CIs) for urinary tract diseases among cancer survivors were calculated with the appropriate morbidity rates among comparisons as reference.

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Results: We observed 1645 childhood cancer survivors ever hospitalized for urinary tract disease yielding an RR of 2.5 (95% CI 2.4–2.7) and an AER of 229 (95% CI 210–248) per 100,000 person-years. The cumulative risk at age 60 was 22% in cancer survivors and 10% in comparisons. Infections of the urinary system and chronic kidney disease showed the highest excess risks, whereas survivors of neuroblastoma, hepatic and renal tumours experienced the highest RRs.
Conclusion: Survivors of childhood cancer had an excess risk of urinary tract diseases and for most diseases the risk remained elevated throughout life. The highest risks occurred following therapy of childhood abdominal tumours.

1. Introduction

Remarkable improvements in therapy for paediatric malignancies have led to an increasing number of adults treated for cancer during childhood. In the Nordic countries, 5-year survival rates after childhood cancer now exceed 80% [1] and almost 1 in 1000 adults in the general population is a childhood cancer survivor [2]. However, a considerable number of survivors experience long-term therapy-related complications [3,4]. Only few and relatively small studies are available on the risk of diseases of the urinary tract following treatment for childhood cancer [5,6]. Important contributors to renal damage are nephrotoxic chemotherapy, nephrectomy, and abdominal irradiation [7]. The St. Jude Lifetime Cohort Study reported kidney dysfunction in 5% of adult cancer survivors [8]. The aim of this study was to identify urinary tract diseases through long-term follow-up in a large cohort of childhood cancer survivors in the five Nordic countries. To measure the relative and absolute risk of urinary tract morbidities we used diagnostic information available in the national hospital registers including risk estimates for individuals aged >50 years which have not previously been reported in cohort studies of childhood cancer survivors.

2. Methods

This study is part of a Nordic population-based cohort study, Adult Life after Childhood Cancer in Scandinavia (ALiCCS; *www.aliccs.org*) [9–11].

2.1. Patient and comparison cohorts

The basic childhood cancer cohort included 43,909 individuals diagnosed with cancer before the age of 20 years from start of registration in the 1940s and 1950s, until 31st December 2008 (eTable1). Patients had to be alive on or born after the date on which centralised registration of residents of each country was operational to be included. The Nordic cancer registries include nationwide data on incident cases of cancer reported from multiple sources ensuring close to full coverage [12–16]. We obtained information on type of cancer and date of diagnosis and assigned individuals to 1 of 12 main diagnostic groups according to the International Classification Scheme for Childhood Cancer [17].

All residents in the Nordic countries are assigned a unique personal identification number, which allows accurate linkage of information between registries and complete follow-up on vital status and emigration [18].

To measure hospitalization rates for urinary tract diseases in the background population, we randomly selected 219,131 comparison subjects from the population registries (eTable 1). For each childhood cancer patient, five comparisons were selected, who were alive on the date of cancer diagnosis of the corresponding patient, and were of the same sex, age, country of residence, and without a diagnosis of cancer before the age of 20 years. For 317 patients fewer than five comparisons were available (eFig. 1).

Patients, in whom more than one primary cancer was diagnosed before the age of 20 years, were excluded (305 patients). Furthermore, we excluded those who had died, emigrated, or were censored during the first year after the date of cancer diagnosis or an equivalent time lag for the comparisons (6844 patients; 1318 comparisons). We also excluded those who had died or emigrated before the start of the national hospital registries (3600 patients; 4858 comparisons).

In accordance with Nordic regulations, data on cohort members were analysed without personal identifiers. The study was approved by the national bioethics committees and national data protection authorities according to national regulations.

2.2. Hospitalizations for urinary tract diseases

Each hospitalization obtained from the national hospital registries initiated a record including the personal identification number of the patient, date of admission and discharge, a primary discharge diagnosis, and supplementary diagnoses coded according to the

International Classification of Diseases (ICD-7 to ICD-10) [19–21].

We identified all inpatient hospitalizations with a primary or supplementary discharge diagnosis (ICD-10 codes N00-21 and N23-39; ICD-9 codes 580-599; ICD-8 codes 580-583 and 590-599; ICD-7 codes 590-594 and 600-604; for a detailed list of ICD-10 codes please see eTable 2). Diagnostic categories of ICD-7 to ICD-9 were adapted to the ICD-10. Linkage to the hospital registries identified 197 patients and 206 comparisons diagnosed with a congenital chromosomal abnormality (ICD-10 codes Q90-99, e.g. Turner syndrome, Down syndrome, and Klinefelter syndrome); they were excluded because these disorders may potentially confound causal associations between cancer treatment and urinary tract diseases. Finally, we excluded 444 survivors and 1530 comparisons, who had been hospitalized for a urinary tract disease prior to the date of childhood cancer diagnosis (or the equivalent date for comparisons), leaving a total of 32,519 one-year survivors and 211,156 comparisons for analysis (eTable 1, eFig. 1).

