ACTA ONCOLOGICA
2022, VOL. 61, NO. 11, 1309–1316
https://doi.org/10.1080/0284186X.2022.2150092

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Sexually transmitted diseases in cancer patients diagnosed under the age of 20 years – a national registry-based cohort study from Finland

Liisa Korhonen[a,b], Laura Madanat-Harjuoja[a,c], Elli Hirvonen[a], Janne Pitkäniemi[a,d,e], Nea Malila[a] and Mervi Taskinen[f]

[a]Finnish Cancer Registry, Helsinki, Finland; [b]New Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [c]Boston Children's Cancer and Blood Disorders Center, Dana Farber Cancer Institute, Boston, MA, USA; [d]Department of Public Health, University of Helsinki, Helsinki, Finland; [e]School of Health Sciences, University of Tampere, Tampere, Finland; [f]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

ABSTRACT

Background: Adolescents with chronic diseases are shown to be vulnerable for risky sexual behavior. Childhood cancer patients seem to engage in risky health behaviors as frequently as general population, but little is known about sexual issues in this group of patients.

Material and methods: We characterized the risk for sexually transmitted diseases (STD) in a Finnish population-based cohort of over 6,000 childhood cancer patients diagnosed with cancer under the age of 20 years between 1971 and 2009, compared with over 30,000 age- and sex -matched population comparisons. The data were constructed through linkage between national cancer, population, infectious diseases, and hospital discharge registries. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox regression modeling with attained age as the underlying time scale.

Results: Childhood cancer patients had a decreased risk for having an infection with chlamydia, the most common STD in our cohort, when comparing with population comparisons (HR 0.77, 95% CI 0.69–0.86). The risk was lowest among male patients (HR 0.64, 95% CI 0.53–0.79) and patients with central nervous system (CNS) tumors (HR 0.46, 95% CI 0.33–0.63). The overall risk for cervical dysplasia was slightly increased among female cancer patients when compared with their population comparisons (HR 1.28, 95% CI 1.02–1.60). Greatest risk elevation was found among patients diagnosed with cancer in ages 10–14 years (HR 2.31, 95% CI 1.46–3.65) and patients with lymphoma (HR 1.95, 95% CI 1.20–3.16). The risk for all explored outcomes seemed to be decreased among patients with CNS tumors.

Conclusions: Our findings highlight the importance of integrating sexual issues as a part of psychosocial support and having a systematic transition program in the follow-up care of childhood cancer patients.

ARTICLE HISTORY
Received 13 October 2021
Accepted 9 November 2022

KEYWORDS
Survivors of childhood cancer; health risk behaviors; sexually transmitted diseases; register-based cohort

Background

About 200 children and adolescents under the age of 20 years are diagnosed with cancer in Finland annually. With modern treatment protocols, most of the children with cancer reach adulthood. Through last decades the 5-year survival rate has increased up over 85% [1–3].

Adolescents and young adults are in a phase of major psychosocial development. This period aims at building independence from the childhood family, achieving education, forming a healthy body image and self-esteem, and establishing a sexual identity. Having a chronic disease such as cancer at this point of life or even earlier, may disturb these developmental processes [4].

Risky sexual behavior is defined as sexual behavior that places one at risk for contraction of infection or unintended pregnancy [5]. This type of behavior is most common among adolescents and young adults [6,7]. A questionnaire-based study from North America suggested that teenagers with a chronic condition were more likely to have a sexually transmitted disease (STD) compared to peers [8].

Previous research on risky sexual behavior in childhood cancer patients is scarce. No difference has been found between patients and siblings engaging in risky sexual behavior but certain risk factors have been detected in 5-year cancer survivors diagnosed at early years of childhood [9,10]. To our knowledge, there are no previous studies exploring STDs among childhood cancer patients in a registry-based setting.

We aimed to study the hazard of sexually transmitted diseases in childhood cancer patients and compare that to population comparisons.

CONTACT Liisa Korhonen liisa.korhonen@cancer.fi Finnish Cancer Registry, Unioninkatu 22, Helsinki 00130, Finland; Pediatric Research Center, New Children's Hospital, University of Helsinki and Helsinki University Hospital, Stenbäckinkatu 9, Helsinki 00290, Finland

Supplemental data for this article is available online at https://doi.org/10.1080/0284186X.2022.2150092.

Material and methods

Study design and population

We conducted a nationwide cohort study based on Finnish registry data. Our study included all patients ($n = 8,080$) diagnosed with cancer in Finland before the age of 20 years between 1971 and 2009 and age- and sex-matched population comparisons, who were alive and without childhood cancer on the date of cancer diagnosis of the corresponding patient (1:5 ratio, $n = 40,393$). After sampling, there were two cancer patients with less than five comparison subjects, i.e., seven comparisons less than optimal (Supplementary figure 1). Cancer patients were identified from the Finnish Cancer Registry including national population-based information on all cancer diagnoses since 1953. Reporting new cancer cases to the national cancer registry is obligatory in Finland and the coverage of the registry is high [11–13].

