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Cancer Incidence Among Canadian Kidney Transplant Recipients

P. J. Villeneuve[a,*], D. E. Schaubel[b], S. S. Fenton[c], F. A. Shepherd[d], Y. Jiang[e] and Y. Mao[e]

[a] *Department of Public Health Sciences, University of Toronto, Toronto, ON, Canada*
[b] *Department of Biostatistics, University of Michigan, Ann Arbor, MI*
[c] *Division of Nephrology, Toronto General Hospital, Toronto, Ontario, Canada*
[d] *Princess Margaret Hospital, Toronto, Ontario, Canada*
[e] *Center for Chronic Disease Prevention and Control, Public Health Agency of Canada, Ottawa, ON, Canada*
* *Corresponding author: Dr. Paul Villeneuve, paul.villeneuve@utoronto.ca*

A number of studies have observed increased cancer incidence rates among individuals who have received renal transplants. Generally, however, these studies have been limited by relatively small sample sizes, short follow-up intervals or focused on only one cancer site. We conducted a nationwide population-based study of 11,155 patients who underwent kidney transplantation between 1981 and 1998. Incident cancers were identified up to December 31, 1999, through record linkage to the Canadian Cancer Registry. Patterns of cancer incidence in the cohort were compared to the Canadian general population using standardized incidence ratios (SIRs). We examined variations in risk according time since transplantation, year of transplantation and age at transplantation. In our patient population, we observed a total of 778 incident cancers versus 313.2 expected (SIR = 2.5, 95% CI = 2.3–2.7). Site-specific SIRs were highest for cancer of the lip (SIR = 31.3, 95% CI = 23.5–40.8), non-Hodgkin's lymphoma (NHL) (SIR = 8.8, 95% CI = 7.4–10.5), and kidney cancer (SIR = 7.3, 95% CI = 5.7–9.2). SIRs for NHL and cancer of the lip and kidney were highest and among transplant patients. This study confirms previous findings of increased risks of posttransplant cancer. Our findings underscore the need for increased vigilance among kidney transplant recipients for cancers at sites where there are no population-based screening programs in place.

Abbreviations: CCR, Canadian Cancer Registry; C.I., Confidence Interval; CMDB, Canadian Mortality Database; CORR, Canadian Organ Replacement Registry; ESRD, End-Stage Renal Disease; NHL, non-Hodgkin's Lymphoma; SIR, Standardized Incidence Ratio.

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Introduction

The prevalence of end-stage renal disease (ESRD) has risen dramatically in Canada over the past two decades (1,2). This has been accompanied by a concomitant increase of renal transplantation (3), the preferred treatment modality. Compared to dialysis, transplantation has been shown to improve both survival and quality of life (4,5). Nonetheless, transplantation is associated with increased risks for several adverse health events including cancer. In particular, the use of immunosuppressive drugs, essential for preventing organ rejection in transplant recipients has been implicated in the development of cancer (6,7).

While several epidemiologic studies have consistently found increased cancer incidence rates among transplant recipients (8–19), most are subject to several important limitations. Many have been based on a single or small number of centers and therefore it is difficult to describe cancer incidence rates in the reference population that gave rise to the cases. The use of general population rates in such studies may also be biased as the center's referral patterns, or systematic differences in sociodemographic characteristics between the center and the reference population, may lead to noncomparability. In recent years, a number of registry-based studies have provided important insights on cancer risk in kidney transplant recipients (8,13,17,20,21). While such studies have made use of national cancer registries, for the most part, the number of patients has been relatively small with limited follow-up. Therefore, they have had limited ability to examine the long-term probability of developing cancer and limited statistical power to characterize risks for rarer forms of cancer. The largest study conducted to date, consisted of 13,077 patients with 110,395 persons years of follow-up who received a kidney transplant in Australia or New Zealand between 1980 and 2003 (20); a more detailed analyses of a subset of these patients has recently been published (22). Our cohort shares many common features with their patient population including: a population-based design, lengthy follow-up interval and a relatively large sample size.