Table 1
Characteristics for the 32,519 one-year survivors of childhood cancer in the Nordic countries followed for diseases of the urinary tract.

	N (%)	Person-years of follow-up
Total	**32,519 (100)**	**430,614**
Sex		
Female	15,101 (46.4)	206,668
Male	17,418 (53.6)	224,946
Country		
Denmark	7422 (23)	115,158
Finland	7090 (22)	101,370
Iceland	409 (1)	3125
Norway	5269 (16)	15,191
Sweden	12,329 (38)	195,770
Cancer diagnosis		
I. Leukaemia	6843 (21)	70,384
II. Lymphomas	4442 (14)	59,137
III. Central nervous system tumours	7834 (24)	107,295
IV. Neuroblastoma	1290 (4)	15,887
V. Retinoblastoma	818 (3)	15,831
VI. Renal tumours	1367 (4)	21,577
VII. Hepatic tumours	235 (1)	2018
VIII. Malignant bone tumours	1519 (5)	18,014
IX. Soft-tissue sarcomas	1962 (6)	27,397
X. Germ-cell tumours	2097 (6)	28,420
XI. Malignant epithelial tumours	3646 (11)	58,972
XII. Other and unspecified malignant neoplasms	466 (1)	5682
Age at diagnosis		
<4 years	9890 (30)	131,811
5–9 years	5746 (18)	74,606
10–14 years	6374 (20)	85,451
15–19 years	10,509 (32)	138,746
Calendar time at diagnosis		
1943–1959	1047 (3)	26,718
1960–1974	4526 (14)	107,234
1975–1989	10,006 (31)	170,941
1990–2008	16,940 (52)	125,721

3. Statistical analysis

Follow-up in the hospital registries started 1 year after the date of cancer diagnosis (and the corresponding date for comparisons), or at the start of the national hospital registry, whichever occurred last. Follow-up ended on the date of death, the date of emigration, or end of the study period (eTable 1), whichever occurred first. Follow-up also ended if a second primary cancer was diagnosed in a survivor or a first primary cancer in a population comparison. Only the first hospitalization for a specific urinary tract disease was retained, as it was presumed to correspond to the date of diagnosis. Risk analyses were carried out for each of the eight main diagnostic categories, and for each of the 35 subcategories within the main categories (Table 2) including risk estimates for subcategories based on five or more hospitalizations among survivors. The observed numbers of first hospitalizations for a given urinary tract disease among survivors were compared with the expected numbers derived from the appropriate country-, sex-, age-, and calendar period-specific hospitalization rates of the population comparisons. We estimated the significance and 95% confidence intervals (CIs) for the standardized hospitalization rate ratio, taken as the observed-to-expected hospitalizations using Fieller's theorem [22]. Absolute excess risk (AER), i.e. the additional risk for a hospitalization, was derived as the difference between the observed and expected first hospitalization rates per 100,000 person-years, with corresponding 95% CI. To test the robustness of the overall results, we added three sensitivity analyses. First, an analysis with inclusion of urinary tract diseases only notified as a primary diagnosis. Second, an analysis restricted to include 5-year survivors only. Third, an analysis restricted to survivors diagnosed with cancer from 1 year before the start of the national patient registries to the end of the study period.

To estimate the effects of cancer type and age at diagnosis on the risk for urinary tract diseases, we conducted a multivariate analysis within the survivor cohort. A Cox proportional hazards model was used to estimate hospitalization rate (hazard) ratios (HRs) for urinary tract disease for type of childhood cancer (12 diagnostic groups with leukaemia survivors as reference) and for age at diagnosis (four groups with 0–4 years as reference) with time since diagnosis as the underlying time scale and censoring for death. The analysis was stratified by sex and country. The analysis was adjusted for age at diagnosis in 5-year age group interval and year of diagnosis in four calendar year groups (<1980, 1980–1989, 1990–1999, >2000). The statistical software R version 2.12.0 and packages Survival and Design were used for these analyses.

For all other analyses we used SAS version 9.2.

Table 2
The observed and expected numbers of first-time hospitalization for diseases of the urinary tract among 32,519 one-year survivors of childhood cancer and 211,156 population comparisons by eight main categories and 35 subcategories and diagnoses.

