Adverse Health Outcomes among Organ Replacement Patients in Canada (1981-1998): A Historical Cohort Follow-up Study

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In Partial fulfillment of the requirements
For the MSc degree in Epidemiology

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To my dear parents,
Mariana and Florin

ABSTRACT

Background: Organ transplantation is one of the best modalities for treating fatal organ failure. Despite the success of this procedure, an increasing incidence of cancer in this population has drawn the attention of public health officials in recent years.

Objectives: The overall objective of this study is to conduct a detailed examination of adverse health outcomes among Canadian organ transplant recipients, with an emphasis on cancer incidence and mortality.

More specifically, the objectives of this study are:

1. To examine post-transplant mortality in organ replaced patients;
2. To assess the risk of developing cancer in transplant recipients;
3. To determine the impact of risk factors on the association between organ transplant and cancer development.

Methods: This project employed a retrospective cohort follow-up study design, whereby Canadian Organ Replacement Registry records were linked to the Canadian Mortality Database and the Canadian Cancer Registry Database. The study population consisted of over 16,000 solid organ transplant recipients registered between January 1, 1981 and December 31, 1998. This study was designed to assess the risks of developing cancer, overall and site-specific, in transplant recipients in comparison to the general Canadian population, and to determine the impact of risk factors, such as age at transplant, sex and calendar period, on the association between organ transplant and cancer development using Standardized Incidence Ratios (SIR), Standardized Mortality Ratios (SMR), and Proportionate Mortality Ratios (PMR). In addition, Cox and logistic models were used to assess the effects of various risk factors on cancer incidence and mortality in transplant

sub-populations, while cumulative incidence was used to study the patient survival pattern. Lastly, Population Attributable Risk (PAR) was used to quantify the impact of organ transplantation on cancer incidence and mortality.

Results: Among major causes of death, the highest PMRs were due to genitourinary diseases, followed by endocrine, nutritional and metabolic diseases, and infectious diseases. SIRs and SMRs indicate that cancer incidence and were relatively lower than that observed for other major causes of death, and slightly higher than that observed in the general Canadian population. Lastly, logistic regression results indicated that age, year of surgery, and smoking status were significant risk factors in mortality due to all causes, while the Cox regression model showed that age, sex and year of surgery were significant risk factors for cancer incidence. Overall, the PAR in this cohort was very minimal, indicating that the risk of mortality and cancer incidence due to organ transplantation is negligible.

Conclusion: Life threatening diseases such as those of the genitourinary system, as well as endocrine, nutritional and metabolic diseases and infectious diseases are leading causes of death. Future research should be directed at ways of reducing incidence and subsequent mortality due to these causes.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Drs. Yang Mao and Howard Morrison for giving me the opportunity to pursue this project. I feel very fortunate to have been under Dr. Mao's mentorship for the past two years, and I am most thankful for his scientific guidance, generous assistance, patience and for equipping me with the appropriate tools for my future career in Epidemiology.

I am also very thankful to Mr. Robert Semenciw for sharing his expertise with me and for his continual assistance, which was greatly appreciated during this project. I would also like to thank Dr. Ying Jiang for her support and for giving me direction with this project.

I would also like to thank my colleagues in the Evidence and Risk Assessment Division at the Public Health Agency of Canada for their assistance and words of advice, as well as the staff from Statistics Canada for granting me access to their data.

I am also very thankful to the Department of Epidemiology and Community Medicine and my colleagues at the University of Ottawa for their support during my studies.

Lastly, I would like to sincerely thank my family and friends for their understanding, support and encouragement while pursuing this project.

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1. INTRODUCTION

1.1 General Background

Organ transplantation is one of the best modalities for treating fatal organ failure (Hoshida, 2004). According to statistics, more than 20,000 solid organ replacement procedures have been performed in Canada since 1981 (CIHI Report 2010). In recent years, an average of 2,000 transplants per year have been performed, some of the most commonly transplanted organs being kidney, liver, heart, and lung.

From 1998 to 2008, 10,425 kidney transplants were performed, with the largest number, 2,073, performed in Ontario, closely followed by the 1,896 performed in Quebec. Among all these, the average age of patients was between 40 and 45, the largest percentage (40.5%) being between the age of 45 and 64. Sixty-three percent of patients were recorded as male (CIHI Report, 2010).

In the same period, 4,217 liver transplants were registered in the Canadian Organ Replacement Registry (CORR), with more male recipients (64%) than female. The majority of patients (62%) were age 35-59, and the highest rate of liver transplants was recorded in Alberta, with a rate per million population (RPMP) of 16.4 (CIHI Report, 2010).

In addition, 1,643 heart transplants were registered, the largest number of transplants (49%) being performed in recipients age 35-59, of which 74% were male. When considering the population by province, Quebec had the highest RPMP at 6.0 (CIHI Report, 2010).

