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ORIGINAL ARTICLE

Liver Transplantation and Subsequent Risk of Cancer: Findings from a Canadian Cohort Study

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Characterization of the long-term cancer risks among liver transplant patients has been hampered by the paucity of sufficiently large cohorts. The increase over time in the number of liver transplants coupled with improved survival underscores the need to better understand associated long-term health effects. This is a cohort study whose subjects were assembled with data from the population-based Canadian Organ Replacement Registry. Analyses are based on 2034 patients who received a liver transplant between June 1983 and October 1998. Incident cases of cancer were identified through record linkage to the Canadian Cancer Registry. We compared site-specific cancer incidence rates in the cohort and the general Canadian population by using the standardized incidence ratio (SIR). Stratified analyses were performed to examine variations in risk according to age at transplantation, sex, time since transplantation, and year of transplantation. Liver transplant recipients had cancer incidence rates that were 2.5 times higher than those of the general population [95% confidence interval (CI) = 2.1, 3.0]. The highest SIR was observed for non-Hodgkin's lymphoma (SIR = 20.8, 95% CI = 14.9, 28.3), whereas a statistically significant excess was observed for colorectal cancer (SIR = 2.6, 95% CI = 1.4, 4.4). Risks were more pronounced during the first year of follow-up and among younger transplant patients. In conclusion, our findings indicate that liver transplant patients face increased risks of developing cancer with respect to the general population. Increased surveillance in this patient population, particularly in the first year following transplantation, and screening for colorectal cancer with modalities for which benefits are already well recognized should be pursued. ***Liver Transpl 14:1588-1597, 2008.*** © **2008 AASLD.**

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Liver transplantation is an unequivocal procedure for providing effective treatment for patients with acute liver failure, end-stage liver disease, and several primary hepatic malignancies.[1,2] Since the 1980s, the number of patients who have received liver transplants has been increasing in many developed countries.[3-6] In addition, this has been accompanied by a concomitant increase in survival in this patient population. For example, 3-month survival rates of Canadian patients rose from 85.1% in 1995 to 93.3% in 2004, whereas 5-year survival rates rose from 72.6% in 1995 to 76.7% in 1999.[6] The increasing number of liver transplants performed, coupled with improved survival, has contributed to a substantially higher number of individuals being susceptible to long-term health sequelae post-transplant. The finding of an increased risk of cancer has been noted in some follow-up studies of liver trans-

Abbreviations: CCR, Canadian Cancer Registry; CI, confidence interval; CMDB, Canadian Mortality Database; CORR, Canadian Organ Replacement Registry; HCC, hepatocellular carcinoma; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9, International Classification of Diseases, 9th; LTx, liver transplantation; NHL, non-Hodgkin's lymphoma; SIR, standardized incidence ratio.

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plant recipients,[7-12] with the use of immunosuppressive drugs generally identified as the primary culprit.[7] For some cancers, the risks among liver transplant recipients have been reported to be increased up to 70-fold in comparison with the general population.[8-10]

Although previously published studies of liver transplant patients have advanced our understanding of the long-term risks of developing cancer in these patients, for the most part, they have been subject to several key limitations. Some have relied on patient data collected from a single study center,[11,12] and so comparisons to cancer patterns of the general population may not be readily interpretable. Other studies have had the desirable feature of assembling a population-based cohort; however, the number of patients has been relatively small.[9,10] As a result, these studies are not able to precisely characterize the long-term risks of developing rarer forms of cancer.

This study uses data collected from approximately 2000 patients identified from a population-based registry database, the Canadian Organ Replacement Registry (CORR). The tracking of vital status and cancer diagnoses is possible because of the ability of Statistics Canada to link personal identifiable information to national mortality and cancer incidence databases. As a result, we were able to construct longitudinal follow-up for patients identified from the CORR database for up to 15 years.

Using these cohort data, we undertook the objective of characterizing patterns of cancer incidence among liver transplant recipients with respect to rates experienced by the general Canadian population. Particular attention was paid to characterizing variations in risk according to age at transplantation, sex, and time since transplantation. Moreover, internal cohort comparisons were undertaken to evaluate how these factors were interrelated. It is hoped that, taken together, these analyses can provide a better understanding of the long-term cancer risks in this patient population so that surveillance strategies applicable to this patient population can be optimized.

