ORIGINAL ARTICLE

Relative and absolute cancer risks among Nordic kidney transplant recipients—a population-based study

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SUMMARY

Kidney transplant recipients (KTRs) have an increased cancer risk compared to the general population, but absolute risks that better reflect the clinical impact of cancer are seldom estimated. All KTRs in Sweden, Norway, Denmark, and Finland, with a first transplantation between 1995 and 2011, were identified through national registries. Post-transplantation cancer occurrence was assessed through linkage with cancer registries. We estimated standardized incidence ratios (SIR), absolute excess risks (AER), and cumulative incidence of cancer in the presence of competing risks. Overall, 12 984 KTRs developed 2215 cancers. The incidence rate of cancer overall was threefold increased (SIR 3.3, 95% confidence interval [CI]: 3.2–3.4). The AER of any cancer was 1560 cases (95% CI: 1468–1656) per 100 000 person-years. The highest AERs were observed for nonmelanoma skin cancer (838, 95% CI: 778–901), non-Hodgkin lymphoma (145, 95% CI: 119–174), lung cancer (126, 95% CI: 98.2–149), and kidney cancer (122, 95% CI: 98.0–149). The five- and ten-year cumulative incidence of any cancer was 8.1% (95% CI: 7.6–8.6%) and 16.8% (95% CI: 16.0–17.6%), respectively. Excess cancer risks were observed among Nordic KTRs for a wide range of cancers. Overall, 1 in 6 patients developed cancer within ten years, supporting extensive post-transplantation cancer vigilance.

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Introduction

Kidney transplantation has been performed regularly as treatment for end-stage renal disease in the Nordic countries since 1964 [1]. Over time, with the introduction of more efficient immunosuppressive regimens and advances in both surgical techniques and immunosuppressive treatment strategies, patient survival has greatly improved [2,3]. However, as transplantation-related mortality has decreased, the incidence of post-transplant morbidities, such as cancer, has received more attention. Numerous studies demonstrate a twofold to fourfold increased risk of developing cancer post-transplantation compared to the general population [4-18]. Increased risks have been noted especially for cancer types associated with infectious agents, similar to in other immunosuppressive states such as HIV/AIDS [19].

Despite the well-known increased risks of cancer among kidney transplant recipients, few studies have estimated absolute risks of cancer overall and of specific cancer types post-transplantation with account for competing events [11,16,20]. Absolute overall and excess risks can facilitate the understanding of the clinical impact of this serious complication and provide a useful basis for planning of health care and clinical follow-up [21]. Furthermore, although nonmelanoma skin cancer (NMSC) has been shown to be the by far most common cancer after transplantation, few studies have estimated the relative and absolute risks of all cancer including NMSC in transplant recipients [7,8].

The aims of this study were therefore to assess relative and absolute post-transplantation cancer risks among kidney transplant recipients (KTRs) in the Nordic countries in the modern treatment era, to further guide monitoring and follow-up of these patients.

Methods

Study population and data sources

All Nordic residents who underwent their first kidney transplantation during 1995 through 2011 were selected using national personal identity numbers, from national inpatient registries (Sweden, Denmark), the Norwegian Renal Registry, and transplantation clinic registries (Norway, Finland). Data from the Swedish Renal Registry and from ScandiaTransplant (an organ exchange organization owned by participating hospitals in Sweden, Denmark, Finland, Norway, Iceland, and Estonia) were further linked to the patient cohort. ScandiaTransplant data were used to establish graft functional status and donor vital status. Information about cancer occurring after transplantation as well as dates and causes of death were added from national cancer and cause-of-death registries. For all countries in the study, reporting of cancer (including of NMSC) is mandated by law and registration is close to complete (94-98%) [22]. Start of follow-up was set to 30 days after the date of the first transplantation, in accordance with previous studies [8,11,16] and exit date was date of first post-transplantation cancer diagnosis of each single cancer type by anatomic location (Table S1), date of death, or end of follow-up (December 31st of 2011 for Sweden and Denmark, 2013 for Finland, and 2014 for Norway), whichever came first. Patients were not excluded based on previous cancer history. However, patients with a pre-transplantation cancer diagnosis were not followed for post-transplantation risk of that particular cancer type. Any cancers diagnosed within 30 days of transplantation were considered likely present but undiagnosed during transplantation, which was the rationale for starting follow-up 30 days after the date of first transplantation.

We used the publicly available NORDCAN database [23], maintained by the Association of the Nordic Cancer Registries, to obtain data on the number of expected cancer cases stratified by country, age at diagnosis, sex, and calendar period (ICD-10 [International Statistical Classification of Diseases and Related Health Problems, tenth revision] codes in Table S1).

The study was approved by The Regional Ethics Review Boards in Stockholm, Sweden (approval no. 2007/1485-31, 2008/452-39, and 2013/2239-32); the Regional Committee for Medical Research Ethics—South East Norway, Oslo (approval no. 2011/1587/REK sør-øst D); and the Research ethics committee of the Faculty of Medicine, Helsinki (approval no. 117/13/03/00/2014). In accordance with national guidelines, we did not seek an ethics approval in Denmark as the study only included de-personalized data and no individual results are presented, assuring the personal integrity of study persons.

