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Cancer risk and mortality after solid organ transplantation: A population-based 30-year cohort study in Finland

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Abstract

Cancer is a significant cause of morbidity and mortality after solid organ transplantation (SOT) and related to lifelong immunosuppression. This retrospective registry study assessed for the first time in Finland population-based cancer risk and cancer mortality after all SOTs (lung and childhood transplantations included) as standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs). Data from transplant registries were linked with the data of Finnish Cancer Registry and Statistics Finland. We followed 6548 consecutive first SOT recipients from 1 January 1987 to 31 December 2016 translating to 66 741 person-years (median follow-up time 8.9 years [interquartile range 4.0-15.1]). In total, 2096 cancers were found in 1483 patients (23% of all patients). Majority of cancers (53%) were nonmelanoma skin cancers (NMSCs). The overall SIR was 3.6 (95% confidence interval [CI]: 3.5-3.8) and the SIR excluding NMSCs was 2.2 (95% CI: 2.0-2.3). SIR for all cancers was highest for heart (5.0) and lowest for liver (2.7) recipients. Most common cancer types after NMSCs were non-Hodgkin lymphoma (NHL), SIR 9.9 (95% CI: 8.5-11.4) and kidney cancer, SIR 7.3 (95% CI: 6.0-8.8). Cancer-related deaths were 17% (n = 408) of all deaths after first month post transplantation. SMR for all cancers was 2.5 (95% CI: 2.2-2.7) and for NHL 13.6 (95% CI: 10.7-16.8). Notably, overall SIR for cancer was

Abbreviations: CI, confidence interval; IQR, interquartile range; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancers* (*NMSC includes both skin squamous cell carcinoma and basal cell carcinoma); SCC, squamous cell carcinoma; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SOT, solid organ transplantation.

lower in later period (2000-2016), 3.0 (95% CI: 2.8-3.2), than in earlier period (1987-1999), 4.3 (95% CI: 4.0-4.5), $P < .001$. Decrease in cancer incidence was temporally associated with major changes in immunosuppression in the 2000s.

KEYWORDS
cancer risk, mortality, population-based, solid organ transplantation, standardized incidence ratio

What's new?

For solid organ transplant patients, the requirement for life-long immunosuppression is associated with increased cancer risk and cancer mortality. Specifically in Finland, however, studies on cancer incidence after transplantation have been limited. Here, retrospective analyses of patients in Finland reveal an increased risk of cancer and increased cancer mortality after all solid organ transplantations. Nonmelanoma skin cancers accounted for the majority of malignancies among solid organ transplant patients, followed by non-Hodgkin lymphoma and kidney cancer. Cancer mortality was increased 2.5-fold among transplant patients, compared to the general population. Excess cancer risk was lower for more recent transplant recipients (2000-2016).

1 | INTRODUCTION

Cancer is one of the most serious long-term complications after a solid organ transplantation (SOT). Risk of cancer is two to four times higher after SOT in comparison to general population,[1-6] and most elevated after thoracic organ and small intestine transplantation.[7-10] Lymphomas account for up to 21% of all cancers after SOTs, compared to 4% to 5% in the general population.[11,12]

Immunosuppressive therapy after transplantation reduces transplant recipients' ability to control virus infections, thus exposing the recipients to increased risk of infection-associated cancers (especially non-Hodgkin lymphoma [NHL], liver cancer and Kaposi´s sarcoma).[13] Also, the risk of some noninfection associated cancers like kidney and thyroid cancer is elevated.[14] In addition, some immunosuppressive medications such as calcineurin inhibitors and azathioprine promote carcinogenesis by mechanisms independent of their immunosuppressive effects.[15,16] In contrast, newer agents such as mycophenolate mofetil and mammalian target of rapamycin (mTOR) inhibitors may have even antitumor properties.[16,17] Less intensive immunosuppression and lower cumulative dosage is supposed to decrease cancer risk after transplantation.[18] Major changes in immunosuppression protocols has been made in the 2000s.[19]

Helsinki University Hospital is the only SOT center in Finland. The first kidney transplantation was performed in 1964 and by the end of 2019, altogether 10 540 SOTs have been performed. Currently, over 400 SOTs are performed yearly (over 250 kidneys, 60 livers, 50-60 thoracic organs and 30 pancreases). Finland is a member of the Nordic organ exchange organization, Scandiatransplant (http://www.scandiatransplant.org/).

Studies on cancer incidence after SOT in Finland have been restricted to specific organ transplantations[5,6,10,20-23] and no reports exist on lung and pancreas transplantations or including all SOTs combined. There are only scarce publications available on cancer mortality after transplantation in a population-based manner from high quality registries.[24-26] For multiple cancer types, SOT recipients appear to have elevated risk of cancer mortality, even after adjustment for stage and treatment.[27]

Our aim was to quantify cancer risk and mortality for the first time after all SOTs (childhood transplantations included) in Finland over a 30-year period. Furthermore, we wanted to evaluate whether there are changes in the cancer risks between different SOTs or between two transplantation periods (1987-1999 and 2000-2016) possibly reflecting changes in immunosuppression protocols in the 2000s.[19]

2 | MATERIALS AND METHODS

2.1 | Study cohort and data acquisition

The data were collected by combining Helsinki University Hospital's records of SOTs, Finnish Cancer Registry (cancer data) and Statistics Finland (dates and causes of deaths).[28] Finland has a compulsory and comprehensive cancer registry and reporting is obligatory for both clinicians and pathology laboratories.[29] The completeness of cancer data has been estimated to be 96% for solid tumors and 86% for nonsolid tumors (such as hematological malignancies which are not typically histologically verified). In our cancer data, 98% of all cancer cases were histologically verified. Finnish cancer registry also records basal cell carcinoma (since 1964) though it is not included in official statistics.[30,31] All SOTs in Finland are recorded in the Nordic transplantation registry, Scandiatransplant.

Altogether 7497 SOTs had been performed on 6778 patients during the study period of 30 years between 1 January 1987 and 31 December 2016, at the Helsinki University Hospital. Of these, the patients with first SOT (n = 6548), both adults and children (n = 443,