PATIENTS AND METHODS

Study Population

As previously mentioned, the CORR database was used to assemble a population-based cohort of liver transplant patients. The CORR database is a national organ failure registry that contains information on virtually all Canadian patients who have undergone liver transplantation. The cohort comprised those who received their initial liver transplant between June 1983 and October 1998. Demographic variables extracted from the database included date of birth, sex, province of residence, race/ethnicity, primary liver disease, comorbid conditions, and underlying disease that contributed to organ failure.[13,14]

Initially, we identified a total of 2545 individuals who had received a liver transplant between June 1983 and October 1998. From this patient population, we excluded 212 patients who were diagnosed with cancer (excluding nonmelanoma skin cancer) before transplantation. In agreement with previous analyses, we also excluded the follow-up interval within the first 30 days after transplant as these cancers were assumed to be unrelated to transplantation.[9] In all, 278 patients died or were diagnosed with cancer during this 30-day period following transplantation.

Liver transplantation has been considered one of the best treatment options for hepatocellular carcinoma (HCC) because it removes the tumor as well as the cirrhotic liver.[15,16] Despite the use of established criteria for selecting liver transplantation candidates with the lowest risk of HCC recurrence, a high recurrence rate of HCC has been reported after transplant.[17-19] On the other hand, the cancer cases could represent the result of a gradual evolution from chronic liver disease, such as cirrhosis, to HCC. Therefore, it may be possible that some patients had undetectable HCC when they underwent their liver transplants. Until this point can be clarified by further research, we decided not to include liver cancer cases in the study population, so 21 subjects were dropped because they had liver cancer. Therefore, our study is based on the follow-up of 2034 patients, who accrued a total of 10,370.6 person-years of follow-up.

Ascertainment of Health Outcomes

The mortality experience of the cohort members was determined through the linking of the personal identifiable information for the cohort members to the Canadian Mortality Database (CMDB) with a probabilistic linkage procedure called the Generalized Record Linkage System.[20] The CMDB, maintained by Statistics Canada, contains death data for all Canadian residents from 1950 onward. The Generalized Record Linkage System compares common fields in the 2 files to be linked, assigns weights to the resulting links, and calculates the total weight; links with a sufficiently high weight are accepted as a match. This methodology has been widely used in Canada for more than 2 decades, and validation studies have demonstrated that the number of deaths that would be missed would be quite small given the personal identifying information available for this cohort.[21,22] Both of these previous studies found that the probability of correctly identifying deceased and living subjects from record linkage to the CMDB was 98% and close to 100%, respectively. Date-of-death information in our study was used to determine the last day of follow-up so that the person-years of follow-up could be calculated. Where no death link was found, we assumed that the person was alive at the end of follow-up (that is, December 31, 1998).

Incident cancers were also identified through record linkage of the personal identifying information contained in the CORR patient records to the Canadian Cancer Registry (CCR) database.[23] The CCR, housed by Statistics Canada, contains information on Canada's entire population of individuals who have been diagnosed with cancer and confirmed to have cancer, except

TABLE 1. Descriptive Characteristics of 2333 Patients Who Underwent Liver Transplantation Between 1983 and 1998 (Canadian Organ Replacement Registry Database)

Characteristic	Number of Patients	%	Person-Years of Follow-Up	%
Age at surgery (years)				
<10	298	12.8	1,631.2	15.5
10 to <30	282	12.1	1,545.2	14.6
30 to <40	281	12.0	1,401.3	13.3
40 to <50	546	23.4	2,372.2	22.5
50 to <60	563	24.1	2,382.5	22.6
60 to <70	341	14.6	1,170.6	11.1
≥70	22	0.9	53.4	0.5
Sex				
Male	1,238	53.1	5,226.4	49.5
Female	1,095	46.9	5,330.1	50.5
Follow-up interval				
<30 days*	278	11.9	176.2	1.7
30 days to <1 year	278	11.9	1,709.0	16.2
1 to < 5 years	838	35.9	5,631.2	53.3
5 to <10 years	729	31.2	2,646.8	25.1
10+ years	210	9.0	393.3	3.7
Primary diagnosis				
Acute hepatic failure	203	8.7	725.7	6.9
Chronic hepatic failure	1,782	76.4	8,169.4	77.4
Hepatic tumors	23	1.0	82.8	0.8
Metabolic disorders and others	221	9.5	1,094.9	10.3
Missing	104	4.5	483.7	4.6
Total	2,333	100.0	10,556.5	100.0
Total (excluding first 30 days and all liver cancer patients)	2,034	87.2	10,370.6	98.2