In this investigation, we report on patterns of cancer incidence among 11,155 individuals who received a renal

transplant between 1981 and 1998 using a national Canadian organ transplantation registry. This represents one of the largest cohorts of renal transplant patients assembled to date, with follow-up for some subjects extending up to 19 years. These features permitted us to characterize cancer risk according to the time since transplantation, age at transplantation and calendar period.

Material and Methods

Study population

The cohort was constructed with transplant recipients identified by using the Canadian Organ Replacement Register database (CORR). This database is a national organ failure registry that contains information for patients who initiated renal replacement therapy (RRT) in Canada from January 1, 1981. Patients who were on RRT prior to January 1, 1981, were not registered and thus even though they may have received a transplant after 1981, they are not included in this analysis. The cohort used for this analysis was comprised of all patients who initiated RRT from January 1981, to December 31, 1998, and who received a first kidney transplant during that time. These data were provided to CORR by all 27 kidney transplant programs in Canada. The data collected included: date of birth, sex, province of residence, race/ethnicity, primary kidney disease, and since 1988 a number of co-morbid medical conditions present at the time of RRT, and initial RRT modality. The renal programs report on an annual basis changes in dialysis modality, new kidney transplants, kidney transplant failures and deaths. Comparisons between data submitted from hospitals, and provincial Organ Procurement Organizations provide an indication of the completeness of the CORR database. Analyses of these data suggest that there is minimal (<4%) underreporting of kidney transplants within CORR (23). In addition, CORR performs active follow-up surveillance of these patients and approximately 1% of these patients have been lost to follow-up. A more detailed description of the CORR registry has been published elsewhere (23,24).

Initially, we identified a total of 11,391 individuals who had received a renal transplant between 1981 and 1998. From this patient population, we excluded 233 patients who were diagnosed with cancer (excluding nonmelanoma skin cancer) before transplantation. Patients were followed from the date of the first recorded renal transplant. Three individuals were excluded as we were unable to determine their sex. There were a total of 11,155 patients that remained. Consistent with previous analyses we also excluded follow-up interval within the first 30 days after transplant (8). A total of 122 patients died or were diagnosed with cancer during this period. Therefore, our risk estimates are based on 11,033 patients.

Ascertainment of health outcomes

The mortality experience of the cohort was determined by linking the cohort to the Canadian Mortality database using a probabilistic procedure referred to as the generalized record linkage system (GRLS). GRLS compares common fields in the two files to be linked, assigns weights to the resulting links and calculates a total weight. Links with a sufficiently high weight are accepted as a match. The Canadian Mortality Database (CMDB) maintained by Statistics Canada, contains death data for all Canadian residents from 1950 onwards. It is possible that some deaths may have been missed because patients died outside the country. For out of country deaths, only those that occur in the United States are reported, and Canada currently receives abstracted death data from approximately 20 states (25). Previous research suggests that the number of deaths that would be missed would be quite small given the personal identifying information available for this cohort (26,27). Both these studies found that the probability of correctly identifying deceased and alive subjects from record linkage to the CMDB was 98% and close to 100%, respectively. While mortality outcomes were not the focus of our investigation, date of death information was used to determine the last day of follow so that the person–years could be determined accurately. Where no death link was found, we assumed that the person was alive at the end of the study interval (December 31, 1999).

In Canada, each province and territory has a Cancer Act and a legislated responsibility for cancer collection and control, and therefore the reporting of primary malignant cancers is in theory complete. Incidence data supplied by the cancer registries are compiled into the Canadian Cancer Registry (CCR) (28), which is maintained by the Health Statistics Division at Statistics Canada. The CCR is a patient-based system that contains information on all Canadian residents, dead or alive, who have been diagnosed with cancer, excluding squamous and basal cell skin cancer. It has been estimated that the CCR captures at least 95% of all incident cancer cases in Canada (29). For the purposes of these analyses, incident cases of cancer diagnosed between 1969 and 1999 were identified through record linkage of the personal identifying information contained in the CORR patient records to the CCR. We linked the cohort to cancer incidence data before transplantation to exclude from analysis those individuals previously diagnosed with cancer. As with the mortality linkage, patients for whom no link to the CCR was found, were assumed to be cancer-free at the last date of follow-up (i.e. date of death or December 31, 1999).

