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The Incidence of Cancer in a Population-Based Cohort of Canadian Heart Transplant Recipients

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To assess the long-term risk of developing cancer among heart transplant recipients compared to the Canadian general population, we carried out a retrospective cohort study of 1703 patients who received a heart transplant between 1981 and 1998, identified from the Canadian Organ Replacement Register database. Vital status and cancer incidence were determined through record linkage to the Canadian Mortality Database and Canadian Cancer Registry. Cancer incidence rates among heart transplant patients were compared to those of the general population. The observed number of incident cancers was 160 with 58.9 expected in the general population (SIR = 2.7, 95% CI = 2.3, 3.2). The highest ratios were for non-Hodgkin's lymphoma (NHL) (SIR = 22.7, 95% CI = 17.3, 29.3), oral cancer (SIR = 4.3, 95% CI = 2.1, 8.0) and lung cancer (SIR = 2.0, 95% CI = 1.2, 3.0). Compared to the general population, SIRs for NHL were particularly elevated in the first year posttransplant during more recent calendar periods, and among younger patients. Within the heart transplant cohort, overall cancer risks increased with age, and the 15-year cumulative incidence of all cancers was estimated to be 17%. There is an excess of incident cases of cancer among heart transplant recipients. The relative excesses are most marked for NHL, oral and lung cancer.

Key words: Cancer incidence, cohort study, heart transplantation, record linkage

Abbreviations: CCR, Canadian Cancer Registry; CI, confidence interval; CMDB, Canadian Mortality Database; CORR, Canadian Organ Replacement Registry; EBV, Epstein–Barr Virus; GRLS, generalized record linkage system; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; PTLD, posttransplant lymphoproliferative disorders; SIR, standardized incidence ratio; PYs, person-years; SE, standard error.

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Introduction

Heart or cardiac transplantation is a well-established procedure to treat patients with end-stage heart disease or severe coronary artery disease (1). In the United States, the number of people living with a functioning heart allograft at year-end increased from 13 829 in 1997 to 18 018 in 2005 (2). As of June 15, 2007, 1-year survival rates were 87.4% for men and 85.5% for women, while 5-year survival rates were 78.7% for men and 75.9% for women (3). In Canada, patient and graft survival have continued to increase in the last decade (4). Heart transplants are now the third most common organ transplant operation with 1633 heart transplants between 1997 and 2006 (5). One-year survival rates of patients with a heart transplant rose from 82.9% in 1995 to 86.9% in 2005, while 5-year survival rates rose from 72.5% in 1995 to 82.7% in 2001 (6,7).

It is known that the improvement in survival of patients following heart transplantation is hampered by a high incidence of cancer (8,9). Posttransplant malignancies have been shown to occur in over 15% of patients with long-term follow-up (10–12). The most commonly reported cancers are skin cancer and posttransplant lymphoproliferative disorders (PTLD) (13). Some studies have also shown that the risk of lung cancer was increased among cardiac-transplant patients resulting in a poor prognosis (14,15). Immunosuppressive drugs have been recognized as the major factor contributing to the increased incidence of cancer in transplant recipients (16).

There have been few large studies of the incidence of cancer following heart transplantation. Most published studies have relied on patient data collected from a single study centre, and the number of patients has been relatively small (10,12,17,18). Therefore, these studies are not able to characterize precisely the long-term risks of developing rarer forms of cancer, and moreover, there may be

constraints in identifying incident cancers among those who have moved to other regions. Recently, a multi-centre Italian study found increased risks of cancer among a cohort of 724 patients following heart (n = 682) or lung (n = 42) transplantation (19). The overall standardized incidence ratio in these patients relative to the general population was 2.6 (95% CI: 2.1–3.2), an excess higher than that found for renal transplant patients in the same cohort. More recently, patterns of cancer incidence in a large cohort of 3393 Spanish patients were described (20), however, analyses of the cohort were restricted to internal cohort comparisons.