Cancer patients and population comparisons were identified from the Digital and Population Data Services Agency of Finland, formerly known as Population Register Center of Finland, founded in 1969 [14]. Finland has a civil registration system with various national population-based administrative registries providing individual level information on a variety of outcomes such as cancer, infectious diseases, and socioeconomic data [14]. Every Finnish citizen is assigned a unique personal identity code that is used in all national registries, enabling accurate linkage of information between registries.

All subjects who had died or emigrated prior to the start of follow-up were left out from the analyses (1,847 cancer patients and their 9,232 matched comparisons, and 307 comparison subjects in analyses regarding the National Infectious Disease Register (NIDR) and 1,390 cancer patients and their 6,947 matched comparisons, and 194 comparison subjects in analyses regarding the Care Register for Health Care (CRHC)). Cancer patients ($n = 15$) diagnosed with an STD in either of the registers before cancer diagnosis were excluded, similarly were the matched comparisons ($n = 75$). Comparison subjects ($n = 75$) diagnosed with an STD before matched patient's cancer diagnosis were also excluded. See Supplementary figure 1 for flow chart. Characteristics of the eligible study population are displayed in Tables 1 and 2.

Registers

Information on STD's was retrieved from two national registers held by The National Institute for Health and Welfare: The National Infectious Disease Register (NIDR) and the Care Register for Health Care (CRHC). The data on microbes and diseases have been collected in NIDR since 1995 and is based on reports made by doctors and laboratories [15]. We identified the following diseases *(the pathogen in cursive)*: Chlamydia *(Chlamydia trachomatis)*, syphilis *(Treponema pallidum)*, gonorrhea *(Neisseria gonorrhea)*, *hepatitis B virus (HBV)*, *hepatitis C virus (HCV)* and *human immunodeficiency virus* (*HIV*), and the date when the positive laboratory result was registered.

Secondly, we identified all hospital contacts linked to a diagnosis of cervical dysplasia (mild, moderate, severe, or unspecified cervical dysplasia or adenocarcinoma *in situ* of cervix uteri) or condyloma from the CRHC. This register replaced former Finnish Hospital Discharge Register in year 1994 and contains nationwide linkable data on all inpatient hospital discharges with personal identification code since 1969 and outpatient visits since 1998 [16]. Sexually transmitted infections caused by *human papillomavirus (HPV)* are not systematically reported in the NIDR but utilizing data from the CRHC, we were able to cover also the clinically relevant cases of HPV related diseases. Information on hospital contacts was gathered from year 1987. Diagnoses were classified according to the Finnish Classification of Diseases 1987 and10th revision of the International Classification of Diseases (Supplementary table 1).

Statistical analyses

Follow-up began on date of cancer diagnosis for patients and on the respective date for comparisons or on the date the corresponding outcome register data became available, i.e., since 1st of January 1987 in the CRHC or 1st of January 1995 in NIDR, whichever occurred last. Follow-up ended at outcome of interest, death, emigration, or the end of follow-up of the study (31st of December 2014), whichever occurred first. Matched comparisons were censored if patient's follow-up ended due to death or emigration.

We calculated the number of STD's and person-years at-risk for patients and comparisons from NIDR and CRHC. We estimated the incidence rates (per 10,000 person-years) of STD and hazard ratios (HR) for STD with 95% confidence intervals (CIs) using Cox regression modeling with attained age as the underlying time scale. In analyses regarding recurrent chlamydia diagnoses, we used Prentice, William, and Peterson gap-time model, where the baseline hazards vary from event to event [17,18]. The comparison was made between patients and comparisons utilizing the matched sampling of the cohort. The baseline hazard was stratified by the matched set comprising the patient and individual comparisons.

We divided the calendar time period of patient's cancer diagnosis into four decades: 1971–1979,1980–1989, 1990–1999 and 2000–2009, and age at cancer diagnosis into four categories: 0–4, 5–9, 10–14 and 15–19 years. This way, we wanted to consider the similarity of diagnostic distribution and treatment regimens by calendar period and age. Cancer diagnoses were classified according to the 12 main diagnostic groups of the International Classification of Childhood Cancer (ICCC-3) [19]. Due to the small number of cases in some diagnostic groups, we analyzed leukemia, lymphoma and central nervous system (CNS) tumors separately and combined all other cancer diagnoses into one group (non-CNS solid tumors).

We present analyses stratified by diagnostic time period, diagnostic age, cancer site and sex. We conducted separate analyses for data retrieved from the NIDR and from the CRHC. Data from the NIDR were separately analyzed for first and recurrent chlamydia infections and first STD diagnoses other than chlamydia. Due to scarce data, other STDs could

Table 1. Basic **characteristics of cancer patients and population comparisons, eligible in analyses regarding sexually transmitted diseases (STDs) registered in the National Infectious Disease Register (NIDR).**