Probabilistic record linkage was done using personal identifying information that included surname, surname at birth, given names, birth date, social insurance numbers and place of residence. Unfortunately, there has been no evaluation of the accuracy of ascertaining incident cancers by linking data to the CCR. However, given the high quality and completeness in the CCR, and the similarity in record linkage methodology used, it is reasonable to assume that record linkage to the CCR will be at least as accurate as record linkage to the CMDB. Nonetheless, it is important to note that some incident cases may have been missed by an inability to identify cases that might have occurred among patients who moved outside of Canada. However, as mentioned previously, it has been estimated that fewer than 5% of cancers would be missed, and therefore, the overall bias on our presented SIRs should be minimal.

Statistical analysis

To exclude cases of cancer prevalent at the time of transplantation, we adopted the same methodology as Adami et al. (8) and excluded the 30-day period immediately after transplantation from our follow-up. Follow-up extended until the earliest of: (i) date of cancer diagnosis, (ii) date of death or (iii) December 31, 1999. The DATAB module in the Epicure software program was used to tabulate these person–years (30).

Person–years of follow-up and incident cases of cancer were tabulated across strata defined by: attained age (18–24, 25–29, 30–34,..., 75–79, ≥80), calendar period of follow-up (1981–1984, 1985–1988, 1989–1993, 1994–1996, 1997–1999), year of transplantation (1981–1984, 1985–1988, 1989–1993, 1994–1998), age at transplantation (<35, 35–44 and ≥45), sex (male, female), and time since transplantation (>30 days to <1 year, 1 to <5, 5 to <10, ≥10 years). Attained age, calendar period and time since surgery were time-dependent variables as their values changed over follow-up.

Cancer risk was evaluated by using the method of indirect standardization to calculate the standardized incidence ratio (SIR), which is the ratio of the observed-to-expected number of incident cancers. The 95% confidence intervals were calculated by assuming that the observed cancers followed a Poisson distribution using formulae detailed elsewhere (31). Stratified analyses were conducted to examine variations in the SIR across categories of

the age at transplantation, sex, length of follow-up and year of transplantation.

Finally, we applied competing risk survival analysis methods to estimate the cumulative incidence of developing certain cancers by time since transplantation. This method allows for the fact that persons who die or develop another form of cancer are no longer at risk of developing the index cancer. This differs from the standard cumulative incidence estimated by the Kaplan Meier, which would introduce bias as it assumes that those who die remain at risk in the future (32). Our estimates of cumulative incidence are based on formulae presented by Gooley et al. (33).

Results

Between January 1, 1981 and December 31, 1998, a total of 11,391 kidney transplants among patients initiating RRT during that period were identified from the CORR database. After excluding individuals who were diagnosed with cancer prior to transplantation, as well as those for whom sex could not be ascertained, our analysis file consisted of 11,155 subjects who had accrued 81,237 person–years of follow-up. A larger proportion of renal transplantations were performed in males (63.2%) than in their female counterparts (Table 1). Nearly half of all transplants occurred among individuals between the ages of 30 and 50. Of note, 12.4% of all transplantations occurred before cyclosporine was widely used in transplantation surgeries (1985).

Patterns of cancer incidence among renal transplant patients were compared to the Canadian population (Table 2). Overall, after applying age–sex and calendar-specific incidence rates to the tabulated person–years of follow-up, the risk of cancer among transplant recipients was 2.5 times higher (95% C.I. = 2.3–2.7) than the general Canadian population. SIRs were highest for cancer of the lip (SIR = 31.3), non-Hodgkin's lymphoma (SIR = 8.8), and kidney cancer (SIR = 7.3). Greater than twofold excesses that were statistically significant were also noted for the following cancer sites: head and neck, stomach, bladder, leukemia, gallbladder, larynx, lung, connective tissue, Hodgkin's disease, vulva, multiple myeloma and thyroid. There were no site-specific cancer SIRs that were less than unity.