The objective of this study was to compare long-term cancer risks among heart transplant recipients to the Canadian population, and to other types of transplant patients drawn from the same national registry.

Materials and Methods

Study population

The Canadian Organ Replacement Registry (CORR) is a national organ replacement registry that contains information on virtually all Canadian patients who have undergone organ transplantation since 1981. We used this database to assemble a heart transplant population-based cohort, comprising those patients who received their initial heart transplant between 1981 and 1998. Demographic variables extracted from the database included date of birth, sex, province of residence, race/ethnicity, primary heart disease, comorbid conditions and the underlying disease that contributed to heart failure (5,21).

After excluding those individuals who were diagnosed with cancer before transplantation, we identified a total of 1908 individuals who had received heart transplantation between 1981 and 1998. Consistent with previous analyses (18,22), patients who died within 30 days of transplantation were excluded from analysis. We also excluded patients who had developed a cancer within the first 30 days after transplantation, as these cancers were assumed to be preexisting and unrelated to the surgery (22). Additionally, all patients who were diagnosed with nonmelanoma skin cancer after transplantation were excluded as Canadian Cancer Registries (CCR) do not consistently record nonmelanoma skin cancers. These cancers occur relatively frequently and are often treated successfully without requiring hospitalization. As a result, it would be difficult to differentiate between excesses in heart transplant patients attributable to the transplantation and excesses due to enhanced surveillance of this patient population. We examined patterns of cancer incidence in a total of 1703 patients who received a heart transplant and who were cancer-free 30 days after receiving a transplant. The follow-up period started after the first 30 days following transplantation.

Ascertainment of health outcomes

The Generalized Record Linkage System (GRLS) (23) was used to link the personal identifiable information of cohort members to the national cancer and mortality databases. The GRLS is a probabilistic linkage procedure, which compares common fields in the two files to be linked, assigns weights to the resulting links, and calculates total weights. Records with a sufficiently high weight are accepted as a match. This methodology has been used extensively in Canada for more than two decades. Canadian national income tax files were linked to help evaluate death searches and confirm vital status.

Deaths among heart transplant patients were determined by linking the CORR database to the Canadian Mortality Database (CMDB) (24). The CMDB contains death data across Canada from 1950 onwards. Validation studies of record linkage that have used GRLS methodology to ascertain vital status in the CMDB, have demonstrated that the potential number of missed deaths is small given the available personal identifying information (25,26). These previous studies found that the probability of correctly identifying deceased and living subjects from record linkage to CMDB was 98% and close to 100%, respectively.

Incident cancer cases among the heart transplant patients were identified by record linkage of the personal identifying information to the Canadian Cancer Registry (CCR) database (27). Since 1969, the CCR has provided information on all Canadian residents who have been diagnosed and confirmed 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 (except nonmelanoma skin cancer) in Canada (28). In this study, our risk estimates are based on the incidence of primary cancers, and therefore, patients diagnosed with cancer were censored at the time of their initial diagnosis. More precisely, in our study follow-up extended until the earliest date of a cancer diagnosis, death, or the end date of December 31, 1998. Where no death or cancer link was found, it was assumed that the person was alive or cancer-free as of December 31, 1998.

Statistical analysis

The incidence rates of cancers in heart transplant patients were compared with those in the Canadian general population using the standardized incidence ratio (SIR). The SIR is the ratio of observed to expected incident cancer, where 'expected' refers to the number expected to occur if heart transplant patients were subject to the same cancer risk as the general population. The Poisson distribution was used to determine 95% confidence intervals (CI) for the SIRs (29). To adjust for differences in the age and sex distribution between the two populations, as well as changes in cancer incidence rates over time, the numbers of person-years (PYs) and observed cases of incident cancers in the cohort were tabulated by age, sex and calendar period. Expected counts were determined by multiplying incidences for these same strata by the corresponding PYs. Absolute excess risk expressed per 10 000 patients per year, was also calculated by subtracting the expected number of cases from the observed number of cases and dividing by the PYs at risk. Nonmelanoma skin cancer was excluded from the analysis because of its underreporting in CCR.

