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Cancer survival in kidney transplant recipients in Ireland

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ABSTRACT

Background. Transplantation is a well-known risk factor for malignancy. However, outcomes of cancer in transplant recipients compared with non-transplant recipients are less well studied. We aim to study the survival in kidney transplant recipients who develop cancer and compare this with cancer outcomes in the general population.

Methods. We linked data from the National Cancer Registry Ireland with the National Kidney Transplant Database. The period of observation was from 1 January 1994 until 31 December 2014. Transplant recipients were considered at risk from the time of diagnosing cancer. We administratively censored data at 10 years post-cancer diagnosis. Survival was compared with all patients in the general population that had a recorded diagnosis of cancer.

Results. There were 907 renal transplant recipients and 426679 individuals in the general population diagnosed with cancer between 1 January 1994 and 31 December 2014. In those with non-melanoma skin cancer, the hazard ratio (HR) for 10-year, all-cause mortality [HR = 3.06, 95% confidence interval (CI) 2.66–3.52] and cancer-specific mortality (HR = 3.91, 95% CI 2.57–5.96) was significantly higher among transplant recipients than the general population. Patients who developed non-Hodgkin lymphoma (HR = 2.89, 95% CI 1.96–4.25) and prostate cancer (HR = 4.32, 95% CI 2.39–7.82) had increased all-cause but not cancer-specific mortality. Colorectal, lung, breast and renal cell cancer did not show an increased risk of death in transplant recipients.

Conclusion. Cancer-attributable mortality is higher in kidney transplant recipients with non-melanoma skin cancer compared with non-transplant patients. The American Joint Committee on Cancer staging should reflect the increased hazard of death in these immunosuppressed patients.

Keywords: cancer, mortality, skin cancer, transplantation

INTRODUCTION

Since the earliest days of transplantation, it has been known that transplantation is associated with an increased risk of malignancy [1]. Patients following renal transplant were found to be three to four times more likely to develop malignancy than the general population [2, 3]. The main contributor to this is the burden of immunosuppression [4].

The most common malignancies in the post-transplant period are the non-melanomatous skin cancers (NMSC), basal cell carcinoma and squamous cell carcinoma. The second most commonly seen cancer is post-transplant lymphoproliferative disorder, a form of non-Hodgkin lymphoma (NHL) that occurs in 1% of all transplant patients [5–7]. However, renal transplant recipients are also at risk of other invasive cancers, including cancers of the lung and kidney [8].

In the early days of transplantation, death from malignancy was rare in patients with solid-organ transplants (SOTs) and only accounted for 1.2% of deaths in those who had a renal transplant between 1970 and 1979 [9]. However, as management improved and death from infection began to fall, the rate of death from cancer began to rise [10]. A recent registry study from Ontario, Canada, suggests that cancer is now the second most common cause of death among all transplant patients and is more likely to occur at a younger age [11, 12]. As our transplant population survives longer, cancer is likely to be increasingly common.

In this analysis of national cancer registry data, we aim to describe the cancer-attributable mortality among kidney transplant recipients in the National Kidney Transplant Programme in Ireland.

MATERIALS AND METHODS

We designed a retrospective, population-based registry study of renal transplant recipients in Ireland.

We linked data from the National Kidney Transplant Programme database with cancer diagnosis, treatment and survival data, as well as patient demographic data, from the National Cancer Registry Ireland (NCRI). The NCRI has prospectively collected data on all patients with a diagnosis of cancer in Ireland since January 1994. Cancer diagnoses are sourced primarily from pathology departments, with further cases registered from sources including electronic coding, hospital-based

KEY LEARNING POINTS

What is already known about this subject?

- It is well known that patients who receive renal transplants are at higher risk of developing cancer than the general population. Studies in North America and Australia show that the rate of death from cancer is increased compared with the general population.

What this study adds?

- This study adds information regarding survival in cancer in a Northern European population that has undergone renal transplant.

What impact this may have on practice or policy?

- This may help understanding of the risk of death post-cancer in the Northern European population. In particular, may have an effect on the aggressiveness of treatment in non-melanomatous skin cancer in a transplant population.

cancer databases, hospital databases and death certificates. Diagnoses were determined using International Classification of Diseases, Tenth Revision codes. Cause of death was derived from death certificate data.

The observation period began on 1 January 1994, the date when NCRI began prospectively collecting data, or on the date of transplantation, whichever came later, and ended on 31 December 2014. Time at risk began at cancer diagnosis. We administratively censored after 10 years, resulting in follow-up time ending at 10 years post-diagnosis, the date of death or 31 December 2014. Patients transplanted before 1 January 1994 were included in the study if they were alive on 1 January 1994. Only those who developed malignancy were included in the analysis. All malignant neoplasms occurring post-transplant were considered *de novo* post-transplant malignancies. Patients who had a pre-transplant malignancy were excluded from the analysis. Patients who developed multiple cancers were included in each analysis, i.e. an individual who developed both breast and colon cancer would be included in the analyses for both cancers. Survival in transplant patients was compared with that in the general population with cancer.