TABLE 1 Characteristics of the study cohort

Transplanted organ	Kidney	Liver	Heart	Lung	Pancreas-kidney	Total	Tx 1987-1999	Tx 2000-2016
Number (N) of patients (% of total)	4514 (69%)	1078 (16%)	599 (9%)	280 (4%)	77 (1%)	6548 (100%)	2374 (36.3%)	4174 (63.7%)
Females, N (%)	1644 (36%)	552 (51%)	147 (25%)	117 (42%)	23 (30%)	2483 (38%)	913 (38.5%)	1570 (37.6%)
Males, N (%)	2870 (64%)	526 (49%)	452 (75%)	163 (58%)	54 (70%)	4065 (62%)	1461 (61.5%)	2604 (62.4%)
Alive at day +30 post Tx, N (% of total)	4492 (70%)	1048 (16%)	532 (8%)	259 (4%)	77 (1%)	6408 (97.9%)	2291 (35.0%)	4117 (62.9%)
Alive at day +30 post Tx, % of original	99.5%	97.2%	88.8%	92.5%	100%	97.9%	96.5%	98.6%
Alive at 1 year post Tx, % of original	97%	91%	83%	82%	97%	94%	91.1%	95.8%
Number at risk at 10 years	2193	465	265	47	0	2970	1597	1373
Age at transplantation, N (%)								
<20	294 (7%)	143 (13%)	86 (14%)	11 (4%)	1 (1%)	535 (8%)	219 (9.2%)	315 (7.5%)
20-40	1054 (23%)	176 (16%)	90 (15%)	50 (18%)	34 (44%)	1404 (21%)	679 (28.6%)	725 (17.4%)
40-60	2152 (48%)	548 (51%)	325 (54%)	145 (52%)	41 (53%)	3211 (49%)	1196 (50.4%)	2015 (48.3%)
>60	1014 (22%)	211 (20%)	98 (16%)	75 (27%)	1 (1%)	1399 (21%)	280 (11.8%)	1119 (26.8%)
Median age at Tx, years (IQR)	49.5 (37-59)	49.8 (36-58)	50.3 (37-57)	53.2 (43-61)	40.6 (35-50)	49.6 (37-59)	45.2 (34-54)	52.2 (40-61)
Follow-up time, median (range)	9.6 (0-30.9)	8.1 (0-30.9)	8.3 (0-29.6)	4.5 (0-25.8)	2.9 (0.4-7.8)	8.9 (0-30.9)	16.4 (0-30.9)	7.0 (0-18)
Person-years	48 823	10 355	5789	1546	228	66 741	35 181	31 560
Year of first transplantation, N (%)								
1987-1996	1315 (29%)	215 (20%)	234 (39%)	49 (18%)	0 (0%)	1813 (28%)		
1997-2006	1545 (34%)	361 (34%)	159 (27%)	66 (24%)	0 (0%)	2131 (33%)		
2007-2016	1654 (37%)	502 (47%)	206 (34%)	165 (59%)	77 (100%)	2604 (40%)		
Re-transplantation of the same organ, one or multiple, N (%)	347 (8%)	94 (9%)	10 (2%)	14 (5%)	0 (0%)	465 (7%)		
Pretransplant cancer, N (%)	172 (3.8%)	177[a] (16.4%)	21 (3.5%)	7 (2.5%)	0 (0%)	377 (5.8%)		
Tx period 1987-1999, N (% of total)	1737 (73.2%)	299 (12.6%)	279 (11.8%)	59 (2.5%)	0 (0%)	2374 (36.3%)		
Tx period 2000-2016, N (% of total)	2777 (66.5%)	779 (18.7%)	320 (7.7%)	221 (5.3%)	77 (1.8%)	4174 (63.7%)		

Abbreviations: IQR, interquartile range; Tx, transplantation.
[a]Cancer was indication for liver Tx in 111 recipients.

aged <16 years at transplantation), were included in our study. Only small intestine (n = 8) and facial tissue transplantations (n = 2) were excluded due to their very limited numbers. Patient follow-up continued despite a possible retransplantation. Figure S1 demonstrates the formation of the study cohort. Altogether 154 patients had received two organs (half of them kidney and pancreas) concurrently or successively, but each patient was recorded only once, and duplicates were removed from subgroups.

History of a pretransplant cancer (nonmelanoma skin cancers [NMSCs] excluded) was present in 5.8% of the SOT recipients (n = 377; Table 1). Primary liver malignancy was diagnosed in 142 liver recipients, and in 111 cases it was the indication for liver transplantation. Malignant neoplasms of kidney had been diagnosed in 39 kidney recipients, but none was an indication for transplantation. Unexpectedly, two adeno and two squamous cell carcinomas were found from the explanted lungs after lung transplantation.

The median length of follow-up for all recipients was 8.9 years (interquartile range [IQR] 4.0-15.1; Table 1). Five years of follow-up was reached in 71% and 10 years in 46% of all recipients. A total of 66 741 person-years were recorded from 6548 patients (38% females). Most of the patients had received a kidney transplant (69%). Patients' median age at transplantation was 49.6 years (IQR 37-59). Table 1 shows the patient characteristics and Table S1 indications for transplantation.

As immunosuppression protocols have changed, we compared earlier transplantation period (1987-1999) with 2374 SOT recipients (35 181 person-years) to later transplantation period (2000-2016) with 4174 SOT recipients (31 560 person-years). The gender distribution and proportion of thoracic organ transplantations did not differ between these two periods (Table 1).

2.2 | Data linkage

The SOT cohort data were linked with the data from the Statistics Finland's National Registry of dates and causes of death, and the cancer data from the national Finnish Cancer Registry until the end of 2017. Finnish Cancer Registry's (since year 1953) data include date and age at diagnosis, cancer stage, ICD-O-3 topography, morphology and behavior and basis of diagnosis. Data were collected on both pretransplant and posttransplant cancers. Official personal identity codes, given to every Finnish resident and used in all official registries, allow reliable deterministic record linkage between different registries. As a result, patients' data recording was nearly complete as follow-up data were available on 99.8% of the cohort. Only 11 patients had emigrated or were lost to follow-up.

All recipients were analyzed both in a pooled cohort and in an organ specific group according to the first transplanted organ (Figure S1). Pancreas-kidney-transplantations (n = 77) were analyzed as a separate group. Lung-heart block transplantations (n = 38) were included in the lung group, heart-kidney (n = 4) in the heart group and liver-kidney-transplantations (n = 41) in the liver group (according to the organ determining the immunosuppression).

2.3 | Statistical analysis

Standardized incidence ratios (SIR) and standardized mortality ratios (SMR) for all cancers and for different cancer types were calculated to compare the cancer incidence and mortality with general Finnish population. The expected numbers of cancer cases and cancer deaths in the cohort were calculated by multiplying the number of person-years at risk by the corresponding cancer rate and cancer death rate in the year-matched, gender-matched and age-matched Finnish population. The SIRs and SMRs were calculated by dividing the observed number of cases by the expected number of cases. The 95% confidence intervals (CI) for the SIRs and SMRs were based on the assumption that the number of observed cases follows a Poisson distribution.

Posttransplant cancer follow-up time started 30 days after first SOT to exclude delayed reporting of preexisting cancers (mostly in the explanted organ), and ended at the patient's death, emigration or on 31 December, 2017, whichever came first. Kaplan-Meier method was used to estimate patient survival during the follow-up time in comparison of the two transplantation periods. The log rank test was used for comparisons and a *P*-value less than .05 was considered statistically significant. Overall survival rate was calculated by comparing the number of patients alive with the number of patients at risk. Spline plot function was used to generate spline models for analyzing changes in SIRs during the follow-up and for comparing the SIRs in earlier (1987-1999) and later (2000-2016) transplantation period. Follow-up time dependent splines were used to prevent the risk of bias concerning possible variable follow-up times at time points.

Competing risk analysis was used when the cumulative cancer risk was analyzed, as SOT recipients have an elevated risk of dying of other complications (eg, organ failure, cardiovascular diseases and infections). It was made by R survival package (a Package for Survival Analysis in R), using survfit function with mstate option (R package version 3.1-12, https://CRAN.R-project.org/package=survival).[32] R (https://www.R-project.org/) was used also for spline plot functions and SPSS statistical software version 25.0 (SPSS, Inc., Chicago, Illinois) for all other statistical analysis.