Outcome

The primary outcome was a first cancer diagnosis of each single cancer type post-transplantation. We assessed risk of cancer overall and risk of 36 separate cancer types (Table S1). We also assessed risk of cancer types known or suspected to be infection-related versus cancer types regarded as noninfection-related, in line with previous studies (Table S1) [10,13,19]. NMSC and cancers of the lip, female genitals (uterine cervix, vulva,

vagina), male genitals, ear–nose–throat region, stomach, esophagus, liver and eye, and non-Hodgkin and Hodgkin lymphoma were considered infection-related. Cancers of the kidney, thyroid, gallbladder, lung, pleura, bone and soft tissues, colon, small intestine, bladder and urinary organs unspecified, pancreas, testis, uterus except cervix, central nervous system (CNS), rectum and anus (grouped together in NORDCAN), breast, prostate, ovaries and uterine adnexa, and leukemia, melanoma, and multiple myeloma were considered noninfection-related. We did not perform analyses for basal cell skin cancers as these cancers are not included in NORDCAN.

Statistical analyses

Observed numbers of cancer cases were calculated by country, sex, age group in five-year intervals up to 85 + years (0–4, 5–9,..., 80–84, 85+), and calendar year and compared to corresponding numbers of expected cancer in the NORDCAN database to produce standardized incidence ratios (SIRs). Absolute excess risks (AER) of cancer were estimated using the same source data by calculating the difference between observed and expected number of cancers divided by person-time at risk. Confidence intervals were calculated using an exact method assuming a Poisson distribution for the excess events.

Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) comparing the rate of cancer by several patient- and transplantation-related factors to identify factors associated with an excess cancer risk. The model included sex, age at transplantation (0–49, 50–59 or 60 + years), calendar period of transplantation (1995–99, 2000–05, 2006–11), donor vital status (alive/dead), ongoing dialysis (time-varying exposure categorized as yes/no, with ongoing dialysis indicating loss of graft [function]), underlying kidney disease, and history of cancer before transplantation. The Grambsch–Therneau test on the Schoenfeld residuals was used to test the proportional hazards assumption [24]. As a sensitivity analysis, to assess the impact of the functional form of the possible confounding effect of age at transplantation, we also re-fitted the aforementioned Cox regression model with a restricted cubic spline with four degrees of freedom (knots at the 20th, 40th, 60th, and 80th percentiles of the age distribution) to represent the age association.

The cumulative incidence (i.e., probability of being diagnosed with cancer post-transplantation) was subsequently calculated in the presence of the competing risk of death. This measure was computed using numerical integration of postestimation results (approximation of baseline hazard and the linear predictor) from the above Cox regression model, as described in a tutorial paper by Putter et al. [25]. Confidence intervals were obtained using bootstrapping. Separate models were fitted to estimate risk of any cancer (unadjusted), risk of any cancer and infection/noninfection-related cancer stratified by sex and age, and temporal trends in cumulative incidence stratified by sex and age. Additionally, we assessed the cumulative incidence of colorectal, lung, prostate, breast, kidney cancer, NMSC, and non-Hodgkin lymphoma (NHL) separately.

SAS version 9.4 (Copyright © 2002-2012 by SAS Institute Inc., Cary, NC, USA) and STATA version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) were used to perform the analyses.

Results

In the combined cohort, 12 984 KTRs (4723 Swedish, 3156 Norwegian, 2629 Finnish, and 2476 Danish) were included, with a median age of 50 years (range 0–83) at transplantation (Table 1). The total follow-up time was 98 745 years (median 7.0 years, range 0–20). Two thirds of KTRs were male, and the age distribution was similar by country, except that Norwegian KTRs were somewhat older at transplantation (median 54 years), and Danish KTRs younger (median 46 years) (Table 1).

During post-transplantation follow-up, 2215 cancers were diagnosed in 1845 KTRs, translating to a crude incidence of 2243 cancers per 100 000 person-years. NMSC was most common, accounting for 34% of all cancer cases, followed by lung cancer (7.6%), prostate cancer (7.0%), NHL (6.6%), kidney cancer (5.5%), malignant melanoma (3.9%), and colon cancer (3.9%). Only 3 cases of Kaposi's sarcoma were observed, all of which were located in the skin, and thus classified as NMSC (Table S1).