Statistical methods

Ten-year, all-cause survival analysis was performed. Patients were recorded as being either alive or dead 10 years post-diagnosis. Cox proportional hazards models were used to test whether transplant recipients had a greater hazard than the general population when diagnosed with specific cancers (colorectal, lung, breast, prostate, kidney, NHL and NMSC). Models were adjusted for age, sex, deprivation status, marital status, smoking status, cancer grade and tumor node metastasis (TNM) stage, receipt of surgery, radiotherapy or chemotherapy as treatment in the 12 months following or 1 month before diagnosis, and era of cancer diagnosis. Era of cancer diagnosis was divided between those who developed cancer between 1994 and 2003 and those who developed cancer from 2004 and 2014.

Ten-year competing risk analysis was also performed. At 10 years post-diagnosis, patients were considered alive, dead from cancer or dead from other causes. Death due to cancer was the event of interest. Death due to other causes was flagged as a competing risk. Cumulative incidence functions, with 95% confidence intervals (CIs), were produced to compare the risk of death due to cancer in the transplant and non-transplant cohorts.

Proportional hazards models for the sub-distribution of competing risks were used to test whether transplant recipients had a greater hazard of dying from the cancer of interest than the general population. Models were adjusted for the same factors as the all-cause survival analysis. Adjusted cumulative incidence functions were produced.

The proportional hazards assumption was tested by examining whether the interactions between survival time and the covariates were significant. This was done by the inclusion of time varying covariates (TVC) in the models.

Standardized mortality ratios (SMRs) were also calculated, by cancer type, for all-cause and cancer-specific mortality. SMRs are the ratio of the observed number of deaths due to cancer in the transplant population compared with the expected number of deaths. Expected deaths were determined by calculating the person-years at risk in the transplant cohort, broken down by sex and 5-year age groups and multiplying these by the age- and sex-specific mortality rates for different cancers in the general population of cancer patients.

STATA SE (version 15.1 StataCorp, College Station, TX, USA) was used for the data analysis and graphical presentation.

RESULTS

In total, 3267 patients were included in the study who had renal transplants before 1 January 1994 and were alive on that date or were transplanted between 1 January 1994 and 31 December 2014. During follow-up, we observed cancer in 907 of these kidney transplant recipients. The total number of people affected by cancer in the general population over the time period of interest was 426679. Characteristics of those affected by cancer are described in Table 1.

In the cohort of 907 transplant recipients who developed cancer, all-cause mortality at 5, 10 and 15 years was 25.8, 44.1 and 60.2%. Cancer-related mortality at 5, 10 and 15 years was 10.7, 13.03 and 16%, respectively (Figure 1).

NMSC was the most common form of cancer, affecting 728 recipients (80%). The most common forms of invasive cancer excluding NMSC occurring in renal transplants were NHL ($n = 44$, 4.8%), colorectal cancer ($n = 33$, 3.6%), prostate cancer ($n = 31$, 3.4%), lung cancer ($n = 29$, 3.2%), renal cancer ($n = 23$, 2.5%) and breast cancer ($n = 21$, 2.3%; Table 1).

Table 1. Characteristics of transplant recipients and non-transplant recipients who developed cancer