	Cancer patients ($n = 6,218$)		Population comparisons ($n = 30,704$)	
Characteristics	*n*	%	*n*	%
Sex				
Male	3233	52.0	16003	52.1
Female	2985	48.0	14701	47.9
Age at patient's cancer diagnosis, years				
0–4	2036	32.7	10093	32.9
5–9	1070	17.2	5313	17.3
10–14	1202	19.3	5948	19.4
15–19	1910	30.7	9350	30.5
Period of patient's cancer diagnosis				
1971–1979	675	10.9	3188	10.4
1980–1989	1280	20.6	6303	20.5
1990–1999	2084	33.5	10393	33.8
2000–2009	2179	35.0	10820	35.2
Cancer diagnostic groups				
Leukemia	1561	25.1	–	–
Lymphoma	983	15.8	–	–
Central nervous system tumors	1282	20.6	–	–
Neuroblastoma and other peripheral cell tumors	261	4.2	–	–
Retinoblastoma	125	2.0	–	–
Renal tumors	287	4.6	–	–
Hepatic tumors	52	0.8	–	–
Malignant bone tumors	237	3.8	–	–
Soft tissue sarcomas	369	5.9	–	–
Germ-cell, trophoblastic and other gonadal neoplasms	339	5.5	–	–
Other malignant epithelial neoplasms	680	10.9	–	–
Other and unspecified malignant neoplasms	42	0.7	–	–
Sexually transmitted diseases				
Total	359	5.8	2034	6.6
Chlamydia*	295 (349)	4.7	1824 (2318)	5.9
Other STDs				
All	64	1.0	210	0.7
Hepatitis B	12	0.2	18	<0.1
Hepatitis C	41	0.7	147	0.5
Syphilis	≤5	<0.1	10	<0.1
HIV	≤5	<0.1	6	<0.1
Gonorrhea	≤5	<0.1	29	<0.1
	Median (years)	**Range (years)**	**Median (years)**	**Range (years)**
Attained age at end of follow-up, years (median, range)				
Analyses of chlamydia	28.0	0.0–63.6	27.6	0.0–63.6
Analyses of other STDs	27.9	0.0–63.3	27.5	0.0–63.6
Follow-up time, years (median, range)				
Analyses of chlamydia	17.0	0.0–20.0	16.4	0.0–20.0
Analyses of other STDs	16.7	0.0–20.0	16.2	0.0–20.0
Age at first STD diagnosis				
Chlamydia	22.4	16.2–51.2	21.9	13.8–51.1
Other STDs	23.8	8.2–50.9	24.3	0.5–49.5

*Number of unique persons with chlamydia, overall number of chlamydia infections in parentheses.

not be analyzed separately. Data from the CRHC were analyzed separately for condyloma and cervical dysplasia. A sub-analysis exploring condyloma was conducted for all patients and comparisons, whereas the sub-analysis exploring cervical dysplasia was conducted for female patients and female comparisons only. In analyses regarding data from the CRHC, we explored the first HPV related diagnosis only.

Statistical analyses were conducted using the statistical program R version 3.6.2 [20].

Results

The national infectious disease register

In analyses regarding data from NIDR, 6,218 childhood cancer patients had a median follow-up of 17.0 and 16.7 years, and the 30,704 population comparisons had a median follow-up of 16.4 and 16.2 years, when exploring chlamydia and other STDs, respectively (Table 1). In all, 5.8% ($n = 359$) of childhood cancer patients and 6.6% ($n = 2,034$) of comparisons had at least one STD by the end of follow-up registered in the NIDR. Chlamydia was the most common STD registered in the NIDR. Median age at contracting chlamydia for the first time was 22.4 years (range 16.2–51.2 years) among cancer patients and 21.9 years (range 13.8–51.1 years) among population comparisons (Table 1). The age at the end of follow-up was 28.0 and 27.9 years for patients and 27.6 and 27.5 years for comparisons, when exploring chlamydia and other STDs, respectively (Table 1).

The risk for ever contracting an infection with chlamydia was statistically significantly decreased in childhood cancer patients compared with population comparisons (HR 0.79, 95% CI 0.71–0.88). The results were similar, when looking at the first chlamydia diagnoses only (HR 0.77, 95% CI

Table 2. Basic **characteristics of cancer patients and population comparisons, eligible in analyses regarding sexually transmitted diseases (STDs) registered in the Care Register for Health Care (CRHC).**

	Cancer patients ($n = 6,675$)		Population comparisons ($n = 33,102$)	
Characteristics	*n*	%	*n*	%
Sex				
Male	3496	52.4	17388	52.5
Female	3179	47.6	15714	47.5
Age at patient's cancer diagnosis, years				
0–4	2194	32.9	10919	33.0
5–9	1146	17.2	5702	17.2
10–14	1288	19.3	6403	19.3
15–19	2047	30.7	10078	30.4
Period of patient's cancer diagnosis				
1971–1979	710	10.6	3399	10.3
1980–1989	1553	23.3	7731	23.4
1990–1999	2233	33.5	11152	33.7
2000–2009	2179	32.6	10820	32.7
Cancer diagnostic groups				
Leukemia	1685	25.2	–	–
Lymphoma	1029	15.4	–	–
Central nervous system tumors	1415	21.2	–	–
Neuroblastoma and other peripheral cell tumors	292	4.4	–	–
Retinoblastoma	127	1.9	–	–
Renal tumors	298	4.5	–	–
Hepatic tumors	59	0.9	–	–
Malignant bone tumors	273	4.1	–	–
Soft tissue sarcomas	406	6.1	–	–
Germ-cell, trophoblastic and other gonadal neoplasms	352	5.3	–	–
Other malignant epithelial neoplasms	695	10.4	–	–
Other and unspecified malignant neoplasms	44	0.7	–	–
Sexually transmitted diseases				
Cervical dysplasia	95	3.0 *	359	2.3 *
Condyloma	93	1.4	430	1.3
	Median (years)	**Range (years)**	**Median (years)**	**Range (years)**
Attained age at end of follow-up				
Analyses of cervical dysplasia	27.3	0.0–63.6	26.9	0.0–63.6
Analyses of condyloma	26.6	0.0–63.6	26.2	0.0–63.6
Follow-up time				
Analyses of cervical dysplasia	16.5	0.0–28.0	16.1	0.0–28.0
Analyses of condyloma	16.1	0.0–28.0	15.5	0.0–28.0
Age at first STD diagnosis				
Cervical dysplasia	27.9	15.2–50.2	27.0	15.9–53.3
Condyloma	23.1	12.7–48.7	24.3	3.1–51.8