*These subjects were excluded in the estimation of cancer risks in this cohort.

for squamous and basal cell skin cancer, from 1969 onward. It has been estimated that the CCR captures at least 95% of all incident cancer cases in Canada.[24] Given the high quality and completeness of the CCR and the similarity in record linkage methodology used, we assumed that the accuracy of record linkage to the CCR was as accurate as the linkage to the CMDB. As with the mortality linkage, patients for whom no link to the CCR was found were assumed to be cancer-free as of the last date of follow-up.

Statistical Analysis

Patterns of cancer incidence among liver transplant patients were compared with those of the general Canadian population with the standardized incidence ratio (SIR). The SIR is the ratio of the observed number of incident cancers to the expected number of incident cancers. The 95% confidence intervals (CIs) for the SIRs were constructed under the assumption that the observed number of incident cancers follows a Poisson distribution.[25] To adjust for differences in the age and sex distribution between the 2 populations as well as changes in cancer incidence rates over time, the numbers of person-years and observed cases of incident cancers in the cohort were tabulated by age, sex, and calendar period. Canadian cancer incidence rates for these same strata were multiplied by the person-years of follow-up to calculate the expected number of incident cancers. Absolute excess risk, expressed per 10,000 patients per year, was also calculated by subtraction of the expected number of cases from the observed number of cases and division by the person-years at risk.

Stratified analyses were then performed to examine variations in risk according to age at transplantation (<35, 35 to <50, 50 to <60, and ≥60), sex, time since transplantation (30 days to <1 year, 1 to <5 years, and ≥5 years), and year of transplantation (1983-1990, 1991-1993, 1994-1996, and 1997-1998). This required tabulating the person-years of follow-up within each of these strata, and this was done with the DATAB module in the Epicure software program.[26]

An internal cohort analysis was performed with the Cox proportional hazards regression model to simultaneously evaluate the effects of several covariates on the long-term risk of developing cancer. Specifically, age, sex, and transplant year were used to study the independent effects of these variables on the risk after liver transplant of all cancers, non-Hodgkin's lymphoma (NHL), and liver cancer. Finally, we applied well-established competing risks methods[27] to estimate the cumulative incidence of developing certain cancers follow-

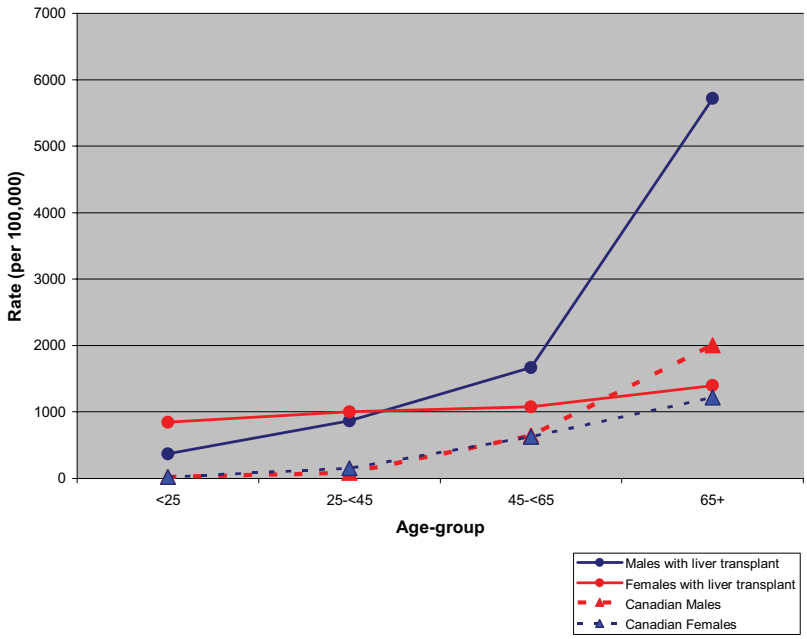

Figure 1. Incident rates for all cancer sites combined among liver transplant patients and the Canadian population by age and sex.