Risk factors for cancer

Female KTRs had a 27% lower rate of cancer compared to male (HR: 0.73, 95% CI: 0.66–0.81), and the rate of cancer increased with age at transplantation (Table 2). Neither ongoing dialysis, donor vital status, nor underlying kidney disease was associated with post-transplantation cancer risk; however, a history of cancer before transplantation was associated with a 36% increased rate of post-transplantation cancer (Table 2). The

Table 1. Distribution of sex, year of and age at 1st transplantation, and median age at 1st transplantation among Nordic kidney transplant recipients 1995–2011

Characteristics	Sweden No. (%)	Norway No. (%)	Denmark No. (%)	Finland No. (%)	Total No. (%)
No. of patients	4723 (100)	3156 (100)	2476 (100)	2629 (100)	12 984 (100)
Sex					
Male	3026 (64)	2119 (67)	1533 (62)	1677 (64)	8355 (64)
Female	1697 (36)	1037 (33)	943 (38)	952 (36)	4629 (36)
Year of 1st Tx					
1995–1999	1213 (25)	784 (25)	646 (26)	721 (27)	3364 (26)
2000–2005	1632 (35)	1100 (35)	829 (33)	949 (36)	4510 (35)
2006–2011	1878 (40)	1272 (40)	1001 (40)	959 (36)	5110 (39)
Age at 1st Tx, years					
0–18	229 (5)	133 (4)	161 (7)	155 (6)	678 (5)
19–49	2140 (45)	1138 (36)	1312 (53)	1181 (45)	5771 (44)
50–59	1284 (27)	709 (22)	634 (26)	730 (28)	3357 (26)
60–69	970 (21)	751 (24)	343 (14)	479 (18)	2543 (20)
70 +	100 (2)	425 (13)	26 (1)	84 (3)	635 (5)
Median	49	54	46	49	50

No, number. Tx, transplantation.

proportional hazards assumption was not violated. In the sensitivity analysis, modeling age at transplantation using a spline instead of a categorical variable did not materially change the results (Table S2 and Figure S1).

Relative risks

We found a 3.3-fold increased risk of cancer overall in KTRs (SIR: 3.29, 95% CI: 3.15–3.43), and a 2.2-fold increased risk when excluding NMSC (SIR: 2.22, 95% CI: 2.11–2.34), compared to the general population (Fig. 1). In all four countries, the SIRs of cancer overall ranged from approximately 3 to 4 (Sweden, SIR: 2.98, 95% CI: 2.75–3.23; Norway, SIR: 3.39, 95% CI: 3.16–3.63; Denmark, SIR: 3.73, 95% CI: 3.35–4.15; Finland, SIR: 3.27, 95% CI: 2.97–3.59; Table S3 and Figure S2). However, the background cancer incidence rates differ between the four countries with lower rates in Sweden and Finland (Figure S3). There was an overall 11-fold increased risk of infection-related cancer in KTRs (SIR: 11.4, 95% CI: 10.7–12.1; Fig. 1). Among infection-related cancers, elevated risks were found for NMSC, lip, vulva and vaginal cancer, NHL, penile, and nasal/sinusoidal cancer, Hodgkin lymphoma, oral cavity, liver, cervical, and stomach cancer. When excluding NMSC, the risk of infection-related cancer was fourfold increased (SIR: 4.18, 95% CI: 3.72–4.67). The risk of noninfection-related cancer was twofold increased (SIR: 1.97, 95% CI: 1.86–2.09). Among these, we found elevated risks of kidney, thyroid, other specified, lung, unknown and ill-defined, gallbladder, pleural, colon, small intestine, bladder/urothelial, bone/soft tissue, pancreatic, and uterine (except cervical) cancer, as well as malignant melanoma and multiple myeloma.

Absolute excess risks and cumulative incidence

The AER of any cancer was 1560 cases per 100 000 person-years (95% CI 1468–1656) (Fig. 1). About half of the excess cancer risk was because of NMSC (AER: 838, 95% CI 778–901). Apart from NMSC, the cancer forms contributing most to the excess cancer risk were NHL (AER: 145, 95% CI 119–174), lung cancer (AER: 126, 95% CI 98.2–157), kidney cancer (AER: 122, 95% CI 98.0–149), melanoma (AER: 66.4, 95% CI 46.6–89.6), and colon cancer (AER: 53.1, 95% CI 33.4–76.2). The cumulative incidence of cancer overall increased with age and was higher among men than among women (Fig. 2). The five-year cumulative incidence of cancer including NMSC was 8.1% (95% CI: 7.6–8.6%) overall, 8.9% (95% CI: 8.3–9.6%) among male, and 6.5% (95% CI: 6.0–7.2%) among female KTRs (Fig. 2). Excluding NMSC, the five-year cumulative incidence was 4.9% (95% CI: 4.5–5.4%) overall, 5.2% (95% CI: 4.8–5.7%) among male and 4.4% (95% CI: 3.9–5.0%) among female KTRs. The cumulative incidence of infection-related cancer among female KTRs was comparable to that of noninfection-related cancer in all age groups, while among older men (60 + years at transplantation), the absolute risk of infection-related cancer was higher than that of noninfection-related

Table 2. Cox regression multivariable analysis of risk factors for first post-transplantation cancer (1845 events) among 12 984 Nordic kidney transplant recipients 1995–2014