Table 1: Characteristics of 11,155 patients* who received a renal transplant, Canadian Organ Replacement Registry, 1981 and 1998

Characteristic	Number of patients	Percentage	Person–years of follow-up†	Percentage
Age at surgery (in years)				
<10	295	2.6	2450.9	3.0
10 < 20	696	6.2	6266.8	7.7
20 < 30	1697	15.2	15,377.8	18.9
30 < 40	2568	23.0	19,892.4	24.5
40 < 50	2581	23.1	18,131.5	22.3
50 < 60	2105	18.9	13,167.5	16.2
60 < 70	1072	9.6	5320.3	6.5
≥70	141	1.3	630.1	0.8
Sex				
Male	7055	63.2	50,604.0	62.3
Female	4100	36.8	30,633.3	37.7
Year of surgery				
1981–1984	1387	12.4	16,993.3	20.9
1985–1988	2642	23.7	26,460.4	32.6
1989–1993	3646	32.7	25,843.4	31.8
1993–1998	3480	31.2	11,940.2	14.7
Total	11,155	100.0	81,237.3	100.0

*Based on characteristics of patients at the time of their first transplant and excludes those individuals who had a previous diagnosis of cancer (excluding nonmelanoma skin cancer) at the time of transplantation.
†Person–years of follow-up calculated from 30 days after transplantation until the earliest of death, cancer diagnosis or December 31, 1999.

In Table 3, we present findings from our stratified SIR analysis by: time since transplantation, year of transplantation, sex and age at transplantation. The SIRs were inversely related to age at transplantation for all cancers, NHL, lip and kidney cancer. For NHL, the SIR was highest in the 30–<365 day posttransplant time interval (SIR = 27.2), but remained significantly increased for the 1–<5, 5–<10 and ≥10 year posttransplant intervals. For kidney cancer, the decrease in the SIR (i.e. as follow-up time increased) was much less pronounced; the same was observed for all cancer sites (combined). Interestingly, for lip cancer, the smallest SIR occurred in the 30–365 posttransplant interval. For each of NHL, lip cancer, kidney cancer and all sites combined, the SIR was significantly increased even in the ≥10 year posttransplant interval. For NHL, the SIRS were highest in more recent calendar periods. SIRs were generally higher among males.

The cumulative incidence of cancer and death among renal transplant patients, by time since transplantation, is presented in Figure 1. After 17 years of follow-up, the cumulative incidence of cancer and death among the transplantation patients was approximately 12% and 38%, respectively. The cumulative incidence estimates for other cancer sites for which high SIRs were observed (non-Hodgkin's lymphoma, kidney cancer, cancer of the lip) are illustrated in Figure 2. As described earlier, these estimates are adjusted for the competing risks of death and diagnoses for other cancers.

Discussion

This investigation provides additional information about the long-term risk of developing cancer following kidney transplantation. The study features a nationwide population-based sample of over 11,000 kidney transplant patients who were followed for up to 19 years. The size of this cohort is slightly less than the patient population of 13,077 in Australia and New Zealand (20), and nearly double that of the next largest cohort for which similar data have been published (8). Increased sample size and length of follow-up lead to more precise SIR estimates and an opportunity to examine less prevalent forms of cancer (e.g. oral). We explicitly estimate the SIR by time since transplantation, which allowed us to characterize separate the short- and long-term risks of developing cancer among transplant recipients.