Renal and urinary tract disease	ICD-10 code	First hospital contacts (n)		RR (95% CI)	AER (95% CI)[b]
		Observed[a]	Expected[a]		
Any renal and urinary tract disease		**1645**	**657.4**	**2.5 (2.4–2.7)**	**229 (210–248)**
Glomerular diseases		124	60.6	2.0 (1.7–2.5)	15 (9–20)
Acute nephritis	N00.0-N01.9	19	13.0	1.5 (0.9–2.4)	1 (−1 to 4)
Haematuria with glomerular pathology	N02.0-8	25	9.8	2.6 (1.6–4.0)	4 (1–6)
Chronic nephritis	N03.0-9	27	11.8	2.3 (1.5–3.5)	4 (1–6)
Nephrotic syndrome	N04.0-9	25	10.2	2.5 (1.6–3.9)	3 (1–6)
Nephritis, unspecified	N05.0-9	16	8.2	2.0 (1.1–3.4)	2 (0–4)
Glomerular disorders in diseases classified elsewhere	N08.0-9	18	7.0	2.6 (1.5–4.4)	3 (1–5)
Renal tubulo-interstitial diseases		33	4.6	7.1 (4.5–11.4)	8 (5–11)
Drug- and heavy-metal–induced tubulo-interstitial and tubular conditions	N14.0-9	17	1.1	15.6 (6.8–35)	5 (2–7)
Disorders resulting from impaired renal tubular function	N25.8-9	11	1.9	5.8 (2.7–12.7)	3 (1–5)
Acute renal failure (excluding glomerular disorders)		120	17.1	7.0 (5.5–9.0)	24 (19–29)
Acute renal failure	N17.0-9	117	15.7	7.5 (5.8–9.6)	24 (19–29)
Chronic kidney disease (excluding glomerular disorders)		264	72.1	3.7 (3.2–4.2)	45 (37–52)
Chronic pyelonephritis	N11.8-9	28	3.6	7.8 (4.6–13.1)	6 (3–8)
Other pyelonephritis, pyelitis and pyelocystitis	N18.0-9	69	25.5	2.7 (2.1–3.6)	10 (6–14)
Chronic renal failure	N19.0-9	116	21.6	5.4 (4.2–6.8)	22 (17–27)
Renal failure, unspecified	N19.0-9	38	8.5	4.5 (3.0–6.6)	7 (4–10)
Hypertensive renal disease with renal failure	I12.0	23	4.1	5.7 (3.3–9.7)	4 (2–7)
Diabetes mellitus with renal complications	E10.2, E11.2, E12.2, E13.2, E14.2	26	13.6	1.9 (1.1–2.9)	3 (0–5)
Cystis renis asqusitas	N28.1	6	1.9	3.2 (1.2–8.1)	1 (0–2)
Urolithiasis		234	134.5	1.7 (1.5–2.0)	23 (16–30)
Calculus of kidney and ureter	N20.0-9	211	126.0	1.7 (1.1–1.9)	20 (13–27)
Calculus of other parts of urinary system	N21.0-9	24	10.2	2.4 (1.5–3.7)	3 (1–6)
Obstructive uropathy		149	60.5	2.5 (2.1–3.0)	21 (15–26)
Pyelonephritis chronica m/ vesicourethral reflux or obstruction	N11.0-1	6	1.6	3.8 (1.4–10.1)	1 (0–2)
Hydronephrosis	N13.0-3	79	31.1	2.6 (2.0–3.4)	11 (7–16)
Kinking and stricture of ureter without hydronephrosis	N13.5	9	2.6	3.5 (1.6–7.6)	1.5 (0.1–2.9)
Obstruction of ureter, not elsewhere classified	N13.8-9	14	5.8	2.4 (1.3–4.4)	1.9 (0.2–2.9)
Bladder-neck obstruction	N32.0	8	3.1	2.6 (1.2–5.7)	1 (0–3)
Stricture of urethra	N35.0-9	42	19.6	2.1 (1.5–3.0)	5 (2–8)
Infections of the urinary system		830	302.3	2.8 (2.5–3.0)	123 (109–136)
Acute pyelonephritis	N10.0-9	151	68.1	2.2 (1.9–2.7)	19 (14–25)
Pyonephrosis	N13.6	5	1.9	2.6 (1.0–7.2)	1 (0–2)
Cystitis	N30.0-9	306	110.0	2.8 (2.4–3.2)	46 (38–54)
Urethritis (non-venereal)	N34.0-9, N37.0	18	9.9	1.8 (1.1–3.0)	1.9 (−0.1 to 3.9)
Urinary tract infection site not specified	N39.0	373	98.2	3.8 (3.4–4.3)	64 (55–73)
Other and unspecified disorders		315	106.2	3.0 (2.6–3.4)	48 (40–57)
Other disorders of kidney and ureter	N23.0-9, N28.8-9, N29.8, N13.7	52	18.5	2.8 (2.1–3.9)	8 (4–11)
Proteinuria, not specified	N06.9, N39.1	7	1.5	4.8 (1.9–12.4)	1 (0–3)
Neuromuscular dysfunction of bladder, not elsewhere classified	N31.0-9	123	11.0	11.1 (8.5–14.7)	26 (21–31)
Others disorders of bladder	N32.1-9, N33.8	68	11.1	6.1 (4.5–8.4)	13 (9–17)
Incontinence	N39.3-4	73	53.8	1.4 (1.1–1.7)	4 (0–9)
Other disorders of urinary tract	N39.8-9	30	11.0	2.7 (1.8–4.1)	4.4 (1.9–7.0)