Characteristics	Events	HR	95% CI	*P*-value
Sex				
Male	1306	Ref	Ref	
Female	539	0.73	0.66–0.81	<0.001
Age at 1st Tx (years)				
0–49	487	0.33	0.29–0.37	<0.001
50–59	596	Ref	Ref	
60–69	596	1.77	1.58–1.99	<0.001
70+	166	2.42	2.01–2.91	<0.001
Year of 1st Tx				
1995–1999	761	Ref	Ref	
2000–2005	713	0.89	0.79–0.99	0.03
2006–2011	371	0.95	0.82–1.09	0.47
Dialysis				
No	1680	Ref	Ref	
Yes	165	1.01	0.83–1.23	0.92
Living donor				
No	1377	Ref	Ref	
Yes	439	0.95	0.84–1.06	0.37
Missing	29	0.68	0.46–0.99	0.04
Underlying kidney disease				
Kidney failure, NOS	397	Ref	Ref	
Diabetes	135	0.87	0.71–1.07	0.19
Immunological/inflammatory diseases*	93	0.96	0.76–1.20	0.70
Hypertension	205	1.17	0.98–1.39	0.09
Glomerular and tubulo-interstitial diseases	659	1.06	0.93–1.20	0.41
Malformations and cystic kidney diseases	356	0.97	0.84–1.12	0.68
History of cancer before Tx				
No	1699	Ref	Ref	
Yes	146	1.36	1.14–1.62	<0.001

*For example, Henoch-Schönlein's purpura, hemolytic uremic syndrome. Abbreviations: HR, hazard ratio. CI, confidence interval. Ref, reference group. Tx, transplantation. NOS, not otherwise specified.

cancer (Fig. 3, Table S4). However, upon exclusion of NMSC (constituting the majority of all infection-related cancers), the five- and ten-year cumulative incidence of infection-related cancers were less than half of the risks of noninfection-related cancers among both men and women (Fig. 3, Table S4). After NMSC, NHL was associated with the highest cumulative incidence after five years among men aged < 50 years at transplantation (Figure S4 and Table S4). Among men aged 50 + years at transplantation, prostate cancer and then lung cancer were the most common cancers after NMSC. Among women, breast cancer was the most common cancer after NMSC regardless of age.

The cumulative incidence of cancer over calendar time increased significantly among men, but not among women, during the study period (Figure S5). The five-year absolute cancer risks for the periods 1995–1999, 2000–2005, and 2006–2011 were 7.9%, 8.5%, and 10.4% among males and 6.0%, 6.1%, and 7.4% among females. However, the overall competing risk of death as first event declined over calendar time. For the aforementioned calendar periods, the five-year probabilities of death as first event among men were 10.2%, 8.0% and 7.9% and among women 10.1%, 7.2%, and 4.5%, respectively.

Discussion

With this population-based study on cancer risk after kidney transplantation in Sweden, Norway, Denmark, and Finland in the modern treatment era, we confirm a 3.3-fold elevated risk of developing any primary cancer after transplantation compared to the general population, and a 2.2-fold risk of any cancer excluding NMSC. Incidence rates of a broad range of both infection-related and noninfection-related cancers were significantly increased. The cumulative incidence of cancer overall