Stratified analyses were then performed to examine variations in risk according to age at transplantation ($<$35, 35–49, 50–59 and $\geq$60), sex, time since transplantation (30 days–$<$1 year, 1–4 years, 5–9 years and $\geq$10 years), and year of transplantation (1981–1989, 1990–1992, 1993–1995 and 1996–1998). This required tabulating the PY of follow-up within each of these strata, which was done using the DATAB module in the Epicure software program (30).

Internal cohort comparisons were made using the Cox regression model to evaluate the effects of several covariates simultaneously on the long-term risk of developing cancer. Age, sex and transplant year were used to examine the independent effects on the risk of all cancers and non-Hodgkin's lymphoma (NHL) after heart transplantation. Additionally, competing risks survival methodology, based on formulae presented by Gooley et al. (31), were applied to estimate the cumulative incidence of developing certain cancers after transplantation. Following this method, persons who die or develop another form of cancer are no longer at risk of developing the index cancer (as a primary cancer). This differs from the complement of the Kaplan–Meier survival estimator which treats patients who die as censored and hence implicitly assumes that they remain at risk to develop the index cancer in the future (32).

Finally, as a subanalysis and as a follow-up to our previous work (33,34), we compared cancer incidence rates in heart transplant recipients to those in kidney and liver transplant patients which also derived from the CORR database. We then fitted two Cox models, adjusting for age, sex and calendar period, one for all cancers and one for NHL.

Results

In the CORR database, the first heart transplantation occurred in July 1982. A total of 1703 heart transplant patients were alive and cancer-free 30 days after transplantation. The cohort was predominantly male (82.5%), and the majority of transplantations (64.8%) were performed among patients between the ages of 40 and 59 (Table 1).

The overall cancer incidence rate per 1000 PYs was 15.4. Hereafter, all rates are reported per 1000 PYs of follow-up. The three most frequent types of cancer were NHL (5.7), lung cancer (2.1) and oral cancer (1.0). For overall cancers, the incidence per 1000 PYs was higher among men than among women (15.7 vs. 13.9). Figure 1 depicts the mean age at the time of diagnosis of cancer and the mean follow-up interval between the date of transplantation and a diagnosis of cancer. Incident cancers were identified in 137 men and 23 women. Among those who were diagnosed with cancer, the mean age with standard error (SE) at the time of a cancer diagnosis was 54.4 (SE, 1.1) years, and the mean length of time from the transplantation to diagnosis was 57.5 (SE, 3.3) months. Patients with a diagnosis of prostate cancer, lung cancer or oral cancer had a higher mean age and a relatively longer length of time from transplantation to a diagnosis of cancer. Patients with a diagnosis of NHL had a lower mean age and a shorter length of time from transplantation.

There were 160 observed cases of cancer in the study versus the 58.9 cases that were expected based on general population rates (SIR = 2.7, 95% CI = 2.3, 3.2) (Table 2). All cancers, oral cancer, lung cancer, NHL and multiple myeloma had significantly elevated ratios (SIR > 1.0) in this patient population, and the highest was for NHL (SIR = 22.7, 95% CI = 17.3, 29.3). Overall, the cohort study group experienced an excess of 9.8 cancer cases per 1000 PYs, and NHL contributed the most to this excess (5.4).

Table 3 shows the SIRs for all cancer sites combined and for NHL among heart transplant patients according to age at surgery, period of surgery, follow-up interval and sex. The SIRs were the highest among younger transplant patients and among patients with less than a year (and at least 30 days) of follow-up, both for all cancers and for NHL. Women had higher rates than men.