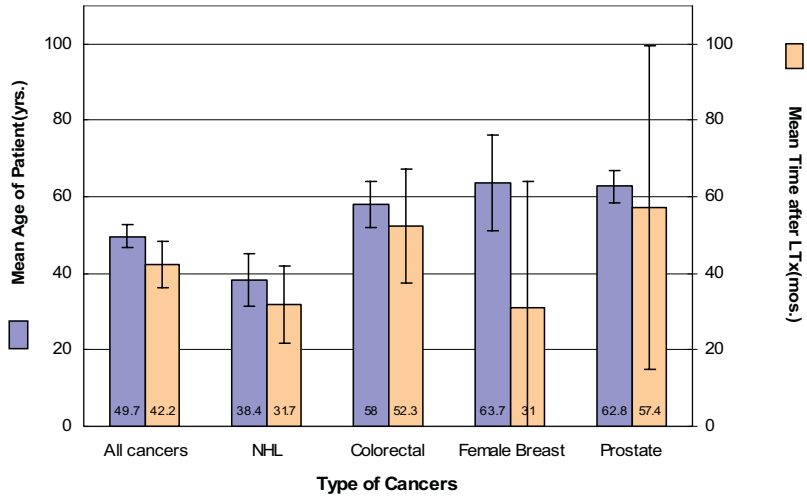

Figure 2. Mean age at the time of cancer diagnosis and mean interval to develop cancers from LTx for various cancers patients. Abbreviations: LTx, liver transplantation; NHL, non-Hodgkin's lymphoma.

ing 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 (as a primary cancer). This differs from the complement of the Kaplan-Meier survival estimator, which treats patients who die as censored and, in doing so, assumes that those who die remain at risk in the future.[28] Our estimates of cumulative incidence were based on formulae presented by Gooley et al.[27]

RESULTS

As outlined in the Patients and Methods section, after the exclusion criteria were applied, our cohort consisted of a total of 2034 liver transplant patients who had no history of cancer (excluding nonmelanoma skin cancer) at the time of transplantation. The first liver transplant in Canada occurred in 1983, and the total number of transplants increased annually from that point onward. Slightly more than half (53.1%) of the liver transplantation procedures were performed in men, and nearly 2 out of 3 (62%) of the liver transplants were performed among patients between 40 and 70 years old (Table 1).

Figure 1 illustrates the higher incidence rates of all cancers (combined) among the liver transplant group with respect to the general population. This trend is evident in both men and women; however, as demonstrated by the curves, the ratio of these rates decreases with increasing age.

Figure 2 depicts the mean age at the time of cancer diagnosis and the mean follow-up interval between the date of transplantation and the diagnosis of cancer. After the exclusion of the 30 days immediately following transplantation, incident cancers were ascertained among 60 men and 53 women. Among those who were diagnosed with cancer, the mean length of follow-up

TABLE 2. SIRs for Selected Cancers Among 2034 Patients Undergoing Liver Transplantation Between 1983 and 1998 (Canadian Organ Replacement Registry Database)

Cancer Site	ICD-9	Observed Cases	Expected Cases	SIR	95% CI	Absolute Excess Risk*
All cancers		113	44.8	2.5	2.1, 3.0	65.8
Oral	140-149	3	1.2	2.5	0.5, 7.3	1.7
Colorectal	153-154	14	5.3	2.6	1.4, 4.4	8.4
Pancreas	157	3	0.9	3.3	0.7, 9.6	2.0
Lung	162	10	7.0	1.4	0.7, 2.6	2.9
Kidney	189	4	1.3	3.1	0.8, 7.9	2.6
Non-Hodgkin's lymphoma	200, 202	40	1.9	20.8	14.9, 28.3	36.7
Leukemia	204-208	4	1.0	3.9	1.0, 9.9	2.9
Unknown primary site	199	5	1.0	4.8	1.5, 11.2	3.9
Male cancers						
Prostate	185	5	4.8	1.0	0.3, 2.4	0.4
Female cancers						
Breast	174	5	8.1	0.6	0.2, 1.4	−5.9
Others		20	12.3	1.6	1.0, 2.5	10.2

NOTE: Individuals were followed up from 30 days after the date of their first liver transplant until the earliest date associated with a diagnosis of an incident cancer, death, or December 31, 1998.
Abbreviations: CI, confidence interval; ICD-9, International Classification of Diseases, 9th; SIR, standardized incidence ratio.
*Absolute excess risk, expressed per 10,000 patients per year, was calculated by subtraction of the expected number of cases from the observed number of cases and division by the person-years at risk (10,370.6 in all: 5123.5 for males and 5247.1 for females).