Table 2: Standardized incidence ratios (SIRs)* for selected cancers among patients undergoing renal transplantation between 1981 and 1998, Canadian Organ Replacement Registry

Cancer site	ICD-9	Observed cases	Expected cases	SIR	95% C.I.
All cancers		778	313.3	2.5	(2.3, 2.7)
Oral	140–149	81	10.5	7.7	(6.1, 9.6)
Lip	140	54	1.7	31.3	(23.5, 40.8)
Head and neck	141–149	27	8.8	3.1	(2.0, 4.5)
Esophagus	150	5	3.2	1.5	(0.5, 3.6)
Stomach	151	15	7.2	2.1	(1.2, 3.4)
Colorectal	153–154	51	37.8	1.4	(1.0, 1.8)
Liver	155	5	2.7	1.8	(0.6, 4.3)
Gallbladder	156	7	1.7	4.1	(1.7, 8.5)
Pancreas	157	7	6.5	1.1	(0.4, 2.2)
Larynx	161	8	4.6	1.7	(0.7, 3.4)
Lung	162	108	51.5	2.1	(1.7, 2.5)
Connective tissue	171	10	2.1	4.8	(2.3, 8.8)
Malignant melanoma	172	20	10.5	1.9	(1.2, 3.0)
Bladder	188	24	12.1	2.0	(1.3, 3.0)
Kidney	189	71	9.7	7.3	(5.7, 9.2)
Nervous system	191,192	8	6.4	1.3	(0.5, 2.5)
Thyroid	193	23	4.6	5.0	(3.1, 7.4)
Non-Hodgkin's lymphoma	200,202	125	14.1	8.8	(7.4, 10.5)
Hodgkin's disease	201	9	2.5	3.6	(1.7, 6.9)
Multiple myeloma	203	13	3.4	3.9	(2.1, 6.6)
Leukemia	204–208	17	7.5	2.3	(1.3, 3.6)
Male cancers					
Prostate	185	37	40.5	0.9	(0.6, 1.3)
Female cancers					
Breast	174	52	39.6	1.3	(1.0, 1.7)
Uterus	179,182	6	6.7	0.9	(0.3, 2.0)
Cervix	180	6	3.9	1.6	(0.6, 3.4)
Ovary	183	7	4.7	1.5	(0.6, 3.0)
Vulva	184.1–184.4	3	0.5	5.5	(1.1, 16.0)

*Individuals were followed up from 30 days after the date of their first renal transplant until the earliest date associated with diagnosis of an incident cancer, death or December 31, 1999.

Overall, we found that renal transplant patients had cancer incidence rates that were two and a half times higher than rates observed in the Canadian population. As previously mentioned, other studies of kidney transplant patients have reported SIR estimates. The lower SIR found in our study is due in part from our exclusion of nonmelanoma skin cancers. Excesses of these cancers, including Kaposi's sarcoma have been widely reported among transplant patients (8,34,35). Indeed, the removal of nonmelanoma skin cancers in the Swedish cohort yields an SIR of 2.5 (95% CI = 2.2, 2.7), an estimate identical to our own. Unfortunately, we were unable to examine nonmelanoma skin cancers in our cohort as Canadian cancer registries do not consistently record nonmelanoma skin cancers. Registration is difficult because these cancers occur relatively frequently, and they are often treated successfully without requiring hospitalization. As a result, when comparing to the general population rates it would be difficult to delineate between excesses in nonmelanoma skin cancer rates in our transplant patients that would be attributable to treatment verses excesses due to increased surveillance of this patient population.

While consistency in SIRs across study populations is a useful means to identify cancer sites for which there is an excess, the interpretation of SIRs between study populations should be done cautiously. The estimation of the SIR is based on the age and sex distribution of the cohort under study, and therefore, even if the same population-based external rates are used, comparing SIRs between populations amounts to comparing risk measures that have different standards (36). Indeed, comparisons of SIRS between groups in the same cohort should also be interpreted cautiously if these groups have different age distributions. There were differences in the age distribution among kidney transplant patients between cohorts. For example, our cohort was comprised of a greater proportions of subjects who were <40 years old (50%) than the Swedish cohort (38%) (8) and the Australian and New Zealand cohort (22). While the bias that may result from comparing SIRs between study populations has led some to advocate making comparisons using the ratio two directly standardized rates, differences between the two methods are usually negligible (37).