Type of cancer	Colorectal		Lung		Breast		Prostate		Renal		NHL		NMSC	
	Tx ($n=33$)	Non-TX ($n=44\,102$)	Tx ($n=29$)	Non-Tx ($n=39\,462$)	Tx ($n=21$)	Non-Tx ($n=47\,321$)	Tx ($n=31$)	Non-Tx ($n=49\,012$)	Tx ($n=23$)	Non-Tx ($n=8950$)	Tx ($n=44$)	Non-Tx ($n=11\,783$)	Tx ($n=728$)	Non-Tx ($n=130\,382$)
Sex														
Male	18 (55)	25 248 (57)	19 (66)	23 674 (60)	–	–	31 (100)	49 012 (100)	15 (65)	5724 (64)	31 (70)	6355 (54)	528 (73)	69 600 (53)
Female	15 (45)	18 854 (43)	10 (34)	15 788 (40)	21 (100)	47 321 (100)	–	–	8 (35)	3226 (36)	13 (30)	5428 (46)	200 (27)	60 782 (47)
Median age (interquartile range)	66 (51–81)	70 (53–87)	62 (51–73	71 (57–85)	51 (35–67)	58 (38–78)	63 (56–70)	69 (56–82)	58 (42–74)	66 (47–85)	52 (33–71)	65 (43–87)	56 (40–70)	70 (52–88)
Age group (years)														
<40	1 (3)	865 (2)	1 (3)	301 (1)	4 (19)	2950 (6)	0 (0)	14 (0)	2 (9)	474 (5)	8 (18)	1163 (10)	56 (8)	4398 (4)
40–49	4 (12)	2343 (5)	3 (10)	1324 (3)	5 (24)	8758 (18)	0 (0)	866 (2)	7 (30)	782 (9)	13 (30)	1152 (10)	153 (21)	9375 (7)
50–59	5 (15)	6281 (14)	6 (21)	5150 (13)	4 (19)	12 601 (27)	8 (26)	7348 (15)	6 (26)	1621 (18)	9 (20)	2120 (18)	226 (31)	18 563 (14)
60–69	9 (27)	11 514 (26)	12 (42)	11 355 (29)	6 (29)	10 431 (22)	20 (64)	18 049 (37)	6 (26)	2452 (27)	8 (18)	2896 (24)	220 (30)	31 354 (24)
≥70	14 (43)	23 099 (53)	7 (24)	21 332 (54)	2 (9)	12 581 (27)	3 (10)	22 735 (46)	2 (9)	3621 (41)	6 (14)	4452 (38)	73 (10)	66 692 (51)
Median time since transplantation, years	12.9 (0.3–36.5)	–	8.3 (0.1–27.2)	–	13.5 (4.3–36.7)	–	9.5 (0–28.1)	–	11 (1.8–23)	–	11.3 (5.5–28.4)	–	7.9 (0–34.4)	–
Deprivation index														
1—least deprived	5 (15)	7423 (17)	7 (24)	5081 (13)	1 (5)	8955 (19)	5 (16)	9043 (19)	3 (13)	1450 (17)	4 (9)	2030 (17)	124 (17)	26 039 (20)
2	4 (12)	5196 (12)	3 (10)	3916 (10)	6 (28)	5729 (12)	4 (13)	6148 (13)	3 (13)	1093 (12)	4 (9)	1503 (13)	84 (12)	15 854 (12)
3	6 (18)	6076 (14)	2 (7)	4964 (12)	3 (14)	6604 (14)	5 (16)	6987 (14)	2 (9)	1272 (14)	10 (23)	1678 (14)	97 (13)	17 987 (14)
4	3 (9)	7931 (18)	6 (21)	6678 (17)	5 (24)	8229 (17)	5 (16)	8926 (18)	4 (17)	1631 (18)	10 (23)	2108 (18)	122 (17)	22 568 (17)
5—most deprived	13 (40)	14 588 (33)	8 (28)	16 571 (42)	5 (24)	14 657 (31)	10 (32)	14 290 (29)	11 (48)	2956 (33)	14 (32)	3632 (31)	243 (33)	39 307 (30)
Missing	2 (6)	2888 (6)	3 (10)	2252 (6)	1 (5)	3147 (7)	2 (7)	3618 (7)	0 (0)	548 (6)	2 (4)	832 (7)	58 (8)	8627 (7)
Marital status														
Married	21 (64)	24 557 (56)	18 (62)	20 662 (52)	15 (71)	27 852 (59)	23 (74)	32 422 (66)	16 (70)	5277 (59)	24 (54)	6719 (57)	376 (51)	51 050 (39)
Single	3 (9)	7509 (17)	7 (24)	6175 (16)	3 (14)	7270 (15)	5 (16)	6659 (14)	6 (26)	1572 (18)	14 (32)	2309 (20)	99 (14)	14 415 (11)
Other	7 (21)	10 156 (23)	1 (4)	10 505 (27)	2 (10)	10 613 (23)	2 (7)	6439 (13)	1 (4)	1721 (19)	3 (7)	2285 (19)	45 (6)	20 926 (16)
Missing	2 (6)	1880 (4)	3 (10)	2120 (5)	1 (5)	1586 (3)	1 (3)	3492 (7)	0 (0)	380 (4)	3 (7)	470 (4)	208 (29)	43 991 (34)
Smoking status														
Never	10 (30)	17 148 (39)	3 (10)	3562 (9)	10 (48)	21 874 (46)	4 (13)	14 814 (30)	6 (26)	3079 (34)	14 (32)	4449 (38)	80 (11)	17 561 (14)
Ex-smoker	4 (12)	8031(18)	8 (28)	10 306 (26)	1 (5)	5422 (12)	5 (16)	8147 (17)	4 (17)	1671 (19)	5 (11)	1801 (15)	37 (5)	7100 (5)
Current	3 (9)	7090 (16)	11 (38)	19 175 (49)	4 (19)	8440 (18)	2 (6)	6903 (14)	2(9)	1840 (21)	9 (21)	2043 (17)	42 (6)	8343 (6)
Missing	16 (49)	11 833 (27)	7 (24)	6419 (16)	6 (28)	11 585 (24)	20 (65)	19 148 (39)	11 (48)	2360 (26)	16 (36)	3490 (30)	569 (78)	97 378 (75)
Grade[a]														
1	3 (9)	3122 (7)	0 (0)	1062 (3)	0 (0)	4617 (10)	3 (10)	3502 (7)	0 (0)	501 (6)	2 (4)	950 (8)	136 (19)	11 626 (9)
2	15 (46)	26 538 (60)	10 (35)	4894 (12)	11 (52)	19 786 (42)	23 (74)	25 685 (53)	8 (35)	1889 (21)	28 (64)	7219 (61)	123 (17)	10 650 (8)
3+	4 (12)	5722 (13)	3 (10)	9816 (25)	6 (29)	15 080 (32)	3 (10)	11 465 (23)	5 (22)	2210 (24)	0 (0)	4 (0)	13 (2)	2815 (2)
Unknown	11 (33)	8720 (20)	16 (55)	23 690 (60)	4 (19)	7838 (16)	2 (6)	8360 (17)	10 (43)	4350 (49)	14 (32)	3610 (31)	456 (62)	105 291 (81)
Stage														
I	5 (15)	6205 (14)	4 (14)	5732 (15)	5 (24)	13 658 (29)	1 (3)	423 (1)	12 (52)	2643 (30)	14 (32)	2831 (24)	–	–
II	9 (27)	11 787 (27)	2 (7)	2740 (7)	10 (48)	21 601 (46)	21 (68)	27 080 (55)	2 (9)	673 (8)	5 (11)	1913 (16)	–	–
III	4 (12)	11 153 (25)	9 (31)	9181 (23)	4 (19)	5817 (12)	5 (16)	5000 (10)	1 (4)	1540 (17)	7 (16)	1988 (17)	–	–
IV	5 (15)	9185 (21)	12 (41)	12 791 (32)	0 (0)	3280 (7)	3 (10)	5909 (12)	2 (9)	2180 (24)	10 (23)	2924 (25)	–	–
Unknown	10 (31)	5772 (13)	2 (7)	9018 (23)	2 (9)	2965 (6)	1 (3)	10 600 (22)	6 (26)	1914 (21)	8 (18)	2127 (18)	–	–
Surgery														
Yes	10 (30)	33 449 (76)	7 (24)	6085 (15)	19 (90)	39 943 (84)	4 (13)	15 716 (32)	19 (83)	5877 (66)	7 (16)	1382 (12)	656 (90)	112 850 (87)