(and standard deviation) from the time of transplantation to diagnosis was 42.2 ± 33.8 months (range, 1-184). With respect to all cancer sites combined, patients diagnosed with colorectal cancer were, on average, older with a longer time interval to diagnosis. In contrast, patients with NHL were diagnosed at a younger age with a shorter length of time from transplantation.

In the cohort, we observed a total of 113 incident cancer cases versus the 44.8 cases that were expected on the basis of the general population rates (SIR = 2.5, 95% CI = 2.1, 3.0; Table 2). All cancer sites combined, colorectal cancer, NHL, leukemia, and unknown primary site cancer had significantly elevated ratios (SIR > 1.0) in this patient population, and the highest was for NHL (SIR = 20.8, 95% CI = 14.9, 28.3). An SIR of less than 1 was observed for female breast cancer; however, this was not statistically significant (SIR = 0.6, 95% CI = 0.2, 1.4). Overall, the cohort study group experienced an excess of 66 cancer cases per 10,000 person-years, and NHL contributed the most to this excess (37/66).

Table 3 shows the SIRs for all cancer sites and for NHL among liver transplant patients who received a liver transplant 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. Also, the SIRs were higher in men than in women for all cancers, except for NHL.

As expected, internal cohort analyses using the Cox model indicated increased cancer risks with advanced age after adjustment for sex and period effects. There were no statistical differences in risk between those who underwent liver transplantation before 1990 and those whose surgery was in the periods of 1991-1994 and 1995-1998. For NHL, there were no statistically significant variations in risk found with age, sex, or calendar period (Table 4).

The cumulative incidence of cancer among liver transplant patients by time since transplantation is illustrated in Fig. 3. After 10 years of follow-up, the cumulative incidence for all cancers was estimated to be 8.6%. The figure also presents the cumulative incidence estimates derived under a competing risks model for NHL and colorectal cancer, for which high SIRs were observed. These estimates are adjusted for the competing risks of death and diagnoses for other cancers.

A comparison with our findings for kidney transplant patients based on data from the same CORR registry[29] shows that the SIRs for all cancer sites were similar between the 2 populations (Table 5). Among kidney transplant patients, the SIR was higher for oral (SIR = 7.7) and kidney (SIR = 7.3) cancers than the corresponding SIRs observed among liver transplant patients. However, the risk for NHL was considerably higher in the liver transplant group (SIR = 20.8) than among the kidney transplant patients (SIR = 8.8). We did not formally test for differences in the SIRs between these 2 groups because, in strict terms, the age-sex structures from the 2 transplant populations used to derive these statistics are not identical. Nonetheless, a crude comparison of the SIRs provides some information about which cancer sites are markedly higher for each of the 2 groups versus the general population.

TABLE 3. SIRs for All Cancer Sites and Non-Hodgkin's Lymphoma Among 2034 Patients Who Received a Liver Transplant Versus the Transplantation Date, Follow-Up Intervals, Gender, and Age at Transplantation

	All Cancers			Non-Hodgkin's Lymphoma		
Characteristic	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Transplantation date*						
1983-1988	18	7.7	2.3 (1.4, 3.7)	3	0.3	9.7 (1.9, 28.3)
1989-1991	32	11.5	2.8 (1.9, 3.9)	15	0.5	30.6 (17.1, 50.5)
1992-1994	36	14.5	2.5 (1.7, 3.4)	15	0.6	23.4 (13.1, 38.7)
1995-1998	27	11.1	2.4 (1.6, 3.5)	7	0.5	14.6 (5.8, 30.0)
Follow-up interval						
30 days to <1 year	32	7.2	4.4 (3.0, 6.3)	19	0.3	59.9 (36.1, 93.6)
1 to <5 years	49	24.0	2.0 (1.5, 2.7)	15	1.0	14.5 (8.1, 24.0)
≥5 years	32	13.6	2.4 (1.6, 3.3)	6	0.6	10.5 (3.8, 22.8)
Sex						
Male	60	21.5	2.8 (2.1, 3.6)	20	1.0	19.1 (11.7, 29.6)
Female	53	23.3	2.3 (1.7, 3.0)	20	0.9	22.8 (13.9, 35.1)
Age at transplantation (years)						
<35	25	1.6	15.6 (10.1, 23.1)	15	0.1	137.6 (77.0, 227.0)
35 to <50	36	9.3	3.9 (2.7, 5.4)	15	0.5	30.4 (17.0, 50.2)
50 to <60	24	16.9	1.4 (0.9, 2.1)	5	0.7	7.0 (2.3, 16.4)
≥60	28	17.0	1.6 (1.1, 2.4)	5	0.6	8.2 (2.6, 19.1)
Total	113	44.8	2.5 (2.1, 3.0)	40	1.9	20.8 (14.9, 28.3)