Moreover, 1,399 lung transplants were performed, 70.0% of them being bilateral. Among provinces and territories, Alberta had the highest RPMP at 7.00 (CIHI Report, 2010).

While the number of transplants performed between 1998 and 2010 has increased by up to 70%, there has also been a growing demand for transplants, with an increase greater than 200% in the number of patients in need of a transplant over 10 years—from 42 patients in 1997 to 129 in 2008 (CIHI Report, 2010).

Given the escalating number of procedures being performed, the increase in adverse health outcomes and health care utilization has captured the attention of public health officials. In particular, cancer is being recognised as a major source of morbidity among transplant patients, with up to 30% of otherwise successfully treated recipients developing cancer, according to a 30-year follow-up study (Sheil, 1993).

Several major studies show that the distribution by site of cancers varies with time post-transplantation (Sheil, 1998, Villeneuve, 2007, Jiang 2008). According to reports, the cumulative incidence of cancer among renal transplant recipients continues to increase during the 15-20 years post-transplantation; however, very few cancer studies have followed a sufficient number of patients for more than 15 years post-transplantation (Sheil, 1998).

The increased malignancy incidence in transplant patients has been observed and recognized as being the result of a combination of decreased immunosurveillance, activation of oncogenic viruses, chronic stimulation of the immune system, and immunosupression (Muerve, 2005).

More specifically, the pathogenesis of such diseases is a multifactorial process involving genetic, immune, environmental, and, in some cases, viral components, entailing

alterations in the regulation of cell growth, resistance to apoptosis, defects in DNA repair, mutations in tumour suppressor genes and oncogenes, and sustained angiogenesis. In transplant recipients, immunosuppressive drugs severely disrupt immune function and may also have direct effects at the site of tumour formation. In combination, these changes create a setting where cell transformation is enhanced and mutated cells can gain a proliferative advantage (Martinez, 2005).

In addition to these genetic predispositions, the number of *de novo* malignancies developing after solid organ transplants is progressively growing because of the increasing age of the transplant population as well as longer survival of transplant patients (Baccarani, 2006). Moreover, because of events such as rejection and infection, survival and quality of life are generally limited post-transplantation (Bourge, 1997). Other risk factors which have been identified in the development of adverse outcomes include being male, and being Caucasian race (Muerve, 2005).

In recent years, patient survival has improved with the use of newer immunosuppressive drugs, which are essential in organ transplantation and are used to prevent organ allograft rejection. Despite longer patient survival, these long-term and more potent regimens have led to greater morbidity and mortality than observed in the general population (Samhan, 2006).

The most common causes of death post-operation are infection, early graft failure, and acute rejection, followed by genitourinary diseases, subcutaneous diseases, cardiovascular diseases, and nervous system/sense organ diseases (Bourge, 1997). Typically, studies on transplants have focused on the organs that are most frequently grafted— kidney, liver, heart, and lung (CIHI Report, 2010).

1.2 The Denouement of Transplantations

Transplantations serve as an ultimate form of therapy for patients with end-stage diseases. Highly satisfying results may be attributed to the development of new preservation solutions, improvement in surgical techniques, perioperative patient management, and new immunosuppressive drugs (Meerdnik, 2001). With the increasing success of transplantation and fewer episodes of acute rejection and virtual freedom from chronic rejection, long-term survival rates have improved (Jain, 2008).

Transplantation outcome may be gauged by several endpoints, such as survival, physiologic function, quality of life, and cost-effectiveness. Variability in outcome depends on the hospital or institute, type of transplant, risk factors for the transplant population (e.g, age, sex), immunosuppressive regimen, and follow-up time (Aparicio, 2009).

The prognosis of transplantation depends on the stage at which the disease is diagnosed. For early detection of outcomes, both the selection of patients at high risk and effective surveillance programs are important. Studies show that the cumulative incidence of post-transplantation *de novo* malignancies increases with time and they represent a major cause of late death among kidney, liver, and heart recipients (Kauffman, 2002).

Generally, infections occur immediately post-transplantation. Bacterial infections predominate in the first month post-transplantations and are inherently related to surgical procedures (Briggs, 2006). In those who experience early graft failure and rejection, mortality usually occurs during surgery and within the first two weeks (Bourge, 1997).

Over time, surviving patients are likely to experience advanced bone loss, hypertension, and marginal renal function as a result of long-term immunosupression.

Moreover, according to Jain et al. (2008), due to an aging population and an older cohort of transplant recipients, age-related complications such as cardiovascular disease and *de novo* cancers are likely to contribute to long-term graft loss and death.

Because immunosupressed organ recipients develop malignancies much more frequently than their age-, sex- , and race-matched controls, and because these malignancies develop within relatively short time spans compared with controls, transplant recipients serve as a human laboratory model for analyzing the cause, epidemiological characteristics, genetics, and treatment of cancer and other disorders (Jain, 2008).