Table 1: Characteristics of 1908 patients who received a heart transplant between 1981 and 1998. Canadian Organ Replacement Registry Database

Characteristic	No. of patients	%	Person-years of follow-up	%
Age at surgery (in years)				
<10	78	4.1	285.3	2.8
10–<20	91	4.8	509.1	4.9
20–<30	120	6.3	815.3	7.9
30–<40	169	8.9	1019.0	9.8
40–<50	472	24.7	2829.1	27.3
50–<60	765	40.1	4037.4	38.9
≥60	213	11.2	877.4	8.5
Gender				
Male	1575	82.5	8720.0	84.1
Female	333	17.5	1652.5	15.9
Year of surgery				
1981 to 1989	650	34.1	5099.1	49.2
1990 to 1992	416	21.8	2467.1	23.8
1993 to 1995	491	25.7	2035.7	19.6
1996 to 1998	351	18.4	770.8	7.4
Follow-up interval[1]				
< 30 day[2]	205	10.7	143.3	1.4
30 d–<1 year	174	9.1	1464.0	14.1
1–< 5 years	579	30.3	5027.0	48.5
5–<10 years	624	32.7	3044.3	29.3
10 years +	326	17.1	694.0	6.7
Total	1908	100.0	10 372.6	100.0
Total (excluding first 30 days)	1703	88.7	10 368.9	100.0

[1]The person-year calculation in each follow-up interval was the contributions of all patients to the interval not just the patients whose follow-up ended in that interval.
[2]These subjects were excluded in the estimation of cancer risks.

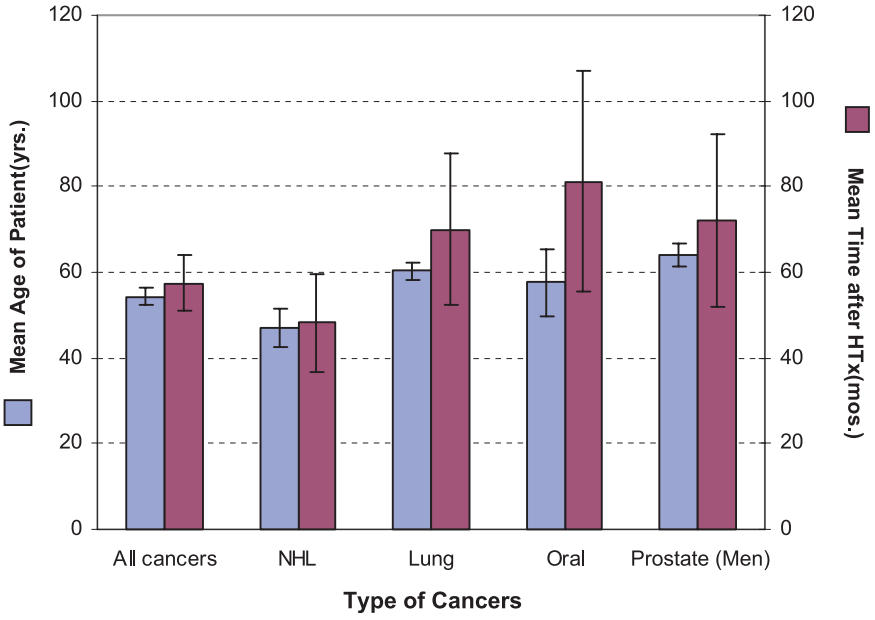

Figure 1: Mean age at the time of cancer diagnosis and mean interval to develop cancers from heart transplantation for various cancers patients.

Results from the Cox regression model indicate higher cancer risks with older patients after adjustment for sex, and calendar period for all cancers. The data suggest an increased risk of cancer among those who received a transplant more recently; however, the category-specific hazard ratios, relative to before 1990, were not statistically significant. For NHL, there were statistical differences in risk between those who underwent transplantation before 1990 and those operated on in 1995–1998 (Table 4). When calendar period was fit as a continuous variable, the incidence rate increased by 7.0% and 11.1% per year for all cancers (HR = 1.07; p = 0.01) and NHL (HR = 1.11; p = 0.02), respectively.