Abbreviations: CI, confidence interval; E, number expected on the basis of general Canadian population rates; O, observed number of incidence cancers; SIR, standardized incidence ratio.
*The cutoff intervals for the transplantation dates are not even because the minimum observed number for publication requested by Statistics Canada is 3.

TABLE 4. Cox Proportional Hazards Model for Risk Factors for Developing All Cancers and Non-Hodgkin's Lymphoma Subsequent to Liver Transplantation

Type of Cancer*	Risk Factor	Patient Number	HR	95% CI	*P* Value
All cancers	Age at transplantation (years)				
	<40	32	1	—	—
	40 to <60	53	1.6	1.0, 2.5	0.04
	≥60	28	3.4	2.0, 5.7	<0.0001
	Sex				
	Female	53	1	—	—
	Male	60	1.2	0.8, 1.7	0.4
	Calendar period				
	1983-1990	41	1	—	—
	1991-1994	45	0.8	0.5, 1.3	0.3
	1995-1998	27	0.9	0.5, 1.6	0.7
Non-Hodgkin's lymphoma	Age at transplantation (years)				
	<40	17	1	—	—
	40 to <60	18	1.0	0.5, 1.9	0.9
	≥60	5	1.0	0.4, 2.9	0.9
	Gender				
	Female	20	1	—	—
	Male	20	1.0	0.5, 1.9	1.0
	Calendar period				
	1983-1990	13	1	—	—
	1991-1994	20	1.2	0.6, 2.4	0.7
	1995-1998	7	0.6	0.2, 1.6	0.3

Abbreviations: CI, confidence interval; HR, hazard ratio.
*All covariates were fit simultaneously in the same model.

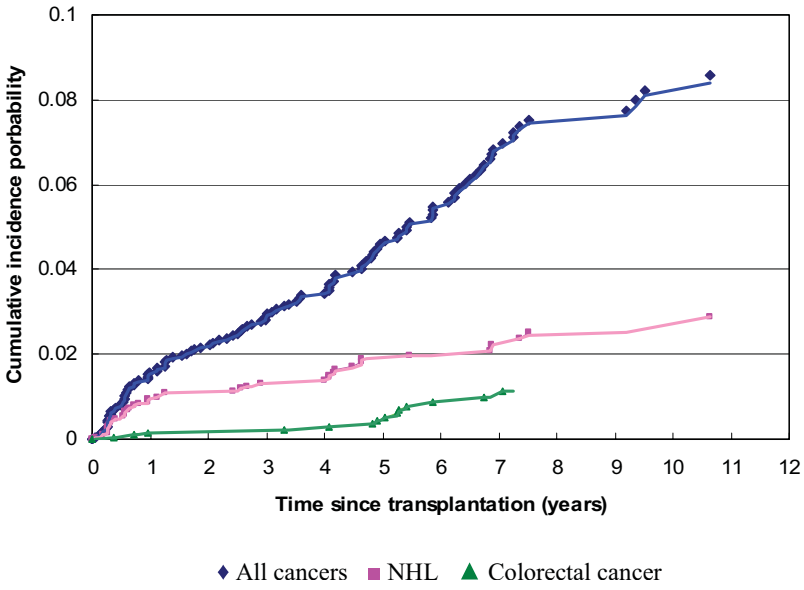

Figure 3. Cumulative incidence of all cancers, NHL, and colorectal cancer versus the time since liver transplantation between 1983 and 1998 (Canada). Abbreviation: NHL, non-Hodgkin's lymphoma.