3 | RESULTS

Patients' overall survival rate in the study was high: 30-day survival was 98% and 1-year survival 94%, varying between the SOT groups (kidney and pancreas-kidney 97%, liver 91%, heart 83% and lung 82%). Long term survival rates for all patients were 86%, 71%, 55% and 43% at 5, 10, 15 and 20 years, respectively. Median survival after transplantation was 18.1 years (95% CI: 17.4-18.8).

Overall survival was better in the later transplantation period (from 2000 to 2016) than in the earlier period (from 1987 to 1999): 1-year survival rates post transplantation were 95.8% and 91.1% and 5-year 87.5% and 84.7% ($P < .001$), respectively. Difference between the two periods remained the same during follow-up time (Figure S2).

TABLE 2 Cancer incidence after all SOTs compared to general Finnish population

Cancer site (ICD-10 codes)	All OBS	All EXP	All SIR (95% CI)	Kidney OBS	Kidney SIR (95% CI)	Liver OBS	Liver SIR (95% CI)	Heart OBS	Heart SIR (95% CI)	Lung OBS	Lung SIR (95% CI)
All cancers	2096	578.1	**3.6 (3.5-3.8)**[a]	1519	**3.6 (3.4-3.8)**[a]	246	**2.7 (2.4-3.1)**[a]	277	**5.0 (4.4-5.6)**[a]	54	**4.0 (3.0-5.3)**[a]
All except basalioma and skin SCC	995	458.1	**2.2 (2.0-2.3)**[a]	690	**2.1 (1.9-2.2)**[a]	138	**2.0 (1.6-2.3)**[a]	139	**3.1 (2.6-3.7)**[a]	28	**2.6 (1.7-3.8)**[a]
Mouth, pharynx (C00-14)	61	10.4	**5.9 (4.5-7.6)**[a]	36	**4.8 (3.3-6.6)**[a]	10	**6.7 (3.2-12.4)**[a]	14	**12.9 (7.1-21.6)**[a]	1	3.8 (0.1-21.1)
Stomach (C16)	16	10.7	1.5 (0.9-2.4)	11	1.4 (0.7-2.5)	3	2.0 (0.4-5.9)	2	1.7 (0.2-6.2)	0	0.0 (0.0-16.9)
Liver (C22-24)	21	10.6	**2.0 (1.2-3.0)**[a]	16	**2.1 (1.2-3.4)**[a]	4	2.6 (0.7-6.5)	1	0.9 (0.2-6.2)	0	0.0 (0.0-15.7)
Pancreas (C25)	34	15.9	**2.1 (1.5-3.0)**[a]	21	**1.8 (1.1-2.8)**[a]	10	**4.0 (1.9-7.4)**[a]	2	1.3 (0.2-4.5)	1	2.9 (0.1-16.0)
Colon and rectum (C18-20)	63	42.7	**1.5 (1.1-1.9)**[a]	45	**1.5 (1.1-1.9)**[a]	12	**1.9 (1.0-3.2)**[a]	6	1.4 (0.5-3.1)	0	0.0 (0.0-3.9)
Digestive organs, other (C15, C17, C21, C26)	16	9.1	**1.8 (1.0-2.9)**[a]	13	**2.0 (1.1-3.3)**[a]	1	0.8 (0.0-4.2)	2	2.1 (0.3-7.6)	0	0.0 (0.0-16.0)
Lung, trachea (C33-34)	92	45.3	**2.0 (1.6-2.5)**[a]	64	**1.9 (1.5-2.5)**[a]	9	1.5 (0.7-2.8)	16	**3.0 (1.7-4.9)**[a]	3	3.1 (0.6-9.0)
Mesothelioma (C45)	4	1.8	2.2 (0.6-5.6)	3	2.3 (0.5-6.6)	0	0.0 (0.0-16.1)	1	4.4 (0.1-24.6)	0	0.0 (0.0-92.4)
Other respiratory or intrathoracic organs (C30-32, C37-39)	4	4	1.0 (0.3-2.6)	2	0.7 (0.1-2.5)	1	2.0 (0.1-11.0)	1	2.1 (0.1-11.6)	0	0.0 (0.0-39.8)
Breast (C50)	50	62	0.8 (0.6-1.1)	38	0.9 (0.6-1.2)	10	0.7 (0.3-1.3)	1	0.4 (0.0-2.3)	1	0.6 (0.0-3.3)
Female genital organs (C51-56)	28	21	1.3 (0.9-1.9)	24	**1.6 (1.0-2.4)**[a]	4	0.8 (0.2-2.1)	0	0.0 (0.0-4.5)	0	0.0 (0.0-7.7)
Prostate (C61)	97	96.3	1.0 (0.8-1.2)	71	1.0 (0.8-1.3)	8	0.7 (0.3-1.5)	18	1.4 (0.8-2.3)	0	0.0 (0.0-1.7)
Male genital, other and unspecified (C60, C62)	7	2.2	**3.2 (1.3-6.6)**[a]	5	**3.0 (1.0-7.0)**[a]	1	4.1 (0.1-22.6)	1	4.5 (0.1-24.9)	0	0.0 (0.0-73.5)
Kidney (C64)	110	15	**7.3 (6.0-8.8)**[a]	90	**8.2 (6.6-10.1)**[a]	7	**3.2 (1.3-6.6)**[a]	11	**7.0 (3.5-12.6)**[a]	2	**5.8 (0.7-20.9)**[a]
Bladder and urinary tract (C65-68)	32	18.4	**1.7 (1.2-2.5)**[a]	23	**1.7 (1.1-2.5)**[a]	3	1.3 (0.3-3.8)	5	2.3 (0.7-5.4)	1	2.6 (0.1-14.3)
Brain, meninges and central nervous system (C70-71)	12	14.6	0.8 (0.4-1.4)	9	0.8 (0.4-1.6)	2	0.8 (0.1-3.0)	1	0.8 (0.0-4.6)	0	0.0 (0.0-10.5)
Soft tissues (C48-49)	3	3	1.0 (0.2-2.9)	2	0.9 (0.1-3.3)	1	2.0 (0.1-11.4)	0	0.0 (0.0-13.5)	0	0.0 (0.0-52.4)
Ill-defined or unknown (C76, C80)	14	7.1	**2.0 (1.1-3.3)**[a]	10	**1.9 (0.9-3.5)**[a]	1	0.9 (0.0-5.2)	2	2.8 (0.3-10.1)	1	7.2 (0.2-39.8)
Endocrine glands (C73, C75)	15	6.7	**2.2 (1.2-3.7)**[a]	15	**3.1 (1.7-5.1)**[a]	0	0.0 (0.0-3.1)	0	0.0 (0.0-8.0)	0	0.0 (0.0-19.7)
Lymphoproliferative, hematological											
Non-Hodgkin lymphomas (C82-85, C88)	185	18.7	**9.9 (8.5-11.4)**[a]	98	**7.2 (5.9-8.8)**[a]	32	**11.1 (7.6-15.7)**[a]	42	**23.3 (16.8-31.5)**[a]	13	**29.0 (15.4-49.6)**[a]
Hodgkin lymphoma (C81)	5	1.9	**2.7 (0.9-6.2)**[a]	2	1.5 (0.2-5.2)	1	3.7 (0.1-20.4)	2	**10.8 (1.3-39.1)**[a]	0	0.0 (0.0-81.9)
Myeloma and other plasma cell tumors (C90)	17	5.7	**3.0 (1.7-4.8)**[a]	14	**3.4 (1.8-5.7)**[a]	2	2.3 (0.3-8.3)	0	0.0 (0.0-6.5)	1	8.2 (0.2-45.8)
Leukemia (C91-92, C95)	8	8.8	0.9 (0.4-1.8)	6	0.9 (0.3-2.0)	1	0.8 (0.0-4.3)	1	1.1 (0.0-6.3)	0	0.0 (0.0-19.8)
Myeloproliferative neoplasms (D45, D47)	10	4	**2.5 (1.2-4.6)**[a]	6	2.1 (0.8-4.5)	3	**4.7 (1.0-13.7)**[a]	0	0.0 (0.0-10.1)	1	10.3 (0.3-57.4)
Other hematological disease (C96, D46)	7	1.5	**4.7 (1.9-9.6)**[a]	4	**3.6 (1.0-9.3)**[a]	2	**8.9 (1.1-32.2)**[a]	1	6.9 (0.2-38.7)	0	0.0 (0.0-121.7)