CI, confidence interval.
Standardized hospitalization rate ratio (RR) and absolute excess risk (AER) per 100,000 person-years are presented. For a detailed list of *International Classification of Diseases, Tenth Revision* (ICD-10) codes please see eTable2.

[a] The sum of observed and expected cases in subcategories does not correspond to the total number of cases observed and expected due to this report including risk estimates for subcategories based on five or more hospitalizations among cancer survivors

[b] The sum of AER in subcategories might not correspond to the sum of AER of diseases within these subcategories because individuals can have a first hospitalization for several diseases

4. Results

The 32,519 one-year survivors were followed in the national hospital registries for 430,614 person-years, median 10 years; range 0–42 years. Table 1 provides characteristics of the survivor cohort.

4.1. Overall risk for diseases of the urinary tract

Fig. 1 shows the relative risk (RR) of hospitalization for any urinary tract disease in all survivors combined and in survivors stratified by sex, age at cancer diagnosis, main diagnostic category of childhood cancer, and time since cancer diagnosis. A total of 1645 survivors had been hospitalized for a urinary tract disease, when 657 were expected, yielding an increased risk of 2.5 and an AER of 229 cases per 100,000 person-years (Fig. 1; Table 2).

The repeated analysis restricted to include only urinary tract diseases reported as the primary discharge diagnosis resulted in a lower risk of 2.0 (95% CI 1.8–2.2). The analysis restricted to include only 5-year survivors resulted in a lower risk of 2.2 (95% CI 2.1–2.4), whereas the analysis restricted to include survivors diagnosed with cancer 1 year before the start of the national patient registries and onwards resulted in a higher risk of 2.9 (95% CI 2.7–3.2).

4.2. Risk of specified diagnostic categories of urinary tract diseases

Survivors were at significantly increased risk of being hospitalized for urinary tract diseases of all eight main diagnostic categories (Table 2). Infections of the urinary system were the most common diagnosis with 830 hospitalizations and an AER of 123 cases per 100,000 person-years. The highest RRs were observed for drug-induced tubulo-interstitial and tubular disorders (RR 15.6) and neuromuscular dysfunction of the bladder (11.1).