TABLE 5. SIRs for Selected Incident Cancers Among Those Who Received Kidney and Liver Transplants (Canadian Organ Replacement Registry Database)

		Kidney Transplant*		Liver Transplant		Test Between Kidney and Liver (*P*)
Cancer Site	ICD-9	Observed Cases	SIR	Observed Cases	SIR	
Total transplant patients		11,155		2034		
All cancers		778	2.5 (2.3, 2.7)	113	2.5 (2.1, 3.0)	0.9
Oral	140-149	81	7.7 (6.1, 9.6)	3	2.5 (0.5, 7.3)	0.4
Colorectal	153-154	51	1.4 (1.0, 1.8)	14	2.6 (1.4, 4.4)	0.3
Pancreas	157	7	1.1 (0.4, 2.2)	3	3.3 (0.7, 9.6)	0.5
Lung	162	108	2.1 (1.7, 2.5)	10	1.4 (0.7, 2.6)	0.6
Kidney	189	71	7.3 (5.7, 9.2)	4	3.1 (0.8, 7.9)	0.5
Non-Hodgkin's lymphoma	200, 202	125	8.8 (7.4, 10.5)	40	20.8 (14.9, 28.3)	0.04
Leukemia	204-208	17	2.3 (1.3, 3.6)	4	3.9 (1.0, 9.9)	0.7
Male cancers						
Prostate	185	37	0.9 (0.6, 1.3)	5	1.0 (0.3, 2.4)	0.9
Female cancers						
Breast	174	52	1.3 (1.0, 1.7)	5	0.6 (0.2, 1.4)	0.5

NOTE: Individuals were followed up from 30 days after the date of their first kidney or liver transplant until the earliest date associated with a diagnosis of an incident cancer, death, or December 31, 1998.
Abbreviations: ICD-9, International Classification of Diseases, 9th; SIR, standardized incidence ratio.
*The data were taken from Villeneuve et al.[29]

DISCUSSION

Although several cohort follow-up studies have documented increased cancer risk among liver transplant patients, most of them involved only a single study center and a relatively small number of patients with limited follow-up.[9-12] Our study is a national population-based study with 2034 patients and 10,370 person-years of follow-up, which provide the opportunity to more precisely describe long-term cancer risk, particularly for rarer forms of incident cancers. The size of the study population also allowed us to characterize variations in risk by transplantation date, age at transplantation, sex, and duration of follow-up.

In this study, losses to follow-up and misclassification were minimal because the CORR database was linked to the CCR database and the CMDB, which are mandatory reporting systems in Canada. They both have high-level data quality and close to 100% coverage.[21-24] Moreover, given the medical needs of the liver transplantation patients and the healthcare services provided within Canada, it is unlikely that these patients would move outside the country. Therefore, our

estimates of cancer risks should not be unduly unbiased by patients who were lost to follow-up.

Our study has shown that the risk of cancer among liver transplant patients was increased with respect to the general population. There were 113 cancers (except liver cancer) diagnosed in 2034 patients with at least 30-day survival between 1983 and 1998. The SIR for all cancers was 2.5 with respect to the general Canadian population. This ratio appears to be a lower estimate in comparison with the existing literature. Haagsma et al.[10] reported an overall cancer relative risk of 4.3 from a population-based study in the Netherlands. Adami et al.[9] also found that the SIR for all cancers was 4.0 in patients who underwent transplantation of the kidney, liver, or other organs in Sweden. In the United States, Sheiner et al.[30] found the SIR for all de novo malignancies to be 3.9.

We offer 2 theories to explain the somewhat lower SIR estimate observed in our study with respect to other published findings. First, previous studies included nonmelanoma skin cancers in their derivation of the SIR for all cancer sites. In contrast, in Canada, nonmelanoma cancers are not typically registered as these patients are often treated without requiring hospitalization, so it is difficult for cancer registries to collect complete data. Reports from Europe,[31,32] the United States,[33,34] and Canada[35,36] have shown significant underreporting of cases in cancer registries. Calculating SIRs for nonmelanoma skin cancer will exaggerate the true rate ratio because of this underreporting. Additionally, because patients with nonmelanoma skin cancers make up a relatively large proportion of the all-cancers population,[37,38] the calculation of SIRs for all cancers will also be exaggerated for the same reason. If nonmelanoma skin cancers were excluded from the SIR calculations, the SIRs for the aforementioned studies of Haagsma et al.[10] and Adami et al.[9] would be approximately 2.4 and 2.5, respectively—both very similar to our estimation. Our study concluded that it was not appropriate to provide SIRs for nonmelanoma skin cancer and for all cancers (including skin cancer/nonmelanoma skin cancer) unless there was no underreporting of nonmelanoma skin cancer in the general population. Second, as described in the Patients and Methods section, we have excluded liver cancer from the analysis. This may be a factor contributing to our lower SIR estimate. Obviously, with respect to the nonmalignant melanoma, this bias is much smaller.