1.3 Adverse Health Outcomes Post-Transplantation

1.3.1 Infectious and Parasitic Diseases

Over the past 25 years, advances in immunosuppression, the use of selective anti-microbial prophylaxis, and improved microbiologic diagnostic tools have progressively reduced the risk of infection in solid organ recipients. These advances coincide with a reduced overall incidence and mortality due to infections (Fishman, 2010).

Generally, infections in organ transplant recipients can be derived from various sources, such as donors and recipients, nosocomial and community-acquired events, and travel (Fishman, 2010). In the immediate postoperative period, bacterial infections that develop are mainly related to the technical aspects of the procedure. Following this period, the nature and variety of infectious complications change.

Studies of kidney transplant recipients show that the transplant wound and the urinary tract were the most common sites of infection, occurring in up to 33% and 24% of

recipients, respectively. Septicemia has been reported in approximately 10% of patients, while opportunistic viral, fungal, and actinomycotic infections occurred in 9% of patients. Up to 8% of patients were reported to have died as a result of infection (Fishman, 2010). Similarly, in liver transplant recipients, infection and rejection remain major causes of morbidity and mortality, accounting for up to 85% of deaths in some studies (del Pozo, 2008). Overall, according to del Pozo (2008), 48% of infections were bacterial in nature, 22% were fungal, and 12% were viral.

In heart transplant recipients, Gram-positive bacteria are reported to be the predominant cause (28.6%) of bacterial infections, while mortality is highest (23%) for fungal infections, followed by *protto*zoal, bacterial, and viral infections, which were found in proportions of <10% each (Kirlin, 2004).

Lung transplants have the highest rate of infections among solid organ transplant recipients, with up to 76% of patients developing mild to severe infections post-transplantation (Hussain, 2009, Gottlieb, 2009). Significant contributors to such infections include continuous graft exposure to the environment, impaired cough reflex and mucociliary clearance, interruption of the blood and lymphatic vessels, and donor-transmitted pathogens (Gottlieb, 2009).

1.3.2 Cancers and Skin/Subcutaneous Diseases

The development of cancer in organ transplant recipients is a multifactorial process. Disease development is primarily facilitated by the immunocompromised state, which provides a permissive environment for malignant cell growth, for oncogenic viruses infection or reactivation within the host, for chronic antigen stimulation leading to a

cytokine-rich milieu, and for impaired immune surveillance imposed by chronic immunosuppression (Jain, 2008).

Previous studies have aided in quantifying various cancer incidence risks for transplants, such as for kidney and liver (Briggs, 2006, Jiang, 2008, Villeneuve, 2008). In accordance with most studies, non-melanoma skin cancer and lip cancer showed the highest increased relative risk, followed by tumours that are common also in the general population in organs such as lung, colon, Non-Hodgkin's Lymphoma (NHL), kidney, heart and liver (Briggs, 2006).

Solid organ cancer has a 20% probability of developing 20 years post-transplant, and the prognosis in patients with this is very poor, with a median survival from the time of diagnosis of just under four months (Briggs, 2006).

Overall, a meta-analysis of five population-based studies demonstrated a three-fold increase in risk of cancer in solid organ transplant recipients compared with the general population matched for age, sex, and calendar period (Vajdic, 2009). In some transplants, for example heart, the risk of developing cancer following transplantation has been reported to increase up to 100-fold compared with the general population (Cardillo, 2001).

Though largely under-reported, non-melanoma skin cancer following organ transplantation is extremely common, and by 20 years post-transplant it will have occurred in 50% of patients, particularly in high-incidence areas such as Australia (Vajdic, 2009). Despite high incidence rates, a fatal outcome in this group of patients is uncommon.

1.3.3 Endocrine, Metabolic, Nutritional and Digestive Diseases

The components of metabolic diseases are often aggravated during the post-transplant period by transplant-specific factors like immunosuppression, and have also been reported to be strong predictors of patient morbidity and mortality (Watt, 2010).

While transplant recipients continue to show an increased prevalence of cardiovascular disease (CVD) compared with the general population, the factors that determine this condition are metabolic in nature, such as hyperlipidemia, and in particular diabetes mellitus—which has been identified as a major contributor to cardiovascular disease (Watt, 2010).

In particular, the prevalence of diabetes mellitus in liver transplant recipients rises from 15% pre-transplantation to 30-40% post-transplantation, with hypertension similarly increasing from a pre-transplant prevalence of 15% to 60-70% post-transplantation (Watt, 2010). Although uncommon prior to transplantation, hyperlipidemia is seen in approximately 50-70% of patients post-transplantation. In addition to increasing cardiovascular mortality, it reduces graft function and increases the risks of infections and the percentage of graft loss (