(Continues)

TABLE 2 (Continued)

Cancer site (ICD-10 codes)	All OBS	All EXP	All SIR (95% CI)	Kidney OBS	Kidney SIR (95% CI)	Liver OBS	Liver SIR (95% CI)	Heart OBS	Heart SIR (95% CI)	Lung OBS	Lung SIR (95% CI)
Skin											
Melanoma (C43)	54	19.1	**2.8 (2.1-3.7)**[a]	40	**2.9 (2.1-3.9)**[a]	4	1.4 (0.4-3.5)	7	**3.9 (1.6-8.1)**[a]	3	**5.9 (1.2-17.4)**[a]
Basal cell carcinoma (C44)	700	106.9	**6.5 (6.1-7.1)**[a]	531	**6.8 (6.3-7.5)**[a]	70	**4.1 (3.2-5.2)**[a]	85	**8.5 (6.8-10.5)**[a]	14	**6.0 (3.3-10.0)**[a]
Squamous cell carcinoma, SCC (C44)	401	13.1	**30.7 (27.8-33.9)**[a]	298	**30.9 (27.5-34.7)**[a]	38	**20.2 (14.3-27.7)**[a]	53	**40.3 (30.2-52.7)**[a]	12	**52.5 (27.1-91.8)**[a]
Skin, other (C44)	15	1.1	**13.5 (7.6-22.3)**[a]	11	**13.5 (6.8-24.2)**[a]	3	**17.7 (3.7-51.8)**[a]	1	9.7 (0.2-54.1)	0	0.0 (0.0-147.0)
Merkel (C44)	8	0.2	**40.1 (17.3-79.0)**[a]	8	**55.5 (24.0-109.4)**[a]	0	0.0 (0.0-109.4)	0	0.0 (0.0-203.2)	0	0.0 (0.0-1046.2)
Kaposi's sarcoma (C44)	7	0.1	**52.5 (21.2-108.2)**[a]	3	**29.3 (6.0-85.6)**[a]	3	**210.1 (43.3-614.0)**[a]	1	**68.8 (1.7-383.4)**[a]	0	0.0 (0.0-1806.2)

Note: Standardized incidence ratios (SIRs) shown in all and in different organ transplantation groups.
Abbreviations: CI, confidence interval; EXP, expected number; ICD-10, International Classification of Diseases, Revision 10; OBS, observed number; SIR, standardized incidence ratio.
[a]Bold numbers indicate *P*-value <.05.

3.1 | Cancer risk after solid organ transplantation

In all, 2096 cancers occurred in 1483 patients (23%). Skin cancers were most frequent, as NMSCs constructed 53% (n = 1101) of all cancer cases. Other cancers (NMSC excluded) were found in 14% of the patients (995 cancers in 904 patients). SIR for overall cancer was 3.6 (95% CI: 3.5-3.8) and 2.2 (95% CI: 2.0-2.3) without NMSC. Up to 59% of cancers (NMSC excluded) and 57% of NMSCs occurred during the first 10 years after transplantation.

SIRs for skin squamous cell carcinoma (SCC) were 30.7 (95% CI: 27.8-33.9, 401 cases in 345 patients) and for basal cell carcinoma 6.5 (95% CI: 6.1-7.1, 700 cases in 613 patients). Solely NMSCs were diagnosed in 579 patients (9%). In addition, very high SIRs were observed for two rare skin cancers: 40.1 (95% CI: 17.3-79.0) for Merkel cell carcinoma (8 cases) and 52.5 (95% CI: 21.1-108.2) for Kaposi's sarcoma (7 cases; Table 2).

After skin cancers, risk was most elevated for NHL, SIR 9.9 (95% CI: 8.5-11.4), kidney cancer and mouth and pharynx cancers (Table 2). After childhood transplantations 33 cancers were found in 31 (7%, 31/443) SOT recipients, and 67% of these cases were lymphomas.

Males had higher overall cancer risk than females as SIRs were 4.0 (95% CI: 3.8-4.2) and 2.9 (95% CI: 2.7-3.1), respectively. Males had higher risk than females especially for certain cancer types: skin SCC (SIR 33.8 [95% CI: 30.1-37.7] vs 23.2 [95% CI: 18.6-28.6]), NHL (SIR 11.0 [95% CI: 9.2-13.0] vs 7.7 [95% CI: 5.7-10.2]) and kidney cancer (SIR 8.2 [95% CI: 6.6-10.1] vs 5.0 [95% CI: 3.1-7.6]).

Figure 1 demonstrates how the SIRs changed during the follow-up (for all cancers (A) and for cancers without NMSCs (B)). The overall risk of cancer, NMSCs excluded, was at highest during the first year and again increased by 10 years. During the first-year, cancers (n = 115) consisted of 41 NMSCs (36%), 25 lymphomas (22%) and other cancers, mainly lung (5%), colon (4%), kidney (4%), breast (4%) and prostate (3%) cancers. SIR for NHL was highest during the first year after transplantation, and then from 5 years on slowly increased without a peak by 10 years.

The cumulative cancer risks (NMSCs excluded) were 5.2% (95% CI: 4.7-5.8), 10.8% (95% CI: 10.0-11.7), 16.3% (95% CI: 15.2-17.4) and 20.5% (95% CI: 19.2-21.9) at 5, 10, 15 and 20 years after transplantation, respectively. Competing risk analysis shows the risk of death as a competing risk (Figure 2). Differences were found between SOT subgroups and the competing risk of death was highest in lung recipients (Figure S3). In heart recipients the risk of cancer was more prominent compared to kidney and liver recipients.

3.2 | Cancer risk after different solid organ transplantations

SIR for all cancers was highest for heart recipients, 5.0 (95% CI: 4.4-5.6), and lowest for liver recipients, 2.7 (95% CI: 2.4-3.1), and the result remained similar without NMSCs: 3.1 (95% CI: 2.7-3.7) and 2.0 (95% CI: 1.6-2.3), respectively (Table 2). No cancers were found in pancreas-kidney transplant patients (median follow-up 2.9 years).