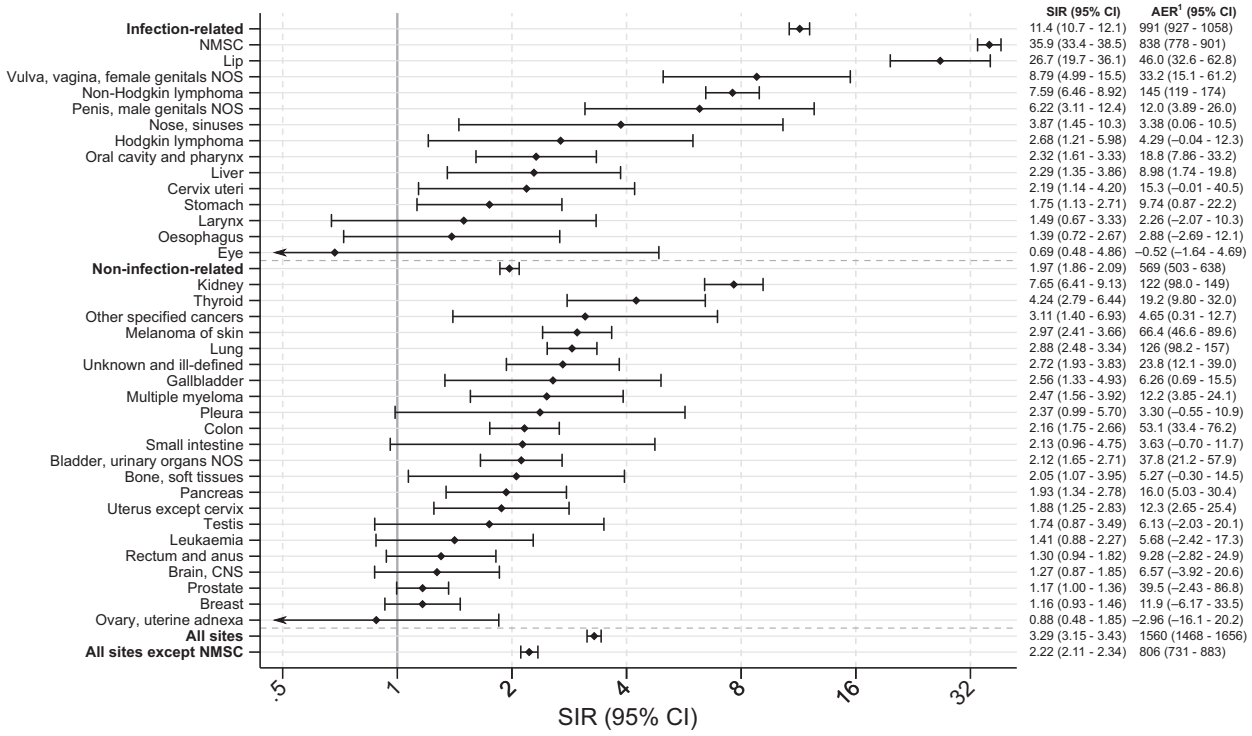

Figure 1 Standardized incidence ratios and absolute excess risks of cancer overall, specific cancer sites and infection- and noninfection-related cancers among Nordic kidney transplant recipients 1995–2014 compared to the general population. [1]AER denotes absolute excess risk per 100.000 person-years. Abbreviations: SIR, standardized incidence ratio. CI, confidence interval. AER, absolute excess risk. NMSC, nonmelanoma skin cancer. NOS, not otherwise specified. CNS, central nervous system.

was 8% five years after transplantation and 17% after ten years. The absolute excess risk was 1560 cancer cases per 100 000 person-years, half of which were because of NMSC. Other cancer types with high excess risks in absolute terms were NHL, lung cancer, kidney cancer, melanoma, and colon cancer.

AERs have seldom been estimated in the previous literature on cancer risk among KTRs. In the large US study by Engels et al. [13], AERs were determined in a cohort of kidney, heart, lung, and liver transplant recipients, but were not presented for kidney transplant recipients separately, and the excess risk of NMSC was not assessed. In a recent Taiwanese study by Tsai et al. [26], with a follow-up period similar to our study, the AER was 770 per 100 000 person-years, almost half of which was accounted for by bladder cancer (AER: 330). As in the present study, the Taiwanese study also reported AERs for, for example, lung cancer (AER: 14.8), kidney cancer (AER: 41.5), and malignant melanoma (AER: 3.8). In contrast to our results, the AER in Taiwan was negative for colorectal cancer (AER: −18.6) and cervical cancer (AER: −33.4), and modest for NMSC (AER: 11.0).

In the present study, NMSC accounted for half of the excess cancer risk among KTRs. High excess risks also pertained to one other infection-related cancer type (NHL) but mostly to more common noninfection-related cancers (cancer of the lung, kidney and colon, and melanoma). From a clinical perspective, the excess risks are more important than relative risks since they reflect the excess number of cases generated by the transplantation procedure and associated diseases, and thus to a larger extent indicate which types of cancers that will occur among KTRs during clinical follow-up.

Previous reports of relative cancer risks among KTRs compared to the general population from the most recent decades demonstrate SIRs of any cancer ranging from 2.9 to 6.5; and, excluding NMSC, from 2.1 to 3.2 [7,8,10-18]. Hence, our relative risk results are well in line with previous literature in this regard. The risk of NMSC was 36-fold compared to the general population. Other studies have found markedly elevated incidence of NMSC, ranging from a 7 to 121 times higher risk than in the general population, with the lowest SIRs for NMSC found in Asian studies [14,15].

Other cancers that have previously been consistently associated with increased risk are Hodgkin lymphoma (SIRs in previous studies 2.4–7.4) and NHL (3.3–16), malignant melanoma (1.8–9.1), multiple myeloma (1.8–