Continued

Table 1. Continued

Type of cancer	Colorectal		Lung		Breast		Prostate		Renal		NHL		NMSC	
	Tx ($n = 33$)	Non-TX ($n = 44\,102$)	Tx ($n = 29$)	Non-Tx ($n = 39\,462$)	Tx ($n = 21$)	Non-Tx ($n = 47\,321$)	Tx ($n = 31$)	Non-Tx ($n = 49\,012$)	Tx ($n = 23$)	Non-Tx ($n = 8950$)	Tx ($n = 44$)	Non-Tx ($n = 11\,783$)	Tx ($n = 728$)	Non-Tx ($n = 130\,382$)
No	23 (70)	10 653 (24)	22 (76)	33 377 (85)	2 (10)	7378 (16)	27 (87)	33 296 (68)	4 (17)	3073 (34)	37 (84)	10 401 (88)	72 (10)	17 532 (13)
Radiotherapy														
Yes	7 (21)	6971 (16)	5 (17)	14 707 (37)	15 (71)	29 866 (63)	21 (68)	16 321 (33)	2 (9)	891 (10)	6 (14)	2223 (19)	12 (2)	6374 (5)
No	26 (79)	37 131 (84)	24 (83)	24 755 (63)	6 (29)	17 455 (37)	10 (32)	32 691 (67)	21 (91)	8059 (90)	38 (86)	9560 (81)	716 (98)	124 008 (95)
Chemotherapy														
Yes	7 (21)	16 533 (37)	5 (17)	10 542 (27)	10 (48)	22 603 (48)	1 (3)	1065 (2)	2 (9)	1144 (13)	29 (66)	7686 (65)	0	225 (1)
No	26 (79)	27 569 (63)	24 (83)	28 920 (73)	11 (52)	24 718 (52)	30 (97)	47 947 (98)	21 (91)	7806 (87)	15 (34)	4097 (35)	728 (100)	130 157 (99)
Median time to treatment, days														
Surgery	0	7	42	32	16	19	0	6	0	0	0	0	0	0
Radiotherapy	45	59	94	50	176	149	190	183	3	64	122	129	28	24
Chemotherapy	108	57	55	33	63	64	36	39	64	43	22	25	–	14
Status														
Alive	12 (36)	17 466 (40)	5 (17)	4872 (12)	13 (62)	31 376 (66)	20 (65)	30 725 (63)	11 (48)	4100 (46)	17 (39)	5945 (51)	470 (65)	90 578 (69)
Died cancer	13 (40)	19 441 (44)	21 (73)	30 898 (78)	4 (19)	10 656 (23)	2 (6)	9379 (19)	5 (22)	3406 (38)	15 (34)	4274 (36)	30 (4)	2102 (2)
Died other	8 (24)	7195 (16)	3 (10)	3692 (10)	4 (19)	5289 (11)	9 (29)	8908 (18)	7 (30)	1444 (16)	12 (27)	1564 (13)	228 (31)	37 702 (29)

[a]Cancer is staged by the TNM staging system. Cancer grading (1: well differentiated; 2: moderately differentiated; 3: poorly differentiated); cancer grading for NHL (1: T cell, 2: T cell, 3: null cell). Tx, transplant.