Table 3: Standardized incidence ratios (SIRs) for selected cancer sites among those who received a kidney transplant, according by age at surgery, period of surgery, follow-up interval and sex

	All cancers				Non-Hodgkin's lymphoma				Lip cancer				Kidney cancer			
Characteristic	O	E	SIR and 95% C		O	E	SIR and 95% CI		O	E	SIR and 95% CI		O	E	SIR and 95% CI	
Follow-up interval																
30 d < 1 year	103	34.7	3.0	(2.4, 3.6)	46	1.6	27.2	(19.7, 36.6)	3	0.2	13.2	(2.6, 38.4)	9	1.1	8.2	(3.8, 15.6)
1 < 5 years	312	130.4	2.4	(2.1, 2.7)	34	5.9	5.8	(4.0, 8.1)	18	0.8	23.3	(13.8, 36.9)	31	4.1	7.6	(5.2, 10.8)
5 < 10 years	268	102.8	2.6	(2.3, 2.9)	33	4.6	7.2	(4.9, 10.1)	26	0.5	49.4	(32.2, 72.3)	22	3.2	7.0	(4.4, 10.5)
≥10 years	95	45.4	2.1	(1.7, 2.6)	12	2.1	5.8	(3.0, 10.1)	7	0.2	35.3	(14.1, 72.7)	9	1.4	6.5	(3.0, 12.3)
Transplantation date																
1981–1984	127	51.2	2.5	(2.1, 3.0)	10	2.4	4.2	(2.0, 7.7)	13	0.3	37.5	(19.9, 64.1)	11	1.6	6.9	(3.5, 12.3)
1985–1988	227	104.7	2.2	(1.9, 2.5)	39	4.6	8.5	(6.0, 11.6)	17	0.6	27.7	(16.1, 44.3)	16	3.2	4.9	(2.8, 8.0)
1989–1993	285	109.7	2.6	(2.3, 2.9)	46	4.9	9.4	(6.9, 12.6)	21	0.6	37.6	(23.3, 57.5)	26	3.4	7.7	(5.1, 11.3)
1994–1998	139	47.7	2.9	(2.4, 3.4)	30	2.3	8.9	(5.4, 13.7)	3	0.2	14.4	(2.9, 42.0)	18	1.5	11.9	(7.0, 18.8)
Sex																
Males	519	201.1	2.6	(2.4,2.8)	83	10.0	8.3	(6.6, 10.3)	43	1.6	27.1	(19.6, 36.5)	48	7.4	6.5	(4.8, 8.6)
Females	259	112.2	2.3	(2.0,2.6)	42	4.2	10.1	(7.3, 13.6)	11	0.1	77.9	(38.8, 139.2	23	2.3	10.0	(6.3, 15.0)
Age at transplantation																
<30	106	12.5	8.5	(6.9, 10.3)	42	1.0	41.9	(30.2, 56.6)	7	0.1	130.1	(52.1, 268.1)	10	0.3	40.0	(19.1, 73.6
30 < 45	191	57.4	3.3	(2.9, 3.8)	35	3.6	9.7	(6.7, 13.4)	18	0.3	56.3	33.4, 89.0)	22	2.0	10.9	(6.8, 16.4)
45 < 60	315	145.1	2.2	(1.9, 2.4)	34	6.2	5.5	(3.8, 7.6)	23	0.8	28.6	(18.1, 42.9)	28	4.8	5.9	(3.9, 8.5)
≥60	166	98.4	1.7	(1.4, 2.0)	14	3.3	4.3	(2.3, 7.1)	6	0.6	10.9	(4.0, 23.7)	11	2.7	4.1	(2.1, 7.4)
Total	778	313.3	2.5	(2.3, 2.7)	125	14.1	8.8	(7.4, 10.5)	54	1.7	31.3	(23.5, 40.8)	71	9.7	7.3	(5.7, 9.2)

O = Observed number of incidence cancer cases; E = Expected number of incidence cancer cases based on age-sex-calendar specific rates for Canada.