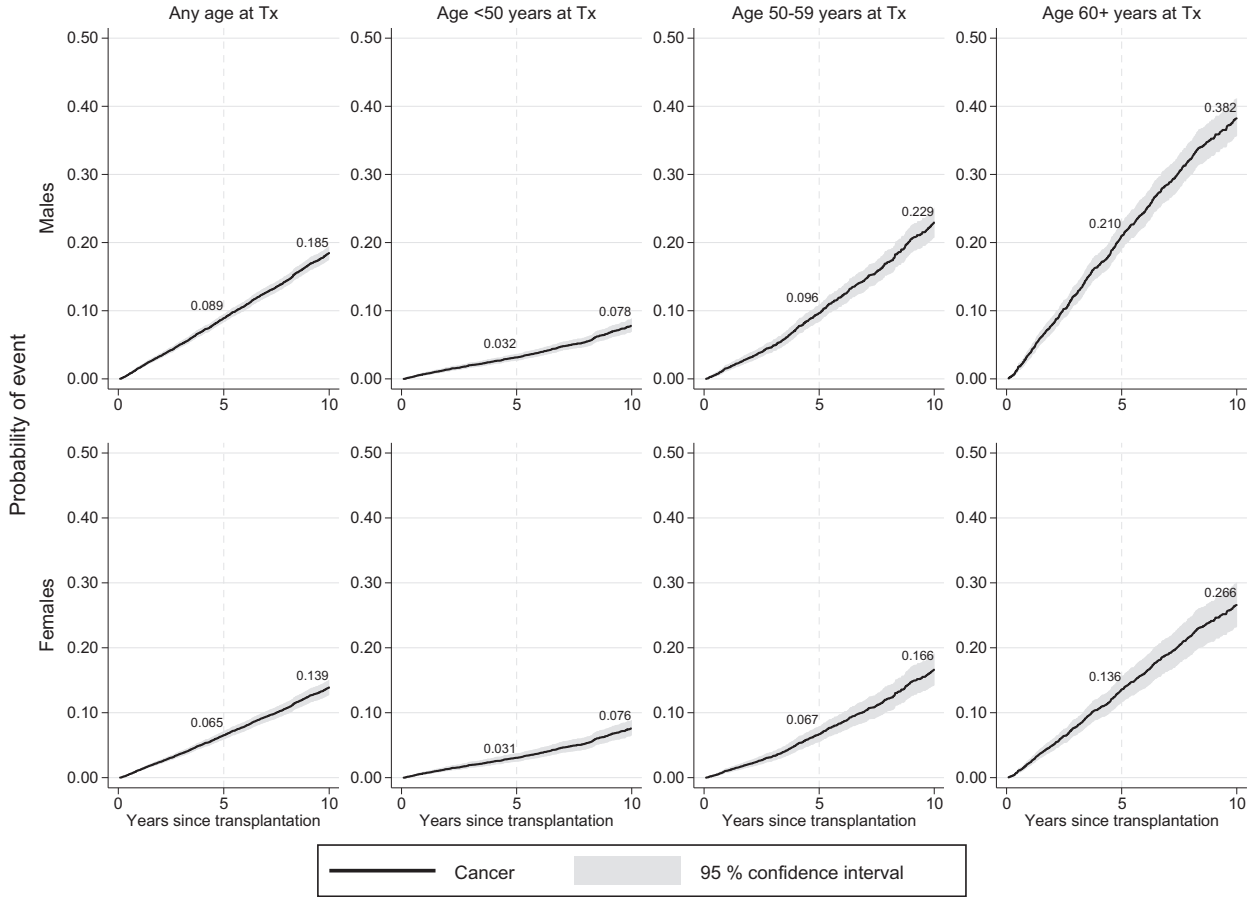

Figure 2 Five- and ten-year cumulative incidence* of cancer among Nordic kidney transplant recipients 1995–2014, stratified by sex and age at transplantation. Abbreviations: Tx, transplantation. * Cumulative incidence is estimated in the presence of the competing risk of death.

3.9), and cancers of the bladder (1.5–43), colorectum (1.2–1.8), oral cavity (2.0–5.5), lip (17–66), lung (1.4–4.8), kidney (4.7–44), liver (2.4–12), thyroid (2.4–8.1), and vulva/vagina (5.5–21) [7,8,11-18]. Most of these cancer types were associated with similarly increased risks among KTRs in our study. The most common cancers in the general population, prostate cancer (among men) and breast cancer (among women), were not associated with an increased risk among KTRs, consistent with previous research.

A handful of previous studies have determined cumulative incidence of any cancer among KTRs, out of which a few also accounted for competing events [11,16,20]. Accounting for the competing risk of death provides a risk estimation that is applicable to the real world, that is, where death is a plausible alternative outcome. These studies demonstrated five-year absolute cancer risks of 4.4%, 4%, and 1.8% excluding NMSC. We present a five-year absolute risk excluding NMSC of 4.9%, which is slightly higher than two of the aforementioned studies, although we did not consider graft failure and re-transplantation (in contrast to Hall et al. [20]) or diagnosis of another cancer (in contrast to Villeneuve et al. [11]) as competing events, which might explain some of the difference. Furthermore, for lung cancer, we found similar 5-year absolute risks among all three age groups (up to 50, 50–59, or over 60 years at transplantation), compared to Hall et al. [20] For kidney and prostate cancer, we found lower absolute risks among KTRs aged up to 60 years at transplantation, but higher among KTRs aged over 60 at transplantation. Finally, for NHL, colorectal, and breast cancer, we found overall higher risks of cancer among all age groups. These differences may be because of differing population rates and definitions of competing events.