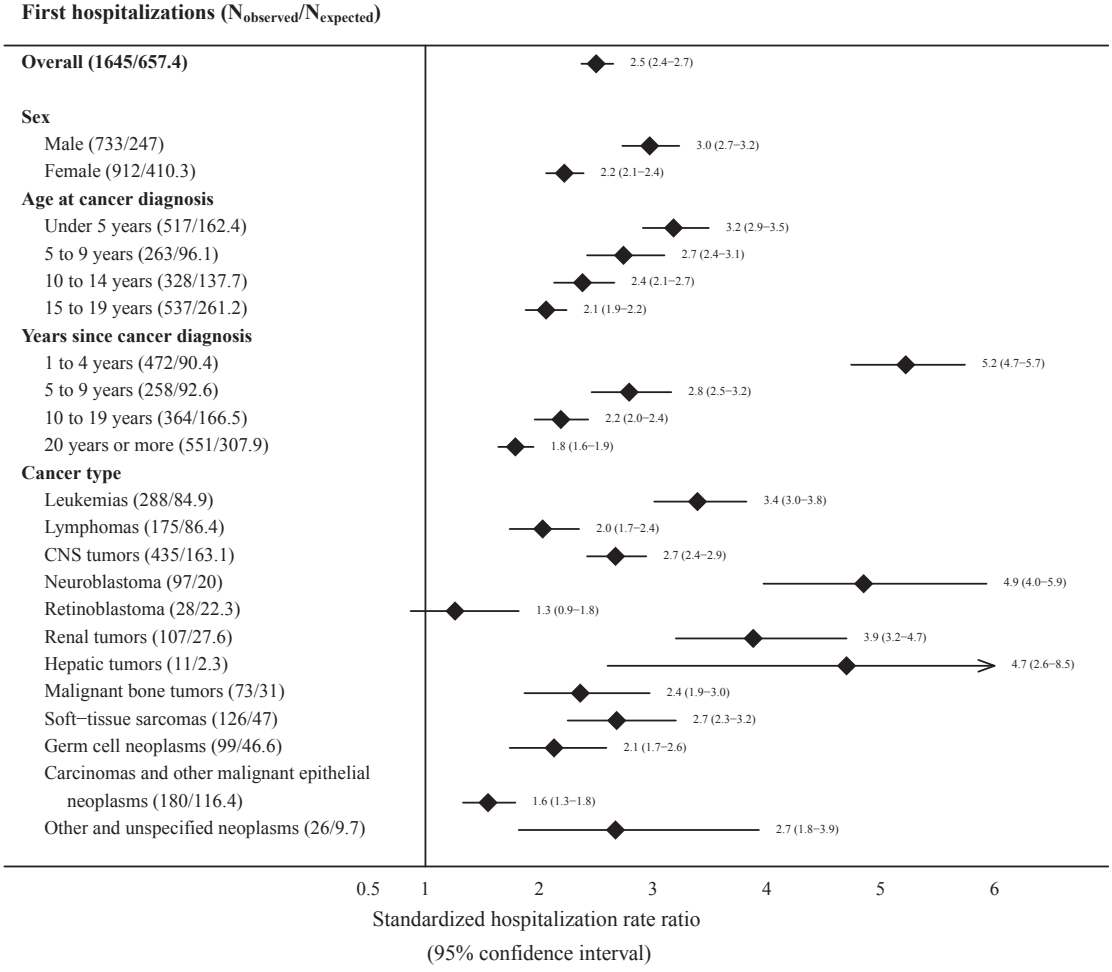

Fig. 1. Standardized hospitalization rate ratios for diseases of the urinary tract of any type among 32,519 one-year survivors. $N_{observed}$ is the number of first hospitalizations among cancer survivors. $N_{expected}$ is the number of hospitalizations expected based upon morbidity rates derived from the comparison cohort.

Table 3
Standardized hospitalization rate ratio (RR) and absolute excess risk (AER) per 100,000 person-years for urinary tract disease of any type by the 12 main diagnostic groups of cancer.

	First hospital contacts in survivors (n)	RR (95% CI)	AER (95% CI) per 100,000 person-years
Leukaemia (n = 6843)			
Any renal or urinary tract disease	288	3.4 (3.0–3.8)	289 (241–336)
Acute renal failure	25	17 (11–26)	33 (19–47)
Renal tubulo-interstitial diseases	4	7.9 (2.7–23)	5 (−0.6 to 11)
Chronic kidney disease	28	3.9 (2.6–5.7)	29 (15–44)
Urolithiasis	44	3.6 (2.7–4.9)	45 (27–64)
Infections of the urinary system	159	3.5 (3.0–4.1)	161 (126–196)
Lymphomas (n = 4442)			
Any renal or urinary tract disease	175	2.0 (1.7–2.4)	150 (106–194)
Acute renal failure	17	6.8 (4.1–11)	24 (11–38)
Central nervous system tumours (n = 7834)			
Any renal or urinary tract disease	435	2.7 (2.4–2.9)	253 (215–292)
Other and unspecified disorders	117	4.6 (3.8–5.6)	85 (66–105)
Acute renal failure	20	4.6 (2.9–7.3)	15 (6–23)
Infections of the urinary system	247	3.4 (2.9–3.8)	162 (133–190)
Neuroblastoma (n = 1290)			
Any renal or urinary tract disease	97	4.9 (4.0–5.9)	485 (363–606)
Acute renal failure	7	22 (10–48)	42 (9–75)
Other and unspecified disorders	32	11 (7.6–16)	183 (113–253)
Chronic kidney disease	19	10 (6.1–15)	107 (53–161)
Obstructive uropathy	12	7.5 (4.2–13.4)	66 (23–108)
Glomerular diseases	12	5.5 (3.1–9.8)	62 (19–105)
Infections of the urinary system	48	4.7 (3.5–6.2)	238 (152–323)
Retinoblastoma (n = 818)			
Any renal or urinary tract disease	28	1.3 (0.9–1.8)	36 (−29 to 102)
Renal tumours (n = 1367)			
Any renal or urinary tract disease	107	3.9 (3.2–4.7)	368 (274–462)
Renal tubulo-interstitial diseases	4	22 (8–63)	18 (−0.5 to 36)
Acute renal failure	11	21 (11–38)	48 (18–79)
Chronic kidney disease	35	13 (9–18)	149 (95–203)
Obstructive uropathy	13	5.4 (3.1–9.4)	49 (16–82)
Infections of the urinary system	46	3.4 (2.6–4.6)	151 (89–212)
Hepatic tumours (n = 235)			
Any renal or urinary tract disease	11	4.7 (2.6–8.5)	429 (107–751)
Renal tubulo-interstitial diseases	1	100 (13–752)	49 (−48 to 146)
Acute renal failure	3	71 (23–226)	147 (−22 to 315)
Chronic kidney disease	2	12 (3.0–48)	91 (−47 to 228)
Obstructive uropathy	2	10.3 (2.6–41)	89 (−48 to 227)
Malignant bone tumours (n = 1519)			
Any renal or urinary tract disease	73	2.4 (1.9–3.0)	233 (140–326)
Renal tubulo-interstitial diseases	4	17 (6.3–49)	21 (−0.8 to 43)
Chronic kidney disease	17	4.5 (2.8–7.3)	73 (28–118)
Soft tissue sarcomas (n = 1962)			
Any renal or urinary tract disease	126	2.7 (2.3–3.2)	288 (208–369)
Renal tubulo-interstitial diseases	6	17 (7.4–41)	21 (3–38)
Acute renal failure	10	6.4 (3.4–12.2)	31 (8–53)
Obstructive uropathy	23	4.9 (3.2–7.5)	5 (−17 to 26)
Germ cell neoplasms (n = 2097)			
Any renal or urinary tract disease	99	2.1 (1.7–2.6)	185 (116–253)
Chronic kidney disease	21	4.1 (2.7–6.3)	19 (3–36)
Carcinomas and other malignant epithelial neoplasms (n = 3646)			
Any renal or urinary tract disease	180	1.6 (1.3–1.8)	108 (62–153)
Other and unspecified neoplasms (n = 466)			
Any renal or urinary tract disease	26	2.7 (1.8–3.9)	286 (110–462)
Renal tubulo-interstitial diseases	1	20 (2.8–148)	17 (−18 to 51)
Acute renal failure	3	9.6 (3.1–30)	47 (−12 to 107)