Few studies have reported cancer risk by posttransplant time interval. Although Adami et al. (8) reported risk estimates by time since transplant, such estimates pertained to comparisons within the transplant population where the period 30 days to <1 year formed the referent category. They found a higher risk of NHL among patients during the first year posttransplant, while no statistically significant differences were found for all cancer sites (combined), lip cancer and nonmelanoma skin cancer. The use of internal cohort comparisons to examine variations in risk by time since transplantation may be biased as some incident cancers may have been present at the time of transplantation. Detection of these cancers posttransplantation may be due to increased surveillance. While Adami and colleagues did not include incident cancers that were identified during the 30 days that followed transplantation, the definition of a suitable follow-up interval so as to exclude cancers present at the time of transplantation is not straightforward. As a result, comparisons of cancer risk by time since transplantation may be biased as individuals with preexisting cancer at the time of transplantation would be included in the referent group.

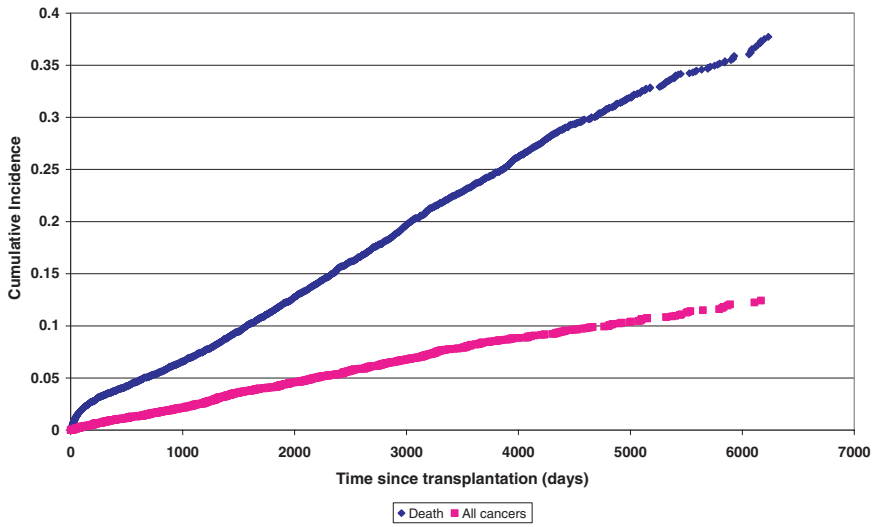

Figure 1: Cumulative incidence of death and cancer among renal transplant patients, by time since transplantation.

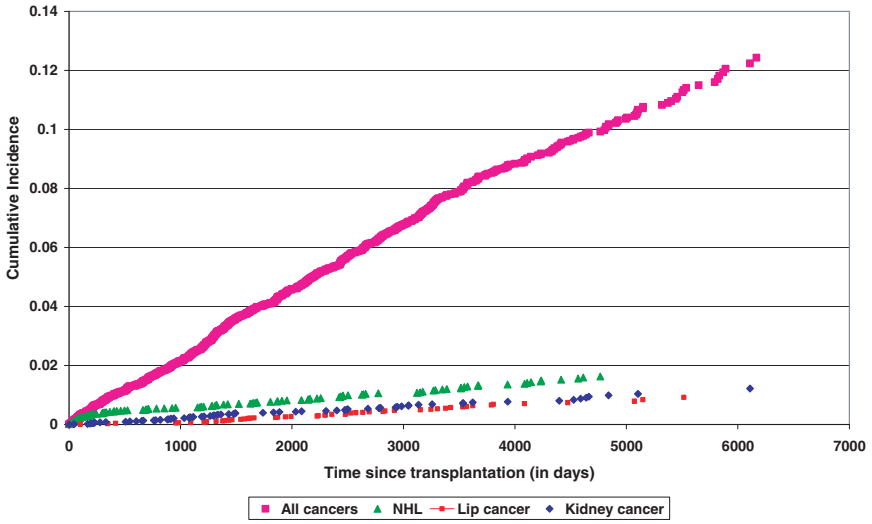

Figure 2: Cumulative incidence of all cancers, lip cancer, NHL and kidney cancer, by time since transplantation.