FIGURE 1: Cumulative incidence function (CIF) of all-cause deaths and cancer-related deaths, with 95% CIs, in renal transplant (Tx) recipients who developed cancer by years of follow-up after cancer diagnosis.

Adjusted for covariates, there was an increased risk of all-cause mortality in those who developed NMSC compared with the general population [hazard ratio (HR) = 3.06, 95% CI 2.66–3.52; $P < 0.001$], NHL (HR = 2.89, 95% CI 1.96–4.25; $P < 0.001$) and prostate cancer (HR = 4.32, 95% CI 2.39–7.82; $P < 0.001$), but no increase for colorectal, lung, breast or renal cancer (Figure 2).

Using competing risks regression to compare the transplant and non-transplant populations who developed cancer, adjusted for covariates, we found there was an increased risk of death from cancer in renal transplant recipients who developed NMSC (HR = 3.91, 95% CI 2.57–5.96; Table 2). There was no significantly increased risk of death from cancer in those who developed other invasive cancers (colorectal, lung, breast, prostate, renal and NHL; Figure 3).

Factors associated with increased all-cause mortality in Irish cancer patients included older age group, male sex, living in a more deprived area, non-married status, being a smoker and being diagnosed in an earlier era (Supplementary data, Table S1). Those with a higher TNM stage or histological grade at diagnosis had worse outcomes. Surgery was associated with improved survival in all forms of cancer, while radiotherapy was associated with a reduced risk of death in colorectal, lung, breast and prostate cancer, but a higher risk of death in NMSC (HR = 1.13, 95% CI 1.08–1.18) and renal cancer (HR = 1.49, 95% CI 1.37–1.63). Chemotherapy was associated with improved survival in colorectal, lung and NHL, but there was an increased hazard in patients with prostate cancer (HR = 1.33, 95% CI 1.24–1.43) and NMSC (HR = 1.57, 95% CI 1.29–1.90).

Cancer-related mortality demonstrated similar findings (Supplementary data, Table S2). Patients who were unmarried, in older age groups and with increased deprivation were at higher risk of death. Undergoing surgery was associated with improved survival; however, undergoing radiotherapy was associated with an increased risk of cancer-related death in NMSC, NHL and renal carcinoma, while undergoing chemotherapy