The risk for NHL was highest among thoracic organ recipients: SIR 29.0 (95% CI: 15.4-49.6) for lung and 23.3 (95% CI: 16.8-31.5) for heart recipients, whereas it was 7.2 (95% CI: 5.9-8.8) for kidney and 11.1 (95% CI: 7.6-15.7) for liver recipients (Table 2). Risk for kidney cancer was 7-fold in the whole cohort (95% CI: 6.0-8.8), mainly driven by the kidney recipients (82% of cases) with SIR of 8.2 (95% CI: 6.6-10.1). In general, the risk for mouth and pharynx cancers was nearly 6-fold (95% CI: 4.5-7.6) with the highest SIR of 12.9 (95% CI: 7.1-21.6) among the heart recipients. The risk for skin SCC was most profound among lung (SIR 52.5, 95% CI: 27.1-91.8) and heart recipients (SIR 40.3, 95% CI: 30.1-52.7).

3.3 | Cancer risk by transplantation period

Cancer incidence after SOTs compared to general population was lower in later transplantation period from 2000 to 2016 (4174 patients, 31 560 person-years) compared to the earlier period from 1987 to 1999 (2374 patients, 35 181 person-years) as SIR for overall cancer had decreased from 4.3 (95% CI: 4.0-4.5) to 3.0 (95% CI: 2.8-3.2; Table S2). SIRs for cancers without NMSCs had also decreased over time, 2.4 (95% CI: 2.2-2.7) and 1.9 (95% CI: 1.7-2.1). Additionally, SIR for NHL was lower in the later period: 11.3 (95% CI: 9.2-13.7) vs 8.6 (95% CI: 6.8-10.6), respectively. Also, mouth and pharynx site cancers had become less frequent, especially lip cancers, as SIR in the earlier period was 9.4 (95% CI 6.9-12.5) whereas in the later period it was only 2.7 (95% CI: 1.5-4.5). The risk of skin SCC was significantly lower in the later period (SIR 19.9 [95% CI: 16.6-23.5]) than in the earlier period (SIR 42.3 [95% CI: 37.4-47.7]). Risk for female genital organ cancer had also decreased over time as SIRs were 2.1 (95% CI: 1.3-3.1) vs 0.5 (95% CI: 0.2-1.2).

Figure 3 shows the cancer incidences compared to general population (SIR) in the two transplantation periods, among all SOT recipients (A) and separately in kidney (B), liver (C) and thoracic organ recipients (heart and lung transplantations combined) (D). The decreasing of SIRs was most evident among thoracic organ (SIRs being at 5 and 10 years: 5.8 and 7.2 in earlier and 2.8 and 2.7 in later period) and kidney recipients (SIRs being at 5 and 10 years: 4.3 and 5.0 in earlier and 3.0 and 3.2 in later period). No difference between the two periods was seen among liver recipients.

3.4 | Lymphoproliferative and hematological malignancies

Lymphomas and plasma cell neoplasms and nonmalignant EBV-associated early lymphoproliferative and polymorphic lesions constitute posttransplantation lymphoproliferative disorders (PTLD).[33] PTLD class malignancies were the vast majority of non-NMSC cancers in this cohort, accounting for 207 cancer cases in 204 patients (23% of all cancer patients); 185 NHLs (SIR 9.9 [95% CI: 8.5-11.4]), 5 Hodgkin lymphomas (SIR 2.7 [95% CI: 0.9-6.2]) and 17 myelomas or other plasma cell tumors (SIR 3.0 [95% CI: 1.7-4.8]). Of all PTLD-patients, 22 patients (10.8%) had received transplantation in childhood. Only two recipients after childhood transplantations got malignant PTLD during the first year after transplantation. Median age at transplantation was lower in PTLD patients compared to other posttransplant cancer patients, 48.3 (IQR 35.7-56.8) and 54.2 (IQR 45.6-60.7), respectively. Risk of myeloproliferative malignancies was moderately elevated (SIR 2.5 [95% CI: 1.2-4.6]), but risk of leukemia did not differ from general population.

3.5 | Cancer mortality

Cancer was classified as the official cause of death in 408 SOT recipients (73% males), constituting 17% of all deaths (n = 2347) after 30 days posttransplantation. Of all cancer deaths, 59% (n = 242) occurred in less than 1 year after the cancer diagnosis. Cancer mortality rate was 611 per 100 000 person-years in all recipients (516 in kidney, 840 in liver, 1019 in heart and 647 in lung recipients). NHL was

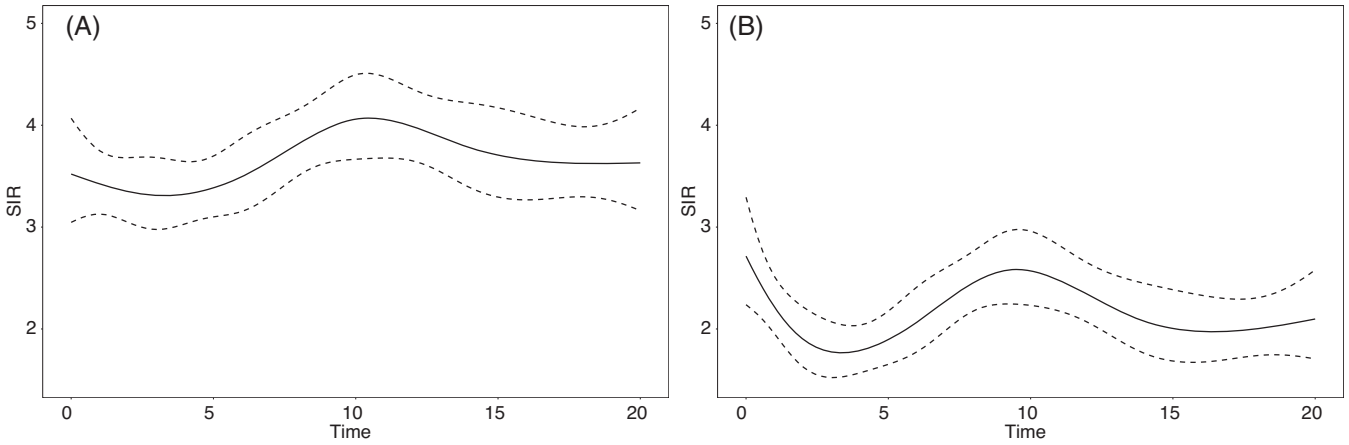

FIGURE 1 Cancer incidence after solid organ transplantation (SOT) compared to general population. Spline plots of standardized incidence ratios (SIRs) for all cancers: (A) shows a peak of SIR by 10 years after SOT and for cancers without nonmelanoma skin cancers (NMSC); (B) shows peaks of SIR in the beginning and again from 7 to 12 years after SOT, with 95% confidence interval (CI) as a function of follow-up time (years)