Stratified analysis, by time since transplantation using the SIR method, provides an alternative to charactering cancer risk by length of follow-up. Our analysis along these lines revealed that even during the 10+ year post-transplant interval, incidence was significantly increased for kidney cancer (SIR = 6.5), NHL (5.8) and lip cancer (SIR = 35.3), while a twofold increase was observed for all cancer sites combined (SIR = 2.1). Recently, Vadjic et al. (22) reported the highest SIRs occurring among kidney transplant patients after 10 years of follow-up. Unfortunately, no cancer site-specific data were presented in their paper.

Our findings by year of transplantation provide some clues about the effects of immunosuppression on cancer risk. Cyclosporine, which has been widely used since the mid-1980s when it was substituted for azathioprine, though many centers used triple therapy with Prednisone, Cyclosporin and Azathoprine, which has been associated with an increase in the incidence of malignant lymphoma, Kaposi's sarcoma and renal cancer (38). While immunosuppressive treatment data were not available on an individual level in our cohort, we did find increased SIRs for NHL and kidney cancer in the more recent time periods. This corresponds to the time that cyclosporine was more widely used to control organ rejection among kidney transplant recipients. Tacrolimus and Mycophenolate mofetil were not used in Canada to any extent until early to mid 1990s and so would have little impact on patterns of cancer incidence in our cohort.

Higher SIRs were observed among younger transplant patients for each of four cancer sites examined (lip, NHL, kidney and all cancers). This result is consistent with the findings in the Swedish cohort (8). This higher excess is due to much smaller background incidence rates observed among younger individuals.

In the present study, losses to follow-up were minimized with respect to residential mobility by linking the cohort to national cancer incidence data collected by all provincial registries, and to the Canadian Mortality Database. As described in detail earlier, cancer registration in Canada is near complete (>95%) through the cooperation of the provincial cancer registries, and the reporting of deaths is mandatory; therefore, few such events occurring in Canada would have been missed. The ability to link the cohort to these databases was excellent, given the detailed personal identifying information available. Given the reliance of cohort members on medical services in Canada, few individuals would be expected to have moved outside the country, and therefore, our observed number of incident cases is unlikely to be unduly affected from underascertainment due to residential mobility.

The clinical practice guidelines committee of the American Society of Transplantation has published a comprehensive set of guidelines for outpatient renal transplant follow-up (39). These guidelines outline in detail the recommended approach for the prevention of disease and complications from renal transplantation, including cancer surveillance. We strongly recommend that all kidney transplant programs have educational programs on the early detection of cancer for their transplant recipients. Ideally such information would be delivered during the transplant work up process, with reinforcement on a regular and recurring basis during posttransplant follow-up. Continuing medical education programs about cancer awareness are also advocated for not only transplant MDs, and nurses working in transplant clinics, but also primary care physicians that continue to see these patients on a regular basis. The particular focus of these educational efforts should be on first, the importance of applying meticulously the guidelines for cancer screening applicable to the general population. In addition those cancers, which typically occur at a much younger age among transplant recipients and for which there are no

recommended screening programs should be highlighted. The high SIRs observed among those who received a kidney transplant before the age of 30 underscore the need for surveillance in this group. In this patient population, the overall cancer SIR population was 8.5, and marked excesses in risk for cancers of the lip (SIR = 130.1), NHL (SIR = 41.9) and kidney cancer (SIR = 40.0) warrant particular concern.

In summary, our investigation provides detailed evidence on the increase in cancer risk faced by kidney transplant recipients for multiple cancer sites. Comparisons between cohort studies need to take into account the age of the transplant recipients, length of follow-up and differences in immunosuppressive regimens. Further analyses will aim to characterize the effects of dialysis on the presentation of cancer in this cohort. While organ transplantation remains the treatment of choice for patients with ESRD, enhanced surveillance and continued vigilance is clearly important among transplant patients.

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