*Proportion of female study subjects.

0.69–0.86). The risk for ever having a chlamydia infection seemed to be even lower among male cancer patients when compared with male comparisons (HR 0.65, 95% CI 0.54–0.79) than among female cancer patients when compared with female comparisons (HR 0.88, 95% CI 0.77–1.00). Stratifying by cancer site, the risk was statistically significantly decreased among patients with CNS tumor when compared with population comparisons (HR 0.48, 95% CI 0.35–0.65) (Table 3).

Overall, 1.0% of cancer patients ($n = 64$) and 0.7% of population comparisons ($n = 210$) were diagnosed with an STD other than chlamydia. The overall risk for a first infection with an STD other than chlamydia seemed to be increased among cancer patients when compared with comparisons (HR 1.46, 95% CI 1.10–1.93). The risk for male patients was similar to their comparisons (HR 1.20, 95% CI 0.82–1.75) but the risk was significantly increased when comparing female cancer patients with their comparisons (HR 1.91, 95% CI 1.26–2.89). The risk estimates were also elevated among patients with leukemia (HR 2.25, 95% CI 1.30–3.89), patients diagnosed at the age of 0–4 years (HR 2.23, 95% CI 1.29–3.87), and patients diagnosed in 1971–1979 (HR 2.37, 95% CI 1.05–5.38) and 1981–1989 (HR 2.12, 95% CI 1.38–3.25), when comparing with population comparisons (Supplementary table 2).

The care register for health care

In analyses regarding data from CRHC, 6,675 childhood cancer patients had a median follow-up of 16.5 and 16.1 years, and the 33,102 population comparisons had a median follow-up of 16.1 and 15.5 years, when exploring cervical dysplasia and condylomas, respectively (Table 2).

In females, 95 of 3,179 (3.0%) cancer patients and 359 of 15,714 (2.3%) comparisons had a diagnosis of cervical dysplasia in the CRHC by the end of follow-up. Condyloma was registered among 93 of 6,675 (1.4%) cancer patients and among 430 of 33,102 (1.3%) population comparisons by the end of follow-up. Median age for females at first diagnosis with cervical dysplasia was 27.9 years (range 15.2–50.2 years) for patients and 27.0 years (range 15.9–53.3 years) for comparisons and median age at first diagnosis with condyloma was 23.1 years (range 12.7–48.7 years) for patients and 24.3 years (range

Table 3. Numbers **and hazards ratios (HR) for first chlamydia infections and HRs for recurrent chlamydia infections with 95 % confidence interval (CI) among cancer patients and population comparisons.**

	Cancer patients ($n = 6,218$)		Population comparisons ($n = 30,704$)			
	n	1000 pyrs	n	1000 pyrs	HR (95% CI)	Overall HR (95% CI)*
Total	295	86.0	1824	414.5	0.77 (0.69–0.86)	0.79 (0.71–0.88)
Sex						
Male	97	44.6	719	215.0	0.64 (0.53–0.79)	0.65 (0.54–0.79)
Female	198	41.4	1105	199.5	0.86 (0.74–0.98)	0.88 (0.77–1.00)
Age at patient's cancer diagnosis, years						
0–4	75	28.7	472	139.7	0.75 (0.60–0.94)	0.77 (0.62–0.95)
5–9	55	14.7	344	71.0	0.76 (0.58–0.99)	0.74 (0.57–0.96)
10–14	62	16.7	388	80.5	0.78 (0.61–1.00)	0.81 (0.64–1.03)
15–19	103	25.9	620	123.3	0.79 (0.65–0.96)	0.82 (0.68–0.99)
Period of patient's cancer diagnosis						
1971–1979	13	12.4	65	57.2	0.94 (0.54–1.62)	0.94 (0.54–1.62)
1980–1989	69	23.6	463	113.3	0.71 (0.56–0.89)	0.71 (0.57–0.89)
1990–1999	133	31.8	812	154.7	0.79 (0.67–0.94)	0.80 (0.68–0.94)
2000–2009	80	18.2	484	89.2	0.78 (0.63–0.97)	0.83 (0.67–1.02)
Cancer diagnostic groups						
Leukemia	71	20.8	424	101.0	0.79 (0.62–0.99)	0.79 (0.63–1.00)
Lymphoma	55	13.7	342	66.0	0.77 (0.59–1.00)	0.77 (0.59–1.00)
Central Nervous System	38	17.1	394	81.5	0.46 (0.33–0.63)	0.48 (0.35–0.65)
Other	131	34.4	664	166.0	0.96 (0.81–1.14)	0.98 (0.83–1.15)

*Recurrent chlamydia infections pooled into the analysis.