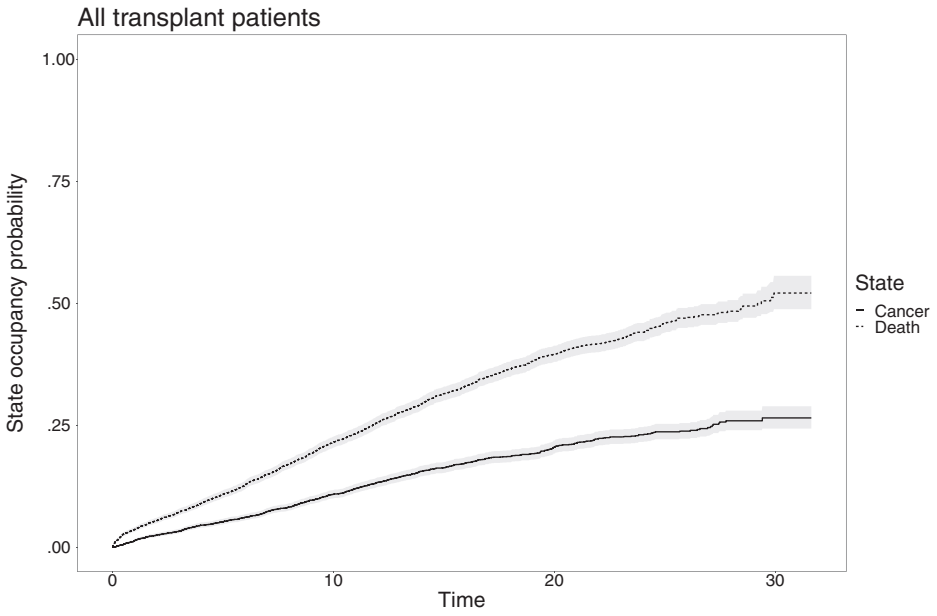

FIGURE 2 Competing risk analysis of cumulative cancer risk (all first cancers, nonmelanoma skin cancers excluded) and death as a competing risk in all solid organ transplant recipients. Solid line shows the cumulative cancer risk and dotted line shows the risk of dying (without diagnosed a posttransplant cancer). The 95% confidence interval (CI) is presented in homogenous gray color

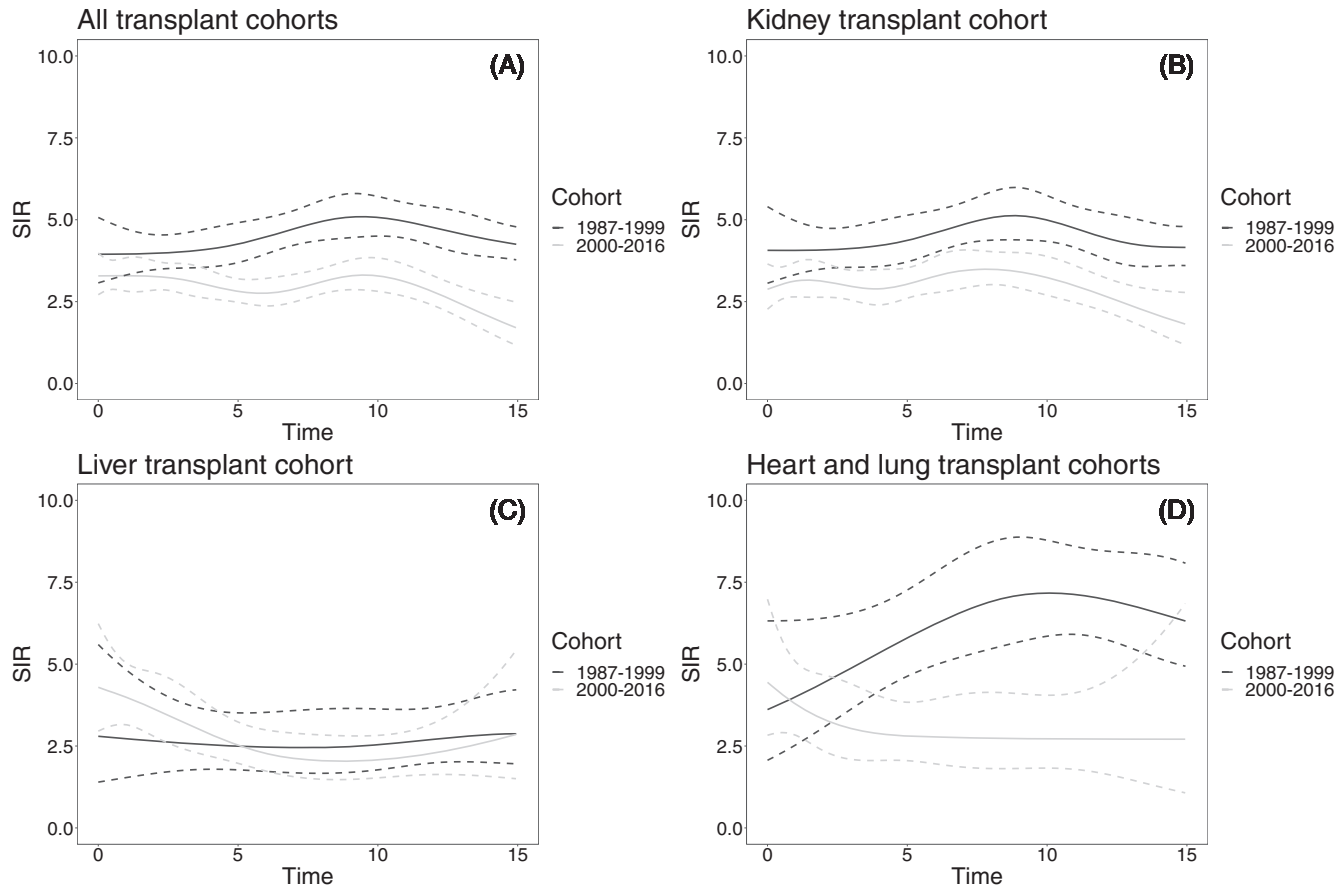

FIGURE 3 Standardized incidence ratio (SIR) for all cancers in two transplantation periods (1987-1999 and 2000-2016) in all solid organ transplantations (SOTs) (A) and in kidney (B), liver (C) and thoracic organ (heart and lung combined) (D) recipients as a function of follow-up time. The splines (with 95% confidence intervals [CIs]) show mainly lower SIRs in the later period compared to the earlier one

the most frequent cause of death due to cancer (20%), followed by lung and trachea cancers (17%) and liver cancers (12%). Half of the patients (n = 742) with a de novo posttransplant cancer (n = 1483, all cancer patients NMSC included) died during the study period and 48% of the deaths were related to the de novo cancer. One-year survival rate after cancer diagnosis (NMSC excluded) was 65%.