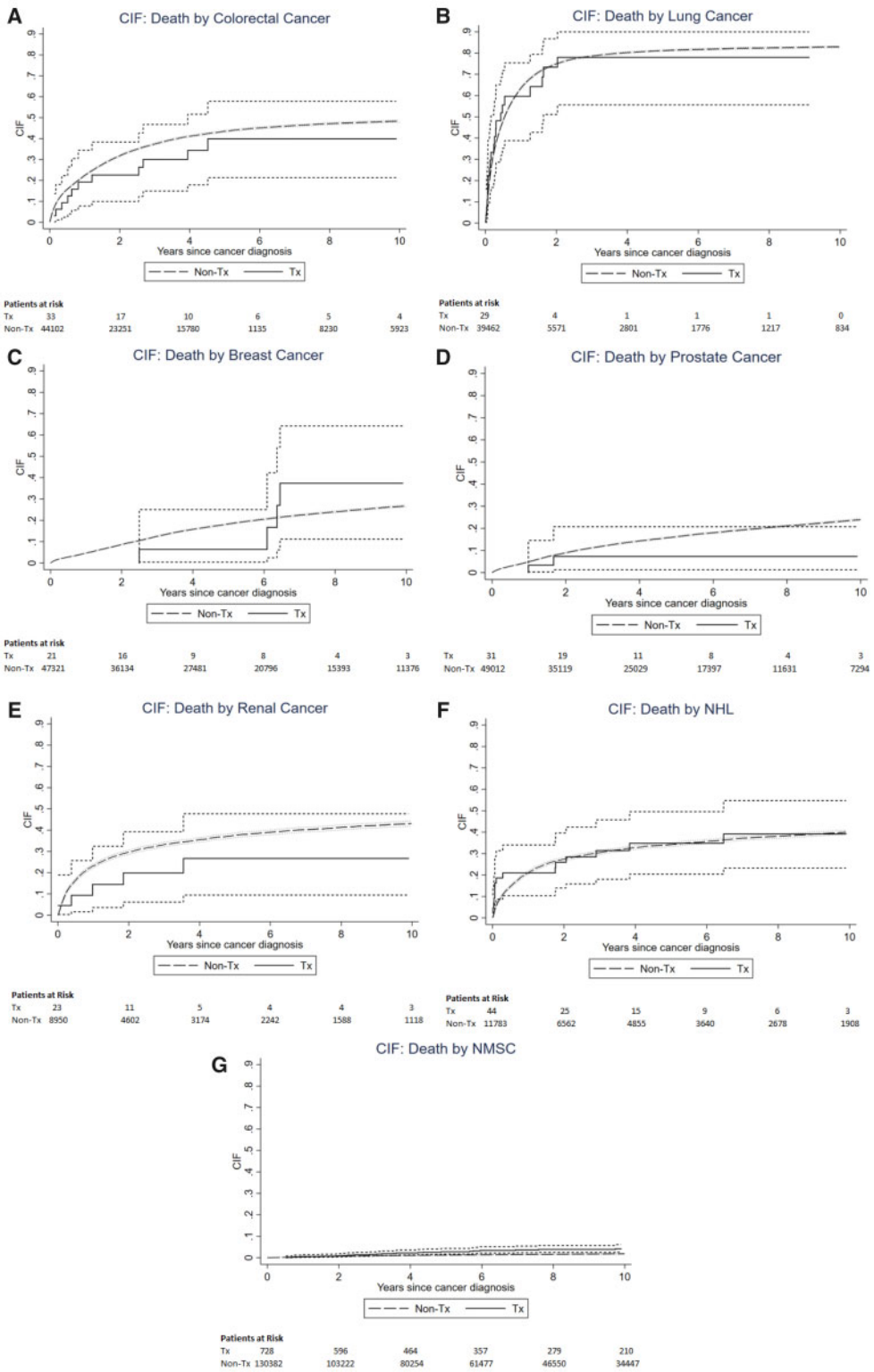

FIGURE 2: Cumulative incidence functions (CIF), with 95% CIs, for cancer-specific mortality in renal transplant (Tx) recipients compared with non-transplant recipients following development of: (**A**) colorectal, (**B**) lung, (**C**) breast, (**D**) prostate, (**E**) renal, (**F**) NHL and (**G**) NMSC.

was associated with an increased risk of death in NMSC, breast and prostate cancer.

SMR for all-cause and cancer-specific mortality was reported in Table 3. All-cause mortality rate and cancer-specific mortality rates were significantly higher in the transplant population than the general population for NMSC (all-cause mortality 2.09 and cancer-specific mortality 3.67) and NHL (all-cause mortality 2.59 and cancer-specific mortality 1.83).

The TVC for the variable of primary interest (whether the patient had a transplant or not) was not significant in any of the

Table 2. HRs, with 95% CIs, for all-cause and cancer-specific deaths for transplant recipients versus non-transplant recipients who developed cancer

Hazard Ratio	HR (95% CI)						
	Colorectal	Lung	Breast	Prostate	Renal	NHL	NMSC
All cause	0.91 (0.58–1.43)	1.25 (0.83–1.88)	1.91 (0.91–4.01)	4.32 (2.39–7.82)	1.46 (0.80–2.65)	2.89 (1.96–4.25)	3.06 (2.66–3.52)
Cancer specific	0.67 (0.32–1.40)	1.27 (0.86–1.88)	1.31 (0.59–2.89)	0.81 (0.19–3.41)	0.85 (0.36–1.99)	1.73 (0.97–3.07)	3.91 (2.57–5.96)

models. Sensitivity analyses (not included) were conducted including other covariates, which were found to have significant TVCs. However, including these variables in the models did not have any effect on the primary variable.

DISCUSSION

This is the first study to look at cancer survival in renal transplant recipients in an Irish population. It examines survival in those who developed NMSC, a population that has been excluded from the largest studies looking at survival in the SOT recipient population post-cancer.

With improving long-term recipient survival following kidney transplantation, cancer is becoming an increasingly important contributor to all-cause mortality [10]. In this retrospective registry study, we compared cancer survival in those who had received a renal transplant to the general population who developed similar cancers. We found no significant difference in cancer-specific mortality in colorectal, breast, prostate, lung or renal cancers, but did observe a significant difference in survival between renal transplant recipients and the general population in those that developed NMSC. When looking at SMR alone, all-cause and cancer-specific mortality ratio was also increased in NHL.

Several studies have shown that the rate of death from cancer in SOT is increased compared with the general population [11, 13]. A registry paper from Ontario showed that SMR is highest in children, but is higher than the general population in all ages. Data by Miao *et al.* from the Israel Penn Registry also showed that stage-specific survival was significantly lower in transplant recipients than those in the general population [14]. An Australian study showed that survival with a functioning graft at 10 years was only 40.6% in renal transplant recipients who developed cancer [15]. Another recent study showed that death from cancer in the transplant population occurs due to *de novo* cancers [16].

Our study highlights, once again, the serious implications of skin cancer in the transplant population. After adjusting for covariates, transplant recipients who developed NMSC were at significantly higher risk of dying from cancer than the general population, with a hazard ratio (HR) of 3.9. Transplant recipients who developed NMSC were also significantly younger, with a median age of 58.5 years (interquartile range: 40–72), compared with 67 years in the non-transplant population ($P < 0.0001$).