CI, confidence interval.
Subcategories of urinary tract diseases with a lower 95% confidence limit of the RR of ≥2.5 were included of each cancer diagnosis with the corresponding AER.

Table 3 provides AER and RRs for a set of combinations of childhood cancer and urinary tract diseases for which the lower 95% confidence limit of RR was ≥2.5. Apart from survivors of retinoblastoma, an increased risk of urinary tract disease in all categories of childhood cancer was identified. Among survivors of neuroblastoma, renal tumours, and leukaemia the risk for acute renal failure was particularly high; similarly the risk for chronic kidney disease was high in survivors of neuroblastoma, renal tumour and hepatic tumour.

Fig. 2 illustrates the observed and expected age-specific hospitalization rates among survivors and comparisons by time since diagnosis for any type of urinary tract disease and for a set of well-defined disease entities. Risk estimates varied considerably by time since diagnosis; the highest absolute risk for being hospitalized for urolithiasis was during the first 9 years after diagnosis; subsequently, the excess risk remained stable with an AER of almost 20 per 100,000 person-years.

Using the urinary tract morbidity in survivors of leukaemia as the standard, the within cohort analysis showed that the risk of being hospitalized for any disease was highest in survivors of neuroblastoma and renal tumours (Table 4). Survivors diagnosed in the age group 15–19 years had the highest risk for a urinary tract disease compared to those diagnosed at younger age, particularly prominent in survivors of leukaemia.

5. Discussion

Our study of 32,519 one-year childhood cancer survivors showed a 2.5-fold increased risk of being hospitalized for a urinary tract disease compared with the general population. Particularly high risks were noted for survivors of neuroblastoma, renal tumours, and leukaemia. The study showed that the excess risk of urinary tract diseases remains high for >20 years after cancer diagnosis.

The aim was to give a comprehensive overview of the risks of various urinary tract diseases among childhood cancer survivors. With the population-based design and complete follow-up of cancer survivors, we were able to eliminate the risk of selection bias.