SMR for all cancers was 2.5 (95% CI: 2.2-2.7), and it was higher in males (2.7; 95% CI: 2.4-3.0) than in females (2.1; 95% CI: 1.7-2.5). SMRs were highest for Merkel cell carcinoma 65.5 (95% CI: 13.5-191.4, $P < .05$) and skin SCC 34.5 (95% CI: 14.9-68.0). Altogether 14 patients died of NMSCs, SCC (8 patients), Merkel cell carcinoma (3 patients) and other (3 patients). The highest SMR, after skin

TABLE 3 Cancer mortality of solid organ transplantation (SOT) recipients compared to general Finnish population as standardized mortality ratio (SMR)

Cancer type (ICD-10 codes)	Observed	Expected	SMR	SMR.lo	SMR.hi	*P*-value	OBS kidney	OBS liver	OBS heart	OBS lung
All cancer deaths	408	162.0	**2.5**	2.3	2.8	<.001	252	87	59	10
All except basalioma and skin SCC	400	161.7	**2.5**	2.2	2.7	<.001	239	87	58	10
Mouth, pharynx (C00-14)	8	3.2	**2.5**	1.1	5.0	<.05	5	1	2	0
Stomach (C16)	10	7.5	1.3	0.6	2.5	.354	7	1	2	0
Liver[a] (C22-24)	51	8.3	**6.1**	4.6	8.1	<.001	12	38	1	0
Pancreas (C25)	31	14.2	**2.2**	1.5	3.1	<.001	19	10	1	1
Colon and rectum (C18-20)	24	14.9	**1.6**	1.0	2.4	<.05	18	4	2	0
Digestive organs, other (C15, C17, C20, C26)	11	6.0	1.8	0.9	3.3	.059	9	1	1	0
Lung, trachea (C33-34)	69	36.5	**1.9**	1.5	2.4	<.001	51	5	11	2
Mesothelioma (C45)	4	1.6	2.5	0.7	6.3	.083	3	0	1	0
Other respiratory or intrathoracic organs (C30-32, C37-39)	2	1.5	1.4	0.2	4.9	.662	0	1	1	0
Breast (C50)	4	9.9	0.4	0.1	1.0	.076	4	0	0	0
Female genital organs (C51-56)	11	6.8	1.6	0.8	2.9	.121	9	2	0	0
Prostate (C61)	16	10.5	1.5	0.9	2.5	.088	7	2	7	0
Male genital, other and unspecified (C60, C62)	0	0.3	0.0	0.0	14.5	1	0	0	0	0
Kidney (C64)	25	5.2	**4.8**	3.1	7.1	<.001	18	3	3	1
Bladder and urinary tract (C65-68)	8	3.4	**2.3**	1.0	4.6	<.05	6	0	1	1
Brain, meninges and central nervous system (C70-71)	2	6.1	0.3	0.0	1.2	.104	2	0	0	0
Soft tissues (C48-49)	0	1.3	0.0	0.0	2.8	.647	0	0	0	0
Illdefined or unknown (C76, C80)	11	5.4	**2.0**	1.0	3.6	<.05	7	1	2	1
Endocrine glands (C73, C75)	2	0.8	2.5	0.3	9.1	.188	2	0	0	0
Non-Hodgkin lymphoma (C82-85, C88)	82	6.0	**13.6**	10.8	16.8	<.001	44	13	22	3
Hodgkin lymphoma (C81)	0	0.4	0.0	0.0	10.1	1	0	0	0	0
Myeloma and other plasma cell tumors (C90)	5	3.3	1.5	0.5	3.6	.268	4	1	0	0
Leukemia (C91-92, C95)	4	4.1	1.0	0.3	2.5	1	3	1	0	0
Myeloproliferative neoplasms (D45, D47)	2	0.8	2.6	0.3	9.3	.184	1	1	0	0
Other hematological disease (C96, D46)	4	0.6	**6.3**	1.7	16.1	<.05	2	1	1	0
Melanoma of the skin (C43)	8	3.1	**2.6**	1.1	5.0	<.05	6	1	0	1
Basal cell carcinoma of the skin (C44)	0	0.0	0.0	0.0	184.1	1	0	0	0	0
Skin, squamous cell carcinoma (C44)	8	0.2	**34.5**	14.9	68.0	<.001	7	0	1	0
Skin, other (C44)	3	0.1	**42.7**	8.8	124.8	<.001	3	0	0	0
Merkel (C44)	3	0.0	**65.5**	13.5	191.4	<.001	3	0	0	0
Kaposi's sarcoma (C44)	0	0.0	0.0	0.0	860.5	1	0	0	0	0

Note: Bold text and numbers indicates results that are statistically significant (*P*-value <.05).

Abbreviations: OBS, observed; SMR, standardized incidence ratio; SMR.lo, lower border of 95% confidence interval; SMR.hi, higher border of 95% confidence interval.

[a]Thirty-four of liver cancer deaths were related to a pretransplant cancer in liver recipients.

cancers, was 13.6 (95% CI: 10.8-16.8) for NHL being 16.8 (95% CI: 13.1-21.2) in males and 6.4 (95% CI: 3.3-11.2) in females. SMR for liver cancers was 6.1 (75% of deaths among liver recipients) and for kidney cancers 4.8 (72% of deaths among kidney recipients). SMR for lung cancers was 1.9 (95% CI: 1.5-2.4). Thirteen percent of cancer deaths (n = 50) were related to a pretransplant cancer, and majority of them were liver cancers (n = 34; Table 3).

Cancer mortality compared to general population was lower in the later transplantation period (SMR 2.2 [95% CI: 1.9-2.6]) compared to earlier period (SMR 2.9 [95% CI: 2.4-3.2]). Risk to die for NHL (SMR 15.9 vs 10.8) and for kidney cancer (SMR 6.5 vs 2.9) was lower in the later period, but differences were not statistically significant.

4 | DISCUSSION

In our comprehensive study of Finnish SOT recipients, we showed that cancer risk after SOT was 3.6-fold (2.2-fold NMSC excluded) and cancer mortality 2.5-fold compared to general population during long-term follow-up. Males were at higher risk than females (SIRs 4.0 vs 2.9 and SMRs 2.7 vs 2.2). As major changes in immunosuppressive protocols have been made in early 2000s and less intensive immunosuppression is associated to lower risk of developing malignancies, we compared two transplantation periods (from 1987 to 1999 and from 2000 to 2016).[18,19] We found that SIRs were lower in the later period, especially in thoracic organ and kidney recipients. Similar difference was not found among liver recipients. The competing risk analysis showed that cancer morbidity was most relevant in heart recipients throughout the follow-up whereas after lung transplantation patient survival was yet more limited as the risk to die from other causes than cancer was more prominent compared to other SOTs.

Similar cancer risks after all SOTs including childhood transplantations have been reported from the United States, Sweden and the United Kingdom (SIRs for all cancers NMSCs excluded 2.1, 2.4 and 2.3, respectively).[2,3,34] Furthermore, in a recent meta-analysis of 72 cohort studies SIR for all cancers was 2.68 (95% CI: 2.48-2.89).[14] In the Swedish study (transplantations from 1970 to 2008) the overall SIR including skin SCC was higher than in our study (kidney 6.5 vs 3.6, liver 3.4 vs 2.7 and thoracic organ 10 vs 5.0 for heart and 4.0 for lung), but without NMSCs, SIRs were nearly the same.[3] The most obvious difference compared to US population was the strikingly lower incidence of liver cancer in Finland (SIR 2.0 [95% CI: 1.2-3.0] vs 43.83 [95% CI: 40.90-46.91]). In the US cohort, the liver cancers occurred mainly in liver recipients within 6-months posttransplantation.[2] The difference is probably due to delayed diagnosis or reporting of liver cancer in the United States and to a lesser extent, remarkable lower incidence of hepatitis C in our cohort than in US cohort.[21]

There is paucity of parallel findings of decreasing cancer SIRs in other population studies. A recent Irish population-based study of adult SOTs reported a decreasing trend in SIR for overall cancer (NMSC excluded) after transplantations performed between 1994 and 2014, but the difference was not statistically significant.[35] Decreasing cancer risk was less evident in a large US registry study (SIR 1.57 and 1.28 in 1987-1996 and 2007-2016, respectively) of 100 000 kidney transplantations than in our study, and after multivariate adjustment the difference was not statistically significant.[36] The study design, however, differed remarkably from ours (no NMSCs, 5 years of follow-up after transplantation, only adults and only first cancers counted). Additionally, increasing use of lymphocyte depleting induction in the United States in contrast to opposite treatment regimen changes made in Finland may partly explain unchanged cancer risk in the United States. However, a decreasing trend of cancer incidence compared to general population has been reported after Nordic liver transplantations.[21]

SIRs were most significantly elevated ($P < .001$) for certain infection-associated malignancies,[13,20,37,38] including NHL, Kaposi's sarcoma, skin SCC and mouth and pharynx cancers. Skin SCC share similar risk factors with other virus-related cancers. No causality between virus infection and skin SCC has been proved, but some studies have shown an association with human papilloma virus (HPV).[39,40] In our study, virus infection-associated cancers (skin SCC included) constituted 51% of all cancers (without basal cell carcinoma) and their incidence was lower in the later than in the earlier transplantation period (833 vs 1285 per 100 000 person-years). The risk for noninfection associated cancers, common in general population, like lung, prostate and breast cancers along with melanoma was unchanged. In conclusion, there seemed to be a decreasing risk for certain infection-associated cancers. The decreased risk of NHL and skin SCC in the later compared to the earlier period has been reported also among Nordic liver recipients.[21] In the United States, SIR for NHL has remained unchanged (no data available on NMSCs).[36] Interestingly, in a UK registry study they had an opposite finding as the incidence of posttransplant lymphoma in kidney recipients had increased 9-fold since 1980s.[34] It was speculated to be caused by more aggressive immunosuppression used in the later years.

In our study, the changes noticed between the transplantation periods were not explained by the shorter follow-up, unequal proportions of the genders or thoracic organ recipients (most cancer-prone SOTs). The follow-up in person-years (35 181 in earlier period vs 31 560 in later period) and the proportion of males and thoracic organ recipients were similar (Table 1). At least 10 years was reached by nearly similar number of patients and 10-year cancer incidences were 10.3% and 11.0%, respectively. The mean age at transplantation has risen in Europe as well as in the United States increasing the general cancer risk.[41-43] In our cohort, the median age at transplantation had risen from 42.2 years (range 0.4-66.0) up to 55.3 years (range 0.4-79.0) for three decades. Noteworthy, SIRs for cancer in older recipients are lower than the younger, because the cancer incidence increases with age also in general population.[44] The decrement seen in cancer risk compared to general population could be partly explained by better patient information (including sun protection), improved diagnostics of premalignant conditions, treatment of virus infections (including asymptomatic viremias) and changes in immunosuppressive treatment protocols. The median follow-up time of patients was naturally shorter in 2000s than in the earlier

transplantation period, thus the results are best comparable during the first 10 years of FOT (Figure 3).

Remarkable changes in immunosuppression were made in early 2000s in Finland, like in other countries.[19] For instance, in kidney transplantations, in 1980s and 1990s the immunosuppressive medications were cyclosporine, azathioprine and corticosteroid. In 2000s cyclosporine has been replaced mainly by tacrolimus, and mycophenolate mofetil has replaced azathioprine. Similar changes in the use of immunosuppressive medication has been made in liver transplantations, but compared to other Nordic countries, maintenance immunosuppression has remained on higher level in Finland.[45] This may partly explain why no decrease in SIRs was seen in liver transplant recipients between the two transplantation periods in our cohort despite the decreasing trend shown in the Nordic study cohort (including Finland). In addition, less than 15% of kidney recipients in our cohort received induction treatment, antithymocyte globulin (2.4% before 2000 and 4.6% in 2000s) or basiliximab (only in 2000s) if there was high risk of rejection. In heart and lung transplantations the use of antithymocyte globulin for induction was regular with high dose (600 mg) in 1990s in Finland, but after 2001 gradually decreased until one third in heart transplantations and has been only rarely used after 2002 in lung transplantations. These changes in immunosuppression regimens have probably a significant effect on cancer incidence.

Cancer mortality was high (SMR 2.5), and especially in NHL (SMR 13.6), compared to the general population. Skin SCC was a rare cause of death but compared to general population SMR was high (34.5 [95% CI: 14.5-68.0]). Our results were comparable with previously published ones.[24,25,46] In Canada with same median age at transplantation, gender distribution and mortality (3586 vs our 3517 deaths per 100 000 person-years), the SMR was 2.84 for all cancers. In Australia and New Zealand, SMR 2.7 in kidney recipients was similar, but SMRs for melanoma 5.8 and kidney cancer 7.8 were higher than in Finland (2.6 and 4.7). SMRs must be interpreted cautiously, because cancer mortality comparison with general population is biased as many cancers form a contraindication for SOT and for instance hepatocellular carcinoma may even be the indication for transplantation.

Strengths of our study were that all transplantations were performed in the same tertiary center together with nearly complete patient recording (due to Finnish personal identity codes that enable adequate data collection from different registries), a high quality national cancer registry,[29] and a long follow-up time. Study limitations were that smoking history, body mass index, comorbidities, and individual immunosuppressive and antiviral medication data were not included due to registry-based set-up of this epidemiologic study. Although Finnish Cancer Registry data is very comprehensive, it does not include sufficient data on relapses.[29,30] However, skin cancers at different primary sites were recorded as multiple primary cancers. Only from 2015 on, skin is considered as one topography site.

Further prospective studies combining patients' genetic, pharmacogenetic (individual response to drug therapy) and clinical data including virus data are needed to be able to recognize the most vulnerable patients whereafter immunosuppression and necessary cancer screening could be tailored individually. Additionally, regular examinations of skin and clinicians' wide awareness of PTLD (associated with high posttransplantation mortality) are important in early diagnosis. Preventive tools against high-risk viruses should be used. HPV vaccinations are given before SOTs in some countries and are also under consideration in Finland.[47]

In conclusion, our population-based study showed that cancer risk compared to general population had decreased over time but was as high as 3-fold and cancer mortality over 2-fold also in the 2000s' transplantations. Personalized immunosuppression and early diagnosis of cancers are crucial to further improve the long-term outcome of these patients.

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CONFLICT OF INTEREST

IH has ongoing consultancy agreement with Novartis and Hansa Biopharma, and he has received research funding from MSD and Hansa Biopharma. Other authors have none to declare.

AUTHOR CONTRIBUTION

Study was designed by Terhi K Friman, Salla Jäämaa-Holmberg, Fredrik Åberg and Birgitta Salmela with the help of the others. Terhi K Friman constructed the study cohort with assistance of Ilkka Helanterä and Salla Jäämaa-Holmberg, and Fredrik Åberg commented frequently and helped with focusing. Terhi K Friman made the statistical analysis and wrote the final article along with Birgitta Salmela. All the authors read the article, gave their comments, and approved it prior to submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved both by the Ethics Committee of the Helsinki University Hospital (194/13/03/00/16) and by the National Institution for Health and Welfare (THL/1001/5.05.00/2016). Written informed consent was not obtained as patient consent is not needed in registry studies according to Finnish regulations.

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