Table 4. Numbers **and hazards ratios (HR) with 95 % confidence interval (CI) for cervical dysplasia among female cancer patients and population comparisons.**

	Female cancer patients ($n = 3,179$)		Female population comparisons ($n = 15,714$)		
	n	1000 pyrs	*n*	1000 pyrs	HR (95% CI)
Total	95	51.2	359	249.2	1.28 (1.02–1.60)
Age at patient's cancer diagnosis, years					
0–4	11	15.9	77	77.8	0.68 (0.36–1.27)
5–9	12	8.8	63	42.9	0.91 (0.49–1.70)
10–14	27	10.2	60	50.0	2.31 (1.46–3.65)
15–19	45	16.3	159	78.5	1.35 (0.97–1.88)
Period of patient's cancer diagnosis					
1971–1979	14	9.5	60	44.2	1.13 (0.63–2.03)
1980–1989	26	16.5	115	80.3	1.09 (0.71–1.66)
1990–1999	43	16.6	145	82.3	1.45 (1.03–2.04)
2000–2009	12	8.6	39	42.4	1.44 (0.75–2.74)
Cancer diagnostic groups					
Leukemia	25	12.6	78	61.7	1.58 (1.00–2.48)
Lymphoma	23	6.8	58	33.3	1.95 (1.20–3.16)
Central Nervous System	10	9.5	70	46.1	0.68 (0.35–1.32)
Other	37	22.3	153	108.1	1.16 (0.81–1.66)

3.1–51.8 years) for comparisons (Table 2). The age at the end of follow-up was 27.3 and 26.6 years for patients and 26.9 and 26.2 years for comparisons, when exploring cervical dysplasia and condyloma, respectively (Table 2).

The overall risk for cervical dysplasia was increased among childhood cancer patients when comparing with population comparisons (HR 1.28, 95% CI 1.02–1.60). In stratified analyses, the increased risk for cervical dysplasia was most pronounced when cancer was diagnosed at age of 10–14 years (HR 2.31, 95% CI 1.46–3.65), in the time period of 1990–1999 (HR 1.45, 95% CI 1.03–2.04) and among patients with leukemia (HR 1.58, 95% CI 1.00–2.48) or lymphoma (HR 1.95, 95% CI 1.20–3.16), when comparing patients with population comparisons. The risk estimates were lowest in patients with CNS tumors (HR 0.68, 95% CI 0.35–1.32), but the results remained insignificant (Table 4).

There was no statistically significant difference in the overall risk for condyloma when comparing cancer patients with population comparisons (HR 1.05, 95% CI 0.84–1.31.

Stratifying by age at cancer diagnosis, the risk for condyloma seemed to be rising with the age at cancer diagnosis. The risk was lowest, when cancer was diagnosed in early childhood, before the age of 5 years (HR 0.47, 95% CI 0.25–0.91), whereas the risk was highest in the oldest age period of 15–19 years (HR 1.41, 95% CI 1.03–1.93).

When looking into stratified analysis by cancer site, the risk for condyloma was statistically increased among lymphoma patients (HR 1.62, 95% CI 1.06–2.49) whereas the risk was decreased among patients with CNS tumors (HR 0.35, 95% CI 0.15–0.80), when compared with population comparisons. Stratifying by diagnostic period, the total risk for having a condyloma diagnosis was highest during the most

Table 5. Numbers **and hazards ratios (HR) with 95 % confidence interval (CI) for condyloma diagnoses among cancer patients and population comparisons.**

	Cancer patients ($n = 6,675$)		Population comparisons ($n = 33,102$)		
	n	1000 pyrs	*n*	1000 pyrs	HR (95% CI)
Total	93	105.6	430	513.3	1.05 (0.84–1.31)
Sex					
Male	26	54.2	159	263.9	0.80 (0.53–1.21)
Female	67	51.4	271	249.4	1.20 (0.91–1.56)
Age at patient's cancer diagnosis, years					
0–4	10	35.1	102	171.3	0.47 (0.25–0.91)
5–9	12	18.4	67	89.6	0.85 (0.46–1.57)
10–14	21	20.6	89	99.9	1.17 (0.73–1.88)
15–19	50	31.6	172	152.4	1.41 (1.03–1.93)
Period of patient's cancer diagnosis					
1971–1979	5	18.0	42	83.6	0.56 (0.22–1.42)
1980–1989	18	34.3	137	166.7	0.64 (0.39–1.04)
1990–1999	46	34.8	194	171.6	1.16 (0.84–1.60)
2000–2009	24	18.5	57	91.4	2.02 (1.25–3.26)
Cancer diagnostic groups					
Leukemia	26	25.3	93	124.0	1.34 (0.86–2.07)
Lymphoma	28	16.4	84	79.8	1.62 (1.06–2.49)
Central Nervous System	6	21.0	83	102.1	0.35 (0.15–0.80)
Other	33	42.9	170	207.4	0.95 (0.65–1.38)

recent time period of 2000–2009 (HR 2.02, 95% CI 1.25–3.26), when comparing cancer patients with comparisons (Table 5).