Most prior studies investigating long-term effects from treatment of childhood cancer were based on self-reported disease outcomes [23]. In the US Childhood Cancer Survivor Study (CCSS), comprising nearly 14,000 five-year survivors and 3900 sibling comparisons, survivors were almost nine times more likely than siblings to report renal failure or dialysis [3]. In our Nordic study, we observed a sevenfold increased risk for acute renal failure and an almost fourfold increased risk for chronic kidney disease among cancer survivors compared with the general population. Acute renal failure was diagnosed in 120 survivors and the risk was

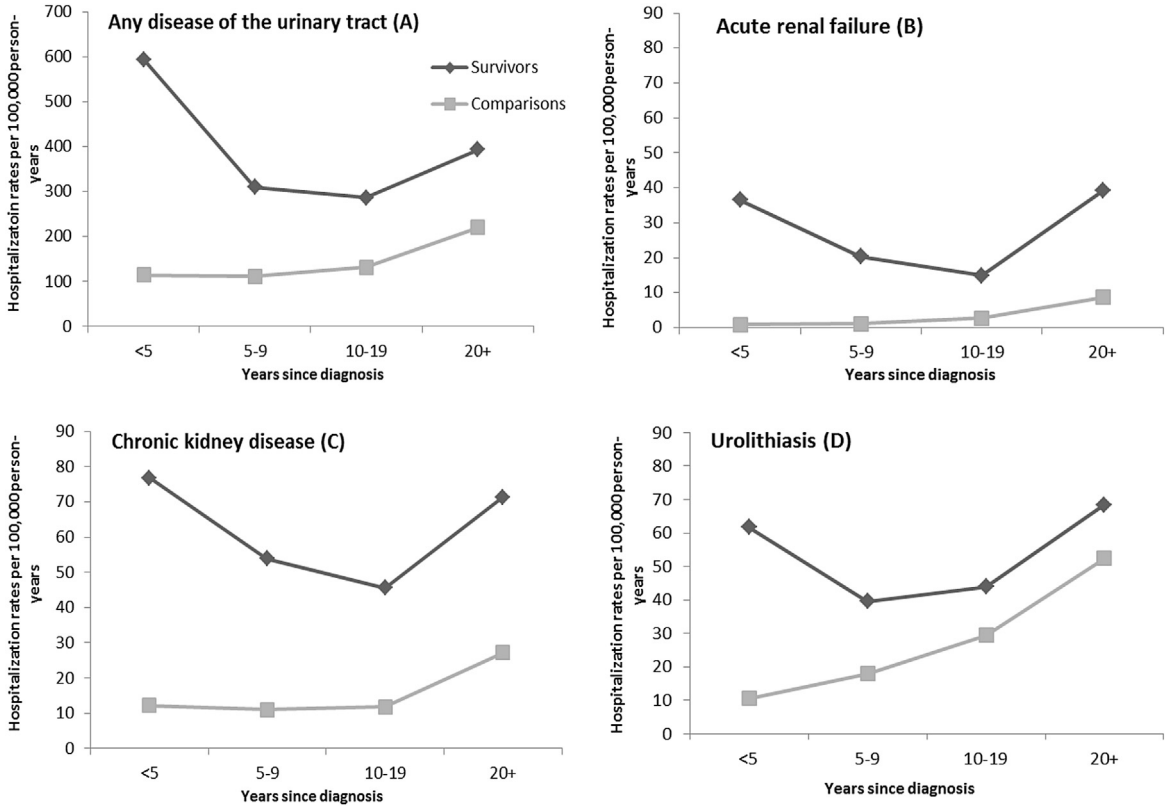

Fig. 2. Observed and expected hospitalizations rates per 100,000 person-years by years since cancer diagnosis for any disease of the urinary tract and for three specific diagnoses. (A) any disease of the urinary tract, (B) acute renal failure, (C) chronic kidney disease, (D) urolithiasis.

Table 4
Within cohort Cox analysis with hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of hospitalization for any disease of the urinary tract according to type of cancer.

Cancer diagnosis	The risk of hospitalization for any disease of the urinary tract
	HR (95% CI)
Leukaemia	1.0
Lymphomas	0.71 (0.58–0.87)
Central nervous system tumours	1.00 (0.85–1.17)
Neuroblastoma	1.61 (1.28–2.04)
Retinoblastoma	0.47 (0.32–0.70)
Renal tumours	1.36 (1.08–1.70)
Hepatic tumours	1.29 (0.70–2.35)
Malignant bone tumours	0.93 (0.71–1.22)
Soft tissue sarcomas	1.12 (0.91–1.39)
Germ cell neoplasms	0.79 (0.62–1.01)
Carcinomas and other malignant epithelial neoplasms	0.66 (0.54–0.82)
Other and unspecified neoplasms	1.01 (0.67–1.51)
Age at time of cancer diagnosis	
0–4 years	1.00
5–9 years	1.00 (0.85–1.16)
10–14 years	1.12 (0.97–1.30)
15–19 years	1.24 (1.07–1.44)
Leukaemia	
Age at cancer diagnosis	
0–4 years	1.0
5–9 years	1.33 (0.98–1.80)
10–14 years	1.91 (1.40–2.60)
15–19 years	2.39 (1.66–3.43)