In transplant recipients, NMSC is significantly more likely to behave aggressively, spread more deeply and have more lymphatic invasion [17]. It occurs 10–30 years earlier than in the non-transplant population [18]. A study by Acuna *et al.* also described a significant increase in mortality among those who developed NMSC [11].

The incidence of NMSC has been linked to immunosuppression, not only in transplant but also in immunosuppressive states like HIV [19–21]. In its eighth edition, the American Joint Committee on Cancer TNM staging noted significant concerns about the impact of immunosuppression on skin cancer and the need to include it in staging classifications for skin cancer [22]. However, it cited a dearth of evidence for its ultimate decision to exclude immunosuppression from the staging classification. Our study adds to the existing body of literature regarding poor outcomes and increased risk of death in immunosuppressed patients who develop NMSC. It is vital that the importance of prevention is emphasized, that patients are educated in adequate skin protection and the avoidance of UV radiation, and that healthcare professionals are vigilant in screening for potential skin lesions at clinics. However, there is increasing evidence for the need for aggressive treatment of these lesions [19, 23].

The majority of NMSC recurrences are locoregional [24, 25]. Recent evidence has shown little benefit of systemic adjuvant chemotherapy in those that develop NMSC [26]. This is reflected in our data where patients with NMSC who underwent chemotherapy had worse all-cause mortality (HR = 1.57, 95% CI 1.29–1.90) and cancer-specific mortality (HR = 4.84, 95% CI 3.26–7.18) than those that did not. Of note, however, only 225 patients (0.17%) in the general population who developed NMSC went on to have chemotherapy. Therefore, those who did receive chemotherapy may have had more severe disease and may not be representative of the general population. Undergoing surgery was associated with a better outcome in all cancers. This may be a surrogate marker for earlier stage or more treatable disease. Nevertheless, the worse outcomes in immunosuppressed and transplant patients who develop NMSC need to be incorporated in future staging guidelines to adequately reflect the advanced nature of their disease process and increased hazard when compared with the general population.

A study drawn from the Penn Israel Transplant Tumor Registry looked at 245 SOT recipients with colon cancer, 246 with non-small cell lung cancer (NSCLC) and 295 with breast cancer. It found that disease-specific, stage-stratified survival was worse in SOT recipients in all stages of colon cancer, but among breast cancer patients showed only a difference in survival among Stage III cases and in NSCLC showed only a