Discussion

In this study, we characterized the risk for having an STD in a large population-based cohort of over 6,000 childhood cancer patients and 30,000 population comparisons. The data suggest that childhood cancer patients have a decreased risk for infection with chlamydia when comparing with age- and sex -matched population comparisons. The risk was lowest among male patients and patients with CNS tumors. The overall risk for cervical dysplasia was slightly increased among female cancer patients when compared with their population comparisons. A statistically significantly increased risk was found among patients diagnosed with cancer in ages 10–14 years, in the 1990s and in patients with leukemia or lymphoma. The overall risk for contracting condyloma was similar for both patients and comparisons. The risk for all explored outcomes seemed to be decreased among patients with CNS tumors.

Current evidence suggests that adolescents with a chronic illness are as likely to engage in risky health behaviors such as tobacco, alcohol, or drug abuse [21] and unsafe sexual practices [4], as healthy comparisons. Adverse socioeconomic events [22] and psychiatric morbidities [21,23] may contribute in increasing vulnerability to risky health behavior.

Disturbance in the sensitive developmental phase of puberty seems to lead to dysfunction in forming healthy sexuality [24]. A Dutch questionnaire-based study showed delay in achieving psychosexual milestones such as dating and sexual debut among childhood cancer survivors compared with general population. Cancer treatment in adolescence was a risk factor for this delay [25]. A North American questionnaire study of adult survivors of childhood cancer showed parallel results in timing of psychosexual milestones, but also highlighted that cancer survivors were generally satisfied with this somewhat lower speed [26]. In our study we found cancer patients to have a decreased risk for chlamydia and an increased risk for female patients for having cervical dysplasia, when comparing with population comparisons. We found the median age at first chlamydia diagnosis to be slightly older in cancer patients than in comparisons, which could reflect delay in psychosexual development among childhood cancer patients. By contrast, the median age at diagnosis for condyloma was over one year younger in patients than in comparisons.

STD rates vary worldwide. Chlamydia is the most reported STD in Europe and the United States. The incidence rate for chlamydia was 269 per 100,000 in Finland and 146 per 100,000 in all countries of the European Union combined in 2018, and 481 per 100,000 in the United States in 2020 [27,28]. There are notable cultural differences in contraceptive use and registration and screening of STDs [6]. In most European countries, STDs are detected more among adolescent females than males [6]. This is thought to be partly due to the current reproductive health care, which is offering counseling for example for contraception, abortion, and screening for cervical cancer and thus targeting more females than males. Our study supports this finding since we also found more STDs among females than males in patients and in comparisons.

A CCSS-based study from North America examined risky sexual behavior in adolescent 5-year survivors of childhood cancer diagnosed with cancer before the age of four years. No difference in engaging in risky sexual behavior was found between survivors and siblings. The risk for having an STD was increased if a person had shorter time period from cancer diagnosis to STD or higher parental education [9]. In our study, the risk estimates for condyloma, and cervical dysplasia were lowest in the youngest age groups at cancer diagnosis. The risk for chlamydia was reduced in all age groups. We also conducted analyses adjusted for highest parental education, but our results and conclusions remained similar.

In cohort studies, childhood cancer survivors seem to have lower rates of marriage and cohabitation compared with general population [21]. This has been pronounced in

male patients and patients with CNS tumors. Higher neurotoxicity of treatment has been shown as a risk factor for impaired psychosexual development [21]. When stratifying by cancer site, we found the patients with CNS tumors to have a decreased risk for being diagnosed with chlamydia (HR 0.48, 95% CI 0.35–0.65) and with condyloma (HR 0.35, 95% CI 0.15–0.80), when compared with population comparisons. When exploring diagnoses of cervical dysplasia, the risk, again, appeared to be reduced among patients with CNS tumors when compared with population comparisons, but the results remained insignificant. We hypothesize that CNS tumor patients may have challenges in finding a partner which could partly explain the reduced rates of STDs in this group.

HPV is the most common sexually transmitted infection worldwide. Most sexually active individuals will acquire it at some point of life, typically as young adults [29]. These infections usually clinically resolve after months. More persistent infection with high-risk HPV is needed for progression to cervical dysplasia and cancer [29]. The HPV vaccination has been part of the national vaccination program since 2013 for girls and since 2020 for boys in Finland, but as our follow-up ended in 2014, information on vaccines was not available in our study [30]. In our study the median age at diagnosis of cervical dysplasia was expectedly older in both groups than median age at diagnosis of other STDs.

We found the age at cancer diagnosis to have a statistically significant effect in the risk for having an HPV-related disease, i.e., cervical dysplasia or condyloma. Cancer diagnosis in early childhood seemed to reduce the risk, whereas the diagnosis in age 10–14 years and 15–19 years increased the risk for cervical dysplasia and condyloma, respectively. In our study, childhood cancer patient's risk for having a diagnosis of cervical dysplasia was slightly increased, when compared with comparisons, whereas the risk for chlamydia was decreased. We speculate that as childhood cancer patients visit specialized health care more often than healthy population comparisons, cervical dysplasia or condyloma may also be found and registered more often. Milder forms of cervical dysplasia and condyloma usually heal without interventions. Cancer survivors are known to be at significantly higher risk for HPV-related morbidities when compared with general population [31]. It has been shown that cancer patients may remain immunocompromised long after treatment. This could increase their risk of HPV acquisition, longer HPV infection persistence and cervical dysplasia [32].