The cumulative incidence of cancer in heart transplant patients by time since transplantation is shown in Figure 2. Unlike typical survival analysis methods (e.g. Kaplan–Meier estimator), cumulative incidence estimates properly account for the competing risks of death and diagnoses for other cancers. At 15 years posttransplantation, the

Table 2: Standardized Incidence Ratios (SIRs)[1] for selected cancers among patients undergoing heart transplantation between 1981 and 1998, CORR

Cancer site[2]	ICD-9	Observed cases	Expected cases	SIR	95% CI	Absolute excess risk[3]
All cancers		160	58.9	2.7	2.3, 3.2	97.5
Oral	140–149	10	2.3	4.3	2.1, 8.0	7.4
Colorectal	153–154	5	7.7	0.6	0.2, 1.5	−2.6
Pancreas	157	4	1.3	3.1	0.8, 7.9	2.6
Larynx	161	3	1.2	2.5	0.5, 7.3	1.7
Lung	162	22	11.1	2.0	1.2, 3.0	10.5
Malignant melanoma	172	5	1.8	2.8	0.9, 6.5	3.1
Bladder	188	3	2.7	1.1	0.2, 3.2	0.3
Kidney	189	6	2.1	2.9	1.0, 6.2	3.8
NHL	200, 202	59	2.6	22.7	17.3, 29.3	54.4
Multiple myeloma	203	5	0.7	7.1	2.3, 16.7	4.1
Male cancers						
Prostate	185	15	11.3	1.3	0.7, 2.2	4.2
Female cancers						
Breast	174	3	2.7	1.1	0.2, 3.2	1.8
Others		25	11.4	2.2	1.4, 3.2	

[1]Individuals were followed from 30 days after the date of their first heart transplant until the earliest date associated with a diagnosis of an incident cancer, death, or December 31, 1998.
[2]Excludes all secondary or later primary cancers following the first malignancy diagnosed subsequent to transplantation.
[3]Absolute excess risk expressed per 10 000 patients per year; was calculated by subtracting the expected number of cases from the observed number of cases and dividing by the person-years at risk (10 368.9 for total, 8717.3 for male and 1651.6 for female).

Table 3: Standardized incidence ratios (SIRs) for all cancer sites and non-Hodgkin's lymphoma among patients who received a heart transplant, by transplantation date, follow-up intervals, gender and age at transplantation

	All cancers			NHL		
Characteristic	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Transplantation date[1]						
1981–1989	72	29.7	2.4 (1.9, 3.1)	23	1.3	17.7 (11.2, 26.5)
1990–1992	47	13.1	3.6 (2.6, 4.8)	16	0.6	26.7 (15.2, 43.3)
1993–1995	27	11.7	2.3 (1.5, 3.4)	13	0.5	26.0 (13.8, 44.5)
1996–1998	14	4.4	3.2 (1.7, 5.3)	7	0.2	35.0 (14.0, 72.1)
Follow-up interval						
30 days–<1 year	33	6.1	5.4 (3.7, 7.6)	24	0.3	80.0 (51.2, 119.0)
1–<5 years	55	25.8	2.1 (1.6, 2.8)	13	1.2	10.8 (5.8, 18.5)
5–<10 years	59	20.8	2.8 (2.2, 3.7)	17	0.9	18.9 (11.0, 30.2)
≥10 years	13	5.7	2.3 (1.2, 3.9)	5	0.2	25.0 (8.1, 58.3)
Sex						
Male	137	51.9	2.6 (2.2, 3.1)	51	2.4	21.3 (15.8, 27.9)
Female	23	7.0	3.3 (2.1, 4.9)	8	0.3	26.7 (11.5, 52.5)
Age at transplantation (years)						
<35	20	1.0	20.0 (12.2, 30.9)	15	0.1	150.0 (83.9, 247.4)
35–<50	38	10.7	3.6 (2.5, 4.9)	18	0.7	25.7 (15.2, 40.6)
50–<60	83	32.9	2.5 (2.0, 3.1)	23	1.4	16.4 (10.4, 24.7)
≥60	19	14.3	1.3 (0.8, 2.1)	3	0.5	6.0 (1.2, 17.5)
Total	160	58.9	2.7 (2.3, 3.2)	59	2.6	22.7 (17.3, 29.3)