The strongest risk factor for cancer in our study was age, with KTRs aged 70 + years at transplantation having a 2.4 times higher rate of cancer than KTRs aged 50–59 years. Also, female sex was associated with a reduced risk, and cancer history prior to transplantation with an increased risk, of new primary malignancy. This is expected as high age, male sex, and cancer history are

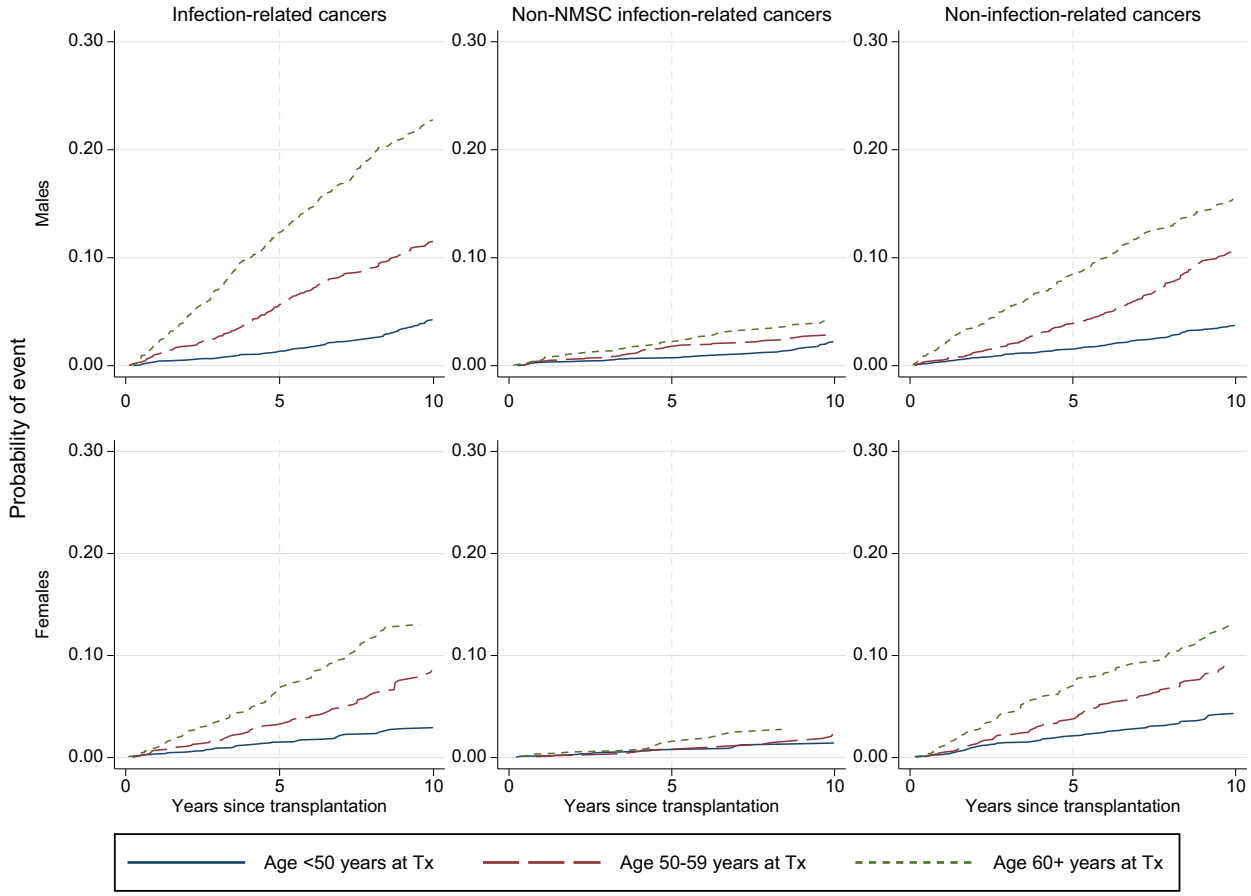

Figure 3 Five- and ten-year cumulative incidence* of infection-related cancers, with and without inclusion of nonmelanoma skin cancer, and noninfection-related cancers among Nordic kidney transplant recipients 1995–2014, stratified by sex and age at transplantation. Abbreviations: Tx, transplantation. NMSC, nonmelanoma skin cancer. * Cumulative incidence is estimated in the presence of the competing risk of death.

factors associated with a higher rate of incident cancer also in the general population. The same Cox regression model yielded no significant time trends in cancer rates by year of transplantation, although the cumulative incidence of death as a competing event declined over time. Also, neither time on dialysis (as a measure of lost graft function), donor vital status, nor underlying kidney disease modified the cancer rates. However, previous studies have shown a lower rate of cancer among KTRs with diabetes, compared to among those with other primary renal diseases [27].

Several cancer-promoting features have been associated with immunosuppression, such as an impaired anti-tumor response, impaired ability to counter infections, carcinogenic features of the medication itself, and increased susceptibility to damaging effects of ultraviolet radiation [19,28]. In terms of infection-related carcinogenesis, an array of different mechanisms has been identified, including, for example, transfer and integration of oncogenes between viruses and host cells, (virus-induced) immunosuppression activating (other) tumor viruses, chronic inflammation, prevention of apoptosis, and promotion of chromosomal instability [29].