In Finland, laboratories do not systematically report HPV findings for national statistics. In this study we analyzed HPV-related diagnoses using data on cervical dysplasia and condylomas registered in the CRHC. Coverage of diagnoses in this register is not complete, partly because there is variance in clinicians' activity to report diagnoses for registers [16]. Some cases of cervical dysplasia and many condylomas are diagnosed and treated in private health care, and therefore not registered in the CRHC. Additionally, condyloma and cervical dysplasia are caused by different types of human papillomavirus: 90% of condylomas are caused by low-risk HPV types 6 and 11, whereas 70% of cervical dysplasia are caused by HPV 16 and 18. This may, in part, explain the difference in our results regarding these two HPV associated outcomes [33].

We did not include mild manifestations of HPV, such as abnormal Pap smear test results (e.g., atypical squamous cells of undetermined significance, ASCUS) in this study, as we wanted to study the disease burden caused by HPV. Therefore, long-lasting infections can be studied using cervical dysplasia as outcome. Finland has organized cervical cancer screening since 1963, for women starting at age 30 since late 1980s [34]. The data from the FCR did not find a material difference in coverage or attendance of screening in former childhood cancer patients and healthy women (personal communication, Malila).

In our study, we did not restrict our study population by age at STD diagnosis. We started follow-up similarly for patients and their matched comparisons and excluded all study subjects diagnosed with an STD before the start of follow-up from the analyses. Childhood cancer patients make up a population with a considerably higher mortality compared with the general population. This was considered in our study, as matched comparisons were censored if patient's follow-up ended due to death or emigration. We found altogether seven STDs before the age of 13 years among patients and comparisons. These infections may have been contracted perinatally or *via* blood transfusions. Overall, most of the diseases grouped as 'other STDs' in our study are blood-borne infections such as hepatitis B and C that can be contracted without risky sexual behavior at any age.

It is necessary to have a large number of patients to study rare diseases such as STDs in childhood cancer patients. One of the greatest advantages of our study is the high quality of Finnish registry data that enables a virtually complete follow-up with no selection or participation bias [11,12].

The risk for an infection with chlamydia trachomatis seemed to be decreased among childhood cancer patients compared with population comparisons. Chlamydia covering the majority of STDs in our data, our results support earlier findings concerning risky sexual behavior of childhood cancer patients. Nevertheless, we found groups of patients with an increased risk for cervical dysplasia and other STDs as well. As childhood cancer patients often develop long-term complications later in life, risky health behavior should be minimized. Sexual issues should be addressed as a part of psychosocial support and counseling, and the value and quality of a systematic transition program deserves to be highlighted.

Ethical considerations

The study is based on record linkage, and we did not directly contact research subjects. Ethical approval was included in the permission process. The study was approved by the National Institute for Health and Welfare (THL/970/5.05.00/2010, THL/520/5.05.00/2016), Population Register Center (VRK854/410/16) and Statistics Finland (TK53-358-16).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Finnish Medical Foundation under Grant [4148] and the Väre Childhood Cancer Foundation under Grant [202000005].

ORCID

Liisa Korhonen http://orcid.org/0000-0001-7696-324X

Data availability statement

The data that support the findings of this study are available from Statistics Finland. Restrictions apply to the availability of these data, which were used under license for this study. Data are available with the permission of Statistics Finland.

References

[1] Madanat-Harjuoja LM, Pokhrel A, Kivivuori SM, et al. Childhood cancer survival in Finland (1953–2010): a nation-wide population-based study. Int J Cancer. 2014;135(9):2129–2134.

[2] Pitkäniemi J, Malila N, Tanskanen T, et al. Syöpä. 2019. Tilastoraportti Suomen syöpätilanteesta. Suomen Syöpäyhdistyksen julkaisuja nro 96 [A statistical report of cancer in Finland]. Helsinki, Finland: The Cancer Society of Finland; 2021[cited 2022 April 26]. Available from: https://syoparekisteri.fi/assets/files/2021/07/Syopa_2019_Tilastoraportti_0107.pdf

[3] Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37513025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391(10125):1023–1075.

[4] Suris J-C, Michaud P-A, Viner R. The adolescent with a chronic condition. Part I: developmental issues. Arch Dis Child. 2004; 89(10):938–942.

[5] Sexual Risk Behaviors Can Lead to HIV, STDs, & Teen Pregnancy. The United States: Centers for Disease Control and Prevention; 2019. cited 2022 April 26]. Available from https://www.cdc.gov/healthyyouth/sexualbehaviors/index.htm.

[6] Avery L, Lazdane G. What do we know about sexual and reproductive health of adolescents in Europe? Eur J Contracept Reprod Health Care. 2010;15(Suppl 2): s 54–66.

[7] Finer LB, Philbin JM. Sexual initiation, contraceptive use, and pregnancy among young adolescents. Pediatrics. 2013;131(5):886–891.