O = observed number of incident cancers; E = expected number based on Canadian general population rates.
[1]The cut-off points for transplantation dates are not even due to the minimum number (3) of observed cases required by Statistic Canadian for public release.

cumulative incidence for all cancers was estimated to be 17%, indicating that 17% of a cohort of heart transplant recipients would be expected to be diagnosed with cancer within 15 years (acknowledging that the patients may die first). Focusing on the cancers for which elevated SIRs were observed, Figure 2 also presents cumulative incidence estimates for NHL (6% after 15 years) and lung cancer (3% after 15 years). Thus, 6% of heart transplant patients are expected to have a primary diagnosis of NHL within 15 years, accounting for the fact that a patient may die or be diagnosed with a different type of cancer first.

Discussion

This is a nationwide cohort study of 1703 heart transplant patients with 10 368.9 PYs of follow-up. The study describes precisely the long-term risk of developing cancer, including rare types of cancer. In addition, it allowed us to characterize variations in risk by transplantation date, age at transplantation, sex and duration of follow-up. The CORR database was linked to Canadian national tax files to validate the resident status. This reduced the potential for outcome misclassification and yielded a better estimation

Table 4: Cox proportional hazards model for risk factors for developing all cancers and NHL subsequent to heart transplantation

	All cancers				NHL			
Risk factor[1]	Patient no.	HR	95% CI	p-Value	Patient no.	HR	95% CI	p-Value
Age at HT (years)								
<40	24	1	–	–	18	1	–	–
40–<60	117	1.9	1.2, 3.0	0.004	38	0.8	0.5, 1.4	0.5
≥60	19	2.4	1.3, 4.5	0.005	3	0.4	0.1, 1.5	0.2
Sex								
Female	23	1	–	–	8	1	–	–
Male	137	1.0	0.7, 1.6	0.9	51	1.3	0.6, 2.8	0.5
Calendar period[2]								
1983–1990	90	1	–	–	27	1	–	–
1991–1994	46	1.2	0.8, 1.8	0.4	20	1.8	1.0, 3.5	0.06
1995–1998	24	1.6	0.9, 2.7	0.08	12	2.4	1.1, 5.2	0.03

HR = hazard ratio; HT = heart transplantation.
[1]All covariates were fit simultaneously in the same model.
[2]A similar analysis was conducted by coding the calendar period as a continuous variable, then the significance of year was found for all cancers and NHL (data not shown).