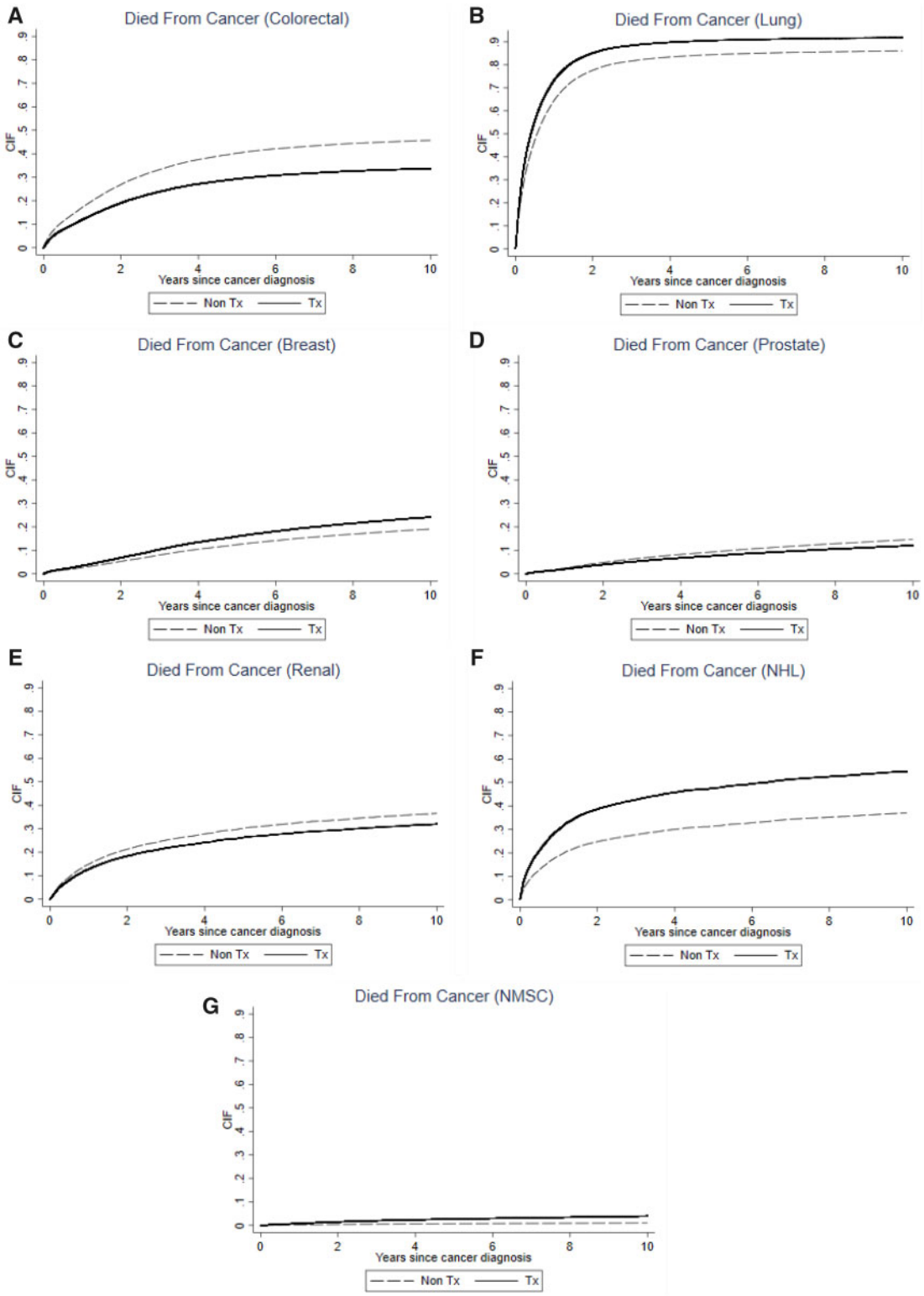

FIGURE 3: Adjusted Cox proportional hazards for cancer-specific mortality in renal transplant (Tx) recipients compared with non-transplant recipients following development of (**A**) colorectal, (**B**) lung, (**C**) breast, (**D**) prostate, (**E**) renal, (**F**) NHL and (**G**) NMSC. CIF, cumulative incidence function.

survival difference in Stage II cases. It did not examine outcomes in NHL. The largest study to date, by D'Arcy *et al.* [13], showed an increased hazard of death among 950 SOT recipients who developed breast cancer and 850 SOT recipients who developed colorectal cancer. Neither study looked at mortality among those who developed NMSC. Other recent studies have demonstrated an increased risk of death in breast, lung, colorectal and prostate cancer.

A strength of our study is our inclusion of NMSC. It will be useful in counselling transplant recipients in Ireland as well as

Table 3. All-cause and cancer-specific SMRs, with 95% CIs, for renal transplant recipients versus non-transplant recipients who developed cancer

SMR	SMR (95% CI)							
	Colorectal	Lung	Breast	Prostate	Renal	NHL	NMSC	All cancers excluding NMSC
All cause	1.28 (0.79–1.96)	1.2 (0.77–1.79)	1.66 (0.71–3.27)	1.76 (0.88–3.14)	1.75 (0.9–3.06)	2.59 (1.71–3.77)	2.09 (1.85–2.36)	1.71 (1.47–1.98)
Cancer specific	1.04 (0.55–1.78)	1.18 (0.73–1.80)	1.02 (0.28–2.59)	0.62 (0.07–2.23)	0.93 (0.29–2.16)	1.83 (1.02–3.02)	3.67 (2.48–5.24)	1.35 (1.17–1.62)

forming the basis for further study of post-transplant cancer epidemiology. This was a population-based study and may be more applicable to a northern European population, as previous studies have been conducted in North American or Australian populations.

Completeness of case ascertainment at NCRI for all invasive cancers, excluding NMSC, was estimated at 97% within 5 years of diagnosis [23]. It does not have an estimate of completeness for NMSC. A potential limitation of this study is that because of the close monitoring of transplant patients, completeness of case ascertainment for NMSC is higher in the transplant population than in the general population. However, as death due to cancer is derived from death certificates, this would mean the HR reported in this study underestimates the true increased risk, if many NMSCs in the general population go unregistered.

Another limitation of this study is a potential immortal time bias, as treatment variables are not determined at the date of diagnosis. This could result in receipt of treatment being associated with better outcomes, as patients must at least survive until the time treatment is received. The impact of this is likely to be limited in respect of surgery, where median time to receipt ranged between 0 and 42 days for all sites examined. The potential impact of immortal time bias was greater for radiotherapy (median time to treatment 3–190 days, depending on site) and chemotherapy (median time to treatment, 14–108 days, depending on site).

Our data did not show an increased risk of death due to cancer in other invasive cancers. The small size of the transplant population is a limitation of this study that meant it had low power to detect differences.

Kidney transplant recipients who develop NMSC are at significantly enhanced risk of death compared with the general population, and they should be counselled, screened and treated appropriately in light of this information.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

Conception of the article and writing of manuscript were done by S.L.M.; data analysis and manuscript preparation were carried out by E.O.L.; paper preparation was done by A.M.D.B.; provision of data was done by S.D., P.O.K. and Y.W.; manuscript preparation and analysis, conception and manuscript preparation were performed by D.J.S.; and conception and manuscript preparation were done by P.J.C.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare. The results presented in this article have not been published previously in whole or part except in abstract form.

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