A striking finding in our study is the approximately 20-fold increased risk of NHL among liver transplant patients with respect to the general population. Similarly, other studies have also found that the relative increase in cancer risk is highest for NHL. For example, Adami et al.[9] and Sheiner et al.[30] observed SIRs of 6.0 and 28.6, respectively. As a proportion of all cancers, NHL represented 55.8% (36.7/65.8) of the absolute excess number of cancers among liver transplant patients.

A key finding in our study was the increased risk of colorectal cancer among liver transplant patients with respect to the general Canadian population. It is likely that some of this increased risk is attributable to a higher prevalence of inflammatory bowel disease (IBD) among patients who receive a liver transplant. It has long been recognized that patients with IBD are at increased risk of developing colorectal cancer. For example, a population-based Canadian study found that individuals with IBD had a 2- to 3-fold increased risk of developing colorectal cancer,[39] a finding consistent with an earlier review on the matter.[40] In our cohort, it is thought that approximately 10% were transplanted for primary sclerosing cholangitis, and of these patients, usually (75%-80%) have coexisting IBD. Unfortunately, information for these conditions was not collected within the CORR database; therefore, we are not able to directly ascertain the extent to which our observed increase in risk is due to a differential prevalence of IBD between the transplant and general populations.

Breast cancer was the only cancer site for which an SIR of less than 1 was observed. However, this statistic was based on only 5 incident cases, and consequently, this study lacks the statistical power to draw conclusions about differences in breast cancer rates between liver transplant recipients and the general population. It has been observed elsewhere that the incidence of breast cancer appears to be reduced among patients shortly after transplantation, and that effect may be due to pretransplant screening.[41] Stewart and colleagues[42] also suggested that immunosuppression could suppress tumor growth during a premalignant phase of breast cancer, thereby conferring a reduced risk. We found no evidence of a reduced risk of breast cancer among a large cohort of renal transplant patients, and other reports of transplant patients have found no statistically significant differences in breast cancer rates in comparison with the general population.[11,12,43-45] Nonetheless, the availability of data from a larger cohort or pooling of breast cancer incidence data across existing cohorts for further investigation would be valuable. This is particularly the case because, among women, breast cancer is more common than cancers occurring at other sites, and screening can play an important role in decreasing subsequent mortality.

We calculated SIRs based on age-specific, sex-specific, and calendar year–specific rates in Canada. The SIRs were more pronounced during the first year of follow-up among all cancers. This finding supports the finding of Galve et al.[46] that cancer tends to occur early after transplantation; this is dissimilar to the other cohort studies of liver transplant patients.[9,11] Further studies should evaluate the extent to which excesses found during the early part of follow-up are due to preexisting cancer at the time of transplantation.

Although other studies[8,47] have demonstrated that the use of immunosuppressive drugs plays a key role in the development of cancer, this study was unable to evaluate these associations as information on immunosuppressive drugs was not collected in CORR. Also, there are no other lifestyle risk factor data collected, such as alcohol consumption, smoking, and sun damage. Further research would be needed to quantify the

effects of multiple factors on cancer development among liver transplant patients. Although such information would certainly help us to better understand differences in cancer rates between liver transplant patients and the general population, such detailed data are typically not collected in this patient population. In addition, such data were not critical for the primary objective of this study, which was to characterize overall patterns of cancer incidence in this cohort for the purpose of providing guidance for developing cancer surveillance strategies in the future.

In summary, cancers are relatively common in the post–liver transplant patient population; NHL is the most common type in comparison with the others. The cancer risk is more pronounced during the first year of follow-up and among those receiving a liver transplant at a younger age. It will be critical to identify measures for prevention, methods of early detection for high-risk individuals on a regular basis, and currently preferred modes of therapy to reduce the impact of additional cancers. Our findings firmly support an increased incidence of cancer in this patient population. We advocate increased surveillance for cancer in these patients and screening for colorectal cancer with modalities for which benefits are already well recognized.

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