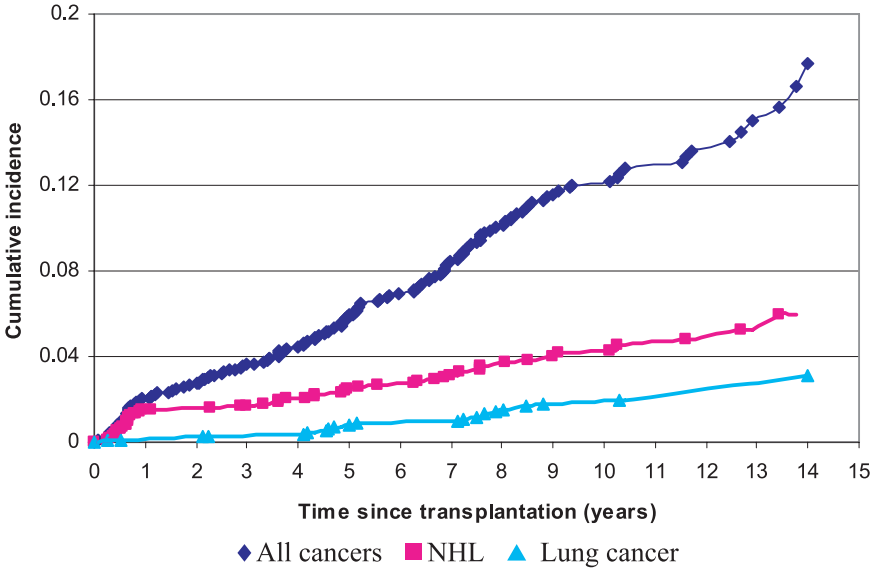

Figure 2: Cumulative incidence of all cancers, NHL and lung cancer, by time since heart transplantation between 1981 and 1998.

of PYs. The CORR was then linked to two mandatory reporting systems, the CCR and the CMDB. They both have a high level of data quality and close to 100% coverage (25–28). Moreover, it is unlikely that heart transplantation patients would move outside the country due to the nature of health care services provided in Canada. Therefore, our estimates of cancer risks are unlikely to be biased by cases lost to follow-up.

Until recently, only limited data were collected on heart transplant recipients. Most studies have focused on the high frequencies of cancers without reference to the general population (8,10–12,17,35). Our study is among the very few studies that compare the risk of developing specific cancers in heart transplant recipients to the general population. The findings are consistent with those noted in a multi-centre Italian study of 724 heart or lung transplant patients (19). For all cancer sites combined, they found an SIR of 2.6 (95% CI: 2.1–3.2), with an elevated risk for non-Hodgkin's lymphoma (SIR = 17.9, 95% CI: 11.2–27.0) and lung cancer (SIR = 2.8, 95% CI: 1.8–4.2). Their study, however, identified a total of only 95 incident cancers among heart or lung transplant patients, and therefore had limited ability to describe risks of developing rarer types of cancer.

Our study has shown an elevated risk of cancer among heart transplant patients. The SIR for all cancers was 2.7 times higher compared to the general Canadian population. This ratio appears to be lower than the relative risk of 7.1 among heart and/or lung transplant recipients in a single institution in Australia (9). A study from Sweden (22) also found a high SIR of 4.0 for all cancers in patients who underwent transplantation of the kidney, liver, heart or other organs. The possible reason for our lower figures is the exclusion of nonmelanoma skin cancer due to its underreporting in Canadian cancer registries. It is difficult for Cancer Registries to collect all cases of nonmelanoma skin cancer since most patients are treated without requiring hospitalization in Canada. As a result, we cannot provide SIRs for nonmelanoma skin cancer and for all cancers including nonmelanoma skin cancer. Otherwise, the true rate ratio would be exaggerated. Our incidence rates of overall cancers per 1000 PYs are similar to those in a study using the International Society for Heart & Lung Transplantation registry data (36), but lower than those in a study from Spain likely due to the exclusion of nonmelanoma skin cancer (20).

An interesting observation of the study is the increased SIRs for all cancers and NHL in the more recent time periods. A closer examination of time trends in the overall cancer incidence in both the cohort and the general population found that rates decreased in both groups, but at a greater rate in the general population. One possible explanation could be differences in the major risk factors in the two populations with better control of major risk factors in the general population.

Using the same national population-based CORR database, the SIR is slightly higher among heart transplant patients than among kidney or liver transplant cases in Canada (33,34). A study from the United States with 674 solid-organ transplant recipients at a single center reported a similar result (12). Furthermore, based on the Cox model comparing each of heart transplant and liver transplant patients to kidney transplant recipients, cardiac patients were at a significant 30% increased risk of developing cancer from all causes combined (HR = 1.30; p = 0.004). In contrast, liver recipients had the same risk of developing cancer (all causes) as kidney recipients (HR = 1.00; p = 0.80). The Italian study (19) showed similar higher SIRs for heart transplant patients relative to kidney transplant patients. A nationwide cohort study in Sweden also revealed that the SIR of cancer was higher among patients who received