HR is presented according to age at time of cancer diagnosis for the entire cohort and for patients with leukaemia alone.

elevated more than 20 years after cancer diagnosis. The high risk of acute renal failure is only partly explained by an underlying chronic kidney disease as only 27 of the 120 survivors had been previously hospitalized for this condition. Some of these late cases might be explained by kidney damage presenting later in life, or the coexistence of congestive heart failure, diabetes mellitus, and/or hypertension [24–26]. Survivors of leukaemia, neuroblastoma, and renal tumours had a notably higher risk of acute renal failure compared with survivors of other cancer types. During treatment, patients with cancer commonly experience infectious events treated with nephrotoxic antibiotics such as aminoglycosides and vancomycin. Acute renal injury has been reported in children treated with vancomycin with risks further increased after concomitant use of nephrotoxic chemotherapeutic agents [27,28]. The substantial increase seen among leukaemia survivors in our study could be explained by the generally extended treatment periods with need of antibiotics and/or by treatment with high-dose methotrexate [6,29–31]. In our cohort, 116 survivors were hospitalized for chronic renal failure during follow-up equivalent to 0.36% of all survivors. This estimate is compatible with the 0.3% of the 5-year survivors reporting chronic renal failure in the CCSS [32].

Some studies have suggested young age at cancer diagnosis to be an independent risk factor for developing a chronic kidney disease [5,33,34], whereas others have not been able to confirm this [35,36]. In our study chronic kidney disease was primarily reported among survivors of renal tumours, neuroblastoma, and leukaemia and in the unadjusted analysis the RR was highest among survivors diagnosed with cancer below the age of 5 years (data not shown); this is the age group where the vast majority of patients with Wilms tumour, neuroblastoma, and leukaemia are diagnosed. A within cohort analysis showed that the risk of being hospitalization for a urinary tract disease was highest in survivors of neuroblastoma and renal tumours and young age at time of cancer diagnosis was not an independent risk factor with the highest adjusted risk observed in those diagnosed with cancer between the age of 15 and 19 years. The highest risk was reported in survivors of leukaemia diagnosed in their late teens which correlates with both acute toxicity and dialysis occurring more frequently in adolescent patients with leukaemia than in younger patients [37].

Based on 44 observed cases, hospitalization for urolithiasis among leukaemia survivors was four times more common compared with the general population and occurred with an excess risk of 4.5 per 10,000 person-years. A study from St. Jude Children's Research Hospital comprising 2095 acute lymphoblastic leukaemia patients reported an incidence for urolithiasis of 1.8 per 10,000 person-years; however, this study was based on three cases only [38]. The relatively high number of survivors with urolithiasis in our study may be explained by increasingly more patients treated with haematopoietic stem cell transplantation and total body irradiation since the beginning of the 1980s [39].

Our study is limited by insufficient or absent information on treatment of the individual patient as this is not available in the cancer registries. Our results might be influenced by better medical surveillance of survivors than of comparisons, leading to potential overestimation of the relative and absolute risks for urinary tract diseases among survivors. We do not anticipate this will affect the more severe diseases such as acute renal failure and chronic kidney disease. Furthermore, the date of first admission is not always the day of the first diagnosis since some diagnoses are made in primary care or in an outpatient clinic before being hospitalized. However, we consider the first day of hospitalization as a reasonable surrogate marker for the date of diagnosis.

In conclusion, this large Nordic population-based study providing a comprehensive overview of diseases of the urinary tract among childhood cancer survivors showed that survivors had a substantially increased risk for virtually all diseases within the urinary tract and for most diseases this risk remained elevated throughout life.

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Conflict of interest statement

H.B. receives personal fees and other from Otsuka, grants from GlaxoSmithKline (GSK), personal fees from Alexion, AstraZeneca, and Novartis, outside the submitted work. The other authors declare no conflicts of interest.

Author's contributions

TGB is the principal investigator. She has contributed in the design, literature search, data analyses and interpretation. She has written all draft and final version of the report and created all tables and figures.

JHO, JFW, and HH contributed to the conception and design.

JHO, SDFL, TG, LT, ASH, LMMH, and FW contributed to the collection and assembly of data.

JHO, JFW, PHA, SDFL, TG, HB, and HH contributed to the data analyses and interpretation.

All authors contributed to preparation of the report and approved the final version.

Ethics committee approval

In accordance with Nordic regulations, data on cohort members were analysed without personal identifiers. The study was approved by the national bioethics committees and national data protection authorities according to national regulations (Denmark: 2010-41-4334, Finland: THL/1284/5.05.00/2013, Iceland: VSN10-041, Norway: 2011/884/REC, and Sweden: Ö 10-2010, 2011/19).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.05.006.

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