[8] Surís JC, Resnick MD, Cassuto N, et al. Sexual behavior of adolescents with chronic disease and disability. J Adolesc Health. 1996; 19(2):124–131.

[9] Klosky JL, Foster RH, Li Z, et al. Risky sexual behavior in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. Health Psychol. 2014;33(8):868–877.

[10] Klosky JL, Howell CR, Li Z, et al. Risky health behavior among adolescents in the childhood cancer survivor study cohort. J Pediatr Psychol. 2012;37(6):634–646.

[11] Leinonen MK, Miettinen J, Heikkinen S, et al. Quality measures of the population-based finnish cancer registry indicate sound data quality for solid malignant tumours. Eur J Cancer. 2017;77:31–39.

[12] Pukkala E, Engholm G, Højsgaard Schmidt LK, et al. Nordic cancer registries – an overview of their procedures and data comparability. Acta Oncol. 2018;57(4):440–455.

[13] Jokela M, Leinonen MK, Malila N, et al. Completeness of pediatric cancer registration in the finnish cancer registry. Acta Oncol. 2019;58(11):1577–1580.

[14] Population Information System – Digital and population data services agency. Digi- ja väestötietovirasto. Finland: Digital and population data services agency; [cited 2022 April 26]. Available from: https://dvv.fi/en/population-information-system.

[15] Finnish National Infectious Diseases Register – Infectious diseases and vaccinations – THL. Finland: Finnish Institute for Health and Welfare (THL); [cited 2022 April 26]. https://thl.fi/en/web/infectious-diseases-and-vaccinations/surveillance-and-registers/finnish-national-infectious-diseases-register.

[16] Sund R. Quality of the finnish hospital discharge register: a systematic review. Scand J Public Health. 2012;40(6):505–515.

[17] Yang W, Jepson C, Xie D, et al. Statistical methods for recurrent event analysis in cohort studies of CKD. Clin J Am Soc Nephrol. 2017;12(12):2066–2073.

[18] Thenmozhi M, Jeyaseelan V, Jeyaseelan L, et al. Survival analysis in longitudinal studies for recurrent events: applications and challenges. Clin Epidemiol Glob Health. 2019;7(2):253–260.

[19] Steliarova-Foucher E, Stiller C, Lacour B, et al. International classification of childhood cancer, third edition. Cancer. 2005;103(7): 1457–1467.

[20] R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria; 2022. Available from https://www.R-project.org/.

[21] Brinkman TM, Recklitis CJ, Michel G, et al. Psychological symptoms, social outcomes, socioeconomic attainment, and health behaviors among survivors of childhood cancer: current state of the literature. J Clin Oncol. 2018;36(21):2190–2197.

[22] Frederiksen LE, Mader L, Feychting M, et al. Surviving childhood cancer: a systematic review of studies on risk and determinants of adverse socioeconomic outcomes. Int J Cancer. 2019;144(8): 1796–1823.

[23] Ahomäki R, Gunn ME, Madanat-Harjuoja LM, et al. Late psychiatric morbidity in survivors of cancer at a young age: a nation-wide registry-based study. Int J Cancer. 2015;137(1):183–192.

[24] Lock J. Psychosexual development in adolescents with chronic medical illnesses. Psychosomatics. 1998;39(4):340–349.

[25] van Dijk EM, van Dulmen-den Broeder E, Kaspers GJL, et al. Psychosexual functioning of childhood cancer survivors. Psychooncology. 2008;17(5):506–511.

[26] Lehmann V, Keim MC, Ferrante AC, et al. Psychosexual development and satisfaction with timing of developmental milestones among adult survivors of childhood cancer. Psychooncology. 2018;27(8):1944–1949.

[27] Chlamydia infection Annual Epidemiological Report for 2018. European Union: European Centre for Disease Prevention and Control. 2018; [cited 2022 April 26]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/AER-for-2018-STI-chlamydia.pdf.

[28] Sexually Transmitted Disease Surveillance, 2020. The United States: Centers for Disease Control and Prevention. 2020; [cited 2022 April 26]. Available from: https://www.cdc.gov/std/statistics/2020/.

[29] Crosbie EJ, Einstein MH, Franceschi S, et al. Human papillomavirus and cervical cancer. Lancet. 2013;382(9895):889–899.

[30] HPV, or human papillomavirus vaccine – THL. Finland: Finnish Institute for Health and Welfare (THL); [cited 2022 April 26]. Available from https://thl.fi/en/web/infectious-diseases-and-vaccinations/vaccines-a-to-z/hpv-or-human-papillomavirus-vaccine.

[31] Ojha RP, Tota JE, Offutt-Powell TN, et al. Human papillomavirus-associated subsequent malignancies among long-term survivors of pediatric and young adult cancers. PLoS One. 2013;8(8): e70349.

[32] Klosky JL, Hudson MM, Chen Y, et al. Human papillomavirus vaccination rates in young cancer survivors. J Clin Oncol. 2017; 35(31):3582–3590.

[33] Dunne EF, Park IU. HPV and HPV-associated diseases. Infect Dis Clin North Am. 2013;27(4):765–778.

[34] Cervical cancer screening. Finland: Finnish Cancer Registry; [cited 2022. April 26]. Available from: https://cancerregistry.fi/screening/cervical-cancer-screening/.