other organ transplants than those who underwent kidney transplantation (22). This may be explained by the more aggressive immunosuppressive therapy in heart and/or lung transplant recipients than in those receiving other organs (37) or it could be due to the fact that those who require a heart transplant are more likely to have engaged in harmful behaviors (e.g. smoking) than those who required a kidney transplant, placing them at a higher risk of cancer at older ages. There is evidence to suggest that an elevated cancer risk among organ transplant recipients is due to the use of immunosuppressive drugs. For heart transplant patients, this risk is even higher as higher doses of immunosuppressive drugs are used. A meta-analytic study (38) asserted that immune deficient patients and immunosuppressed transplant recipients suffer a similar elevated risk of cancer. This suggests that immune deficiency, whether induced by a virus or a drug, may be one of the dominant risk factors for the development of cancer. Moreover, preexisting cancer is a contraindication for a heart transplantation, which is not always the case for a kidney or liver transplantation.

The approximate 23-fold increased risk of NHL among heart transplant patients compared with the general population in our study supports the findings from other published reports (9,39). The association between Epstein-Barr virus (EBV) and the occurrence of lymphoproliferative disorders is known (35,39). In our study, data collection on testing for EBV was incomplete; therefore, it was not possible to determine this association. Also, in contrast with other series (14,40), female gender and a younger age seem to represent more risk of developing cancer after heart transplantation. In addition the SIR for cancer was highest in the first year of follow-up. It most likely results from more aggressive immunosuppression in the first year to avoid the severe consequences of graft failure due to rejection (39). Furthermore, based on the same CORR database, heart and liver transplant patients had a significantly elevated risk of NHL, (HR = 3.50 and 2.2, respectively) relative to kidney transplant patients. It is worth noting that this study period ends in 1998. However, many changes in immunosuppressive protocols have been made since then. Additional studies with more current data should confirm this finding. Studies are also needed to identify how much of the excess found in the early part of follow-up is due to preexisting cancer at the time of transplantation.

In order to exclude patients with preexisting neoplasias, similar cohort studies have censored patients in whom cancer was diagnosed in the first month after organ transplantation (19,22). To be comparable with these study results, we also excluded patients who had a cancer diagnosed in the first 30 days after transplantation. However, the definition of an appropriate exclusion period is not straightforward. The excluded period from the Spanish study was extended to 3 months after heart transplantation (20). In order to expand the comparability, we conducted a sensitivity analysis by excluding also 3- and 6-month intervals after transplantation, respectively. The SIRs showed non-appreciable differences among the three approaches.

The types of drugs used for the induction and maintenance of immunosuppression and the duration of treatment influence both the incidence and the type of cancer although immunosuppression does not entirely account for a causal link to cancer (41,42). In contrast, another immunosuppressive drug, Sirolimus (rapamycin), has been shown recently to prevent tumors and even to cause established tumors to regress (43). Our study was unable to evaluate these associations as information on immunosuppressive drugs was not collected for CORR. Nevertheless, the main conventional risk factors for the development of posttransplant cancer, particularly skin, lung and oral cancer have been identified and include smoking, sun damage, analgesic abuse and previous malignancy (16). Since there was a lack of information on lifestyle factors in the CORR database, we cannot accurately identify risk exposure in the patients. An enhanced database would be required to confirm the impact of immunosuppressive drugs, as well as to identify how known risk factors operate differently in this population versus the general population.

In conclusion, the population-based design of this study as well as an ability to ascertain incident cancers for a follow-up interval up to 18 years provides important insights on cancer risks in a heart transplant population. This study demonstrates a higher incidence of cancer among heart transplant recipients relative to the general population. The relative increases are the greatest for NHL, oral cancer and lung cancer. Female, young age and the immediate post-transplant period are identified as the most common factors associated with the occurrence of cancer. It will be informative to conduct enhanced cancer surveillance, especially for NHL, oral cancer and lung cancer after heart transplantation including data on innovative immunosuppression strategies.

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