In our study, infection-related cancers in particular were associated with an increased risk among KTRs, but our absolute risk analyses showed that these cancer types (except NMSC and NHL) were in fact uncommon compared to noninfection-related ones. This suggests that noninfection-related cancers (and skin cancers and lymphoma) should be in focus when constructing screening protocols for KTRs. In a recent systematic review [30] Acuna et al. concluded that there is wide support for screening for skin cancer and for cancers that are already included in screening programs for the general population (e.g., breast and cervical cancer) or for which screening is recommended (e.g., colorectal, lung [among present and former smokers], and prostate cancer). For other cancers, recommendations are conflicting.

Our findings support the use of established and recommended cancer screening programs in the general

population, although structured clinical follow-up for early detection of a few other cancer forms (such as lymphoma) is also warranted. Recent guidelines recommend close follow-up of recipients seronegative for Epstein–Barr virus (i.e., the majority of children) who receive an organ from a seropositive donor [31] because of risk of lymphoma, but otherwise lymphoma-specific follow-up guidelines are lacking. As post-transplantation cancer treatment is complicated by possible nephrotoxicity and interaction with immunosuppressive treatment, as well as comorbidities preventing surgical cancer treatment, organ transplant recipients could also benefit from earlier or extended screening for some cancers for which screening is not worthwhile in the general population.

Strengths of this study include the population-based design and inclusion of KTRs from four Nordic countries and the use of national registries with virtually complete coverage. However, the study also has several limitations. Firstly, we obtained background cancer rates from NORDCAN, whereby we also accepted its categorization of cancers. For example, Kaposi's sarcoma is categorized by anatomic location both in the NMSC, bone/soft tissues, and other specified cancers groups; however, all three cases in our study were found in the NMSC group. Also, anal cancer (typically virus-related) is grouped together with rectal cancer (typically non-virus-related) in NORDCAN and thus could not be studied separately. Secondly, our study might have underestimated the overall cancer risks to some extent, as patients were followed only until first cancer of each type. Subsequent cancers of the same organ system, probably more common in KTRs than in the population, have therefore been missed. Moreover, for a few cancer types (e.g., bladder/urothelial cancers), registration and classification can differ between the national cancer registers concerned [22], which could possibly influence risk estimates. Lastly, our findings must be interpreted within the limitations of grouped observational data. The presented absolute excess risks are thus not necessarily applicable to individual patients as there are a number of additional important factors, such as smoking status, obesity, and genetic predisposition that determines the individual risk of being diagnosed with cancer.

Conclusion

With improving graft and patient survival after solid organ transplantation, cancer has become an increasingly large threat to organ transplant recipients. This study confirms previous results of relatively higher cancer incidence among KTRs compared to the general population and adds insight into absolute cancer risks reflecting the clinical impact. In particular, we observe high excess risks of specific infection-related (NMSC, lymphoma) and noninfection-related cancers (lung, kidney). Overall, one in 12 KTRs developed any cancer over five years following transplantation, and one in 6 over ten years. Our results support screening for NMSC, and adherence to established screening programs for common cancers in the general population, with the addition of clinical vigilance for lymphoma. Further research should aim to determine the feasibility and outcomes of structured cancer screening programs for KTRs using prospective study designs and taking views from both patients and health care into account.

HB, SE, DOD, MHHS, AN, JC, GM, IH, VH, GE, EP, SSS, ML, and KES: participated in research design. HB, SE, and KES had full access to data and take responsibility for the integrity of the data and the accuracy of the data analyses; performed the analyses and the initial interpretation of data; and drafted the article. HB, SE, DOD, MHHS, AN, JC, GM, IH, VH, GE, EP, SSS, ML, and KES: participated in the interpretation of data and revised the article for important intellectual content. KES supervised the study.

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Conflict of interest

None declared.

Disclosure

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The functional form of the association between age at transplantation and post-transplant cancer risk, with 50 years as reference, when modelling age using a restricted cubic spline with four degrees of freedom in a multivariable Cox regression analysis.

Figure S2. Standardized incidence ratios of select cancers among Nordic kidney transplant recipients 1995–2014, stratified by country.

Figure S3. Age-standardized incidence rates of cancer among the general populations of Sweden, Norway, Denmark and Finland 1995–2014, for all ages.

Figure S4. Five- and ten-year absolute risk of colorectal, lung, prostate, breast and kidney cancer, and non-Hodgkin lymphoma, among Nordic kidney transplant recipients 1995–2014, stratified by sex and age at transplantation.

Figure S5. Five- and ten-year absolute risk of cancer among Nordic kidney transplant recipients 1995–2014, stratified by sex and time period of transplantation.

Table S1. ICD-10 codes used for determining cancer groups among Nordic kidney transplant recipients 1995–2014 and the general population.

Table S2. Cox regression multivariable analysis of risk factors for first post-transplantation cancer (1845 events) among 12 984 Nordic kidney transplant recipients 1995–2014, with age at transplantation modelled using a restricted cubic spline.

Table S3. Standardized incidence ratios of cancer among Nordic kidney transplant recipients 1995–2014 compared to the general population, stratified by country.

Table S4. Five- and ten-year absolute risk (in percent) of infection-related and non-infection-related cancer among Nordic kidney transplant recipients 1995–2014, stratified by sex and age at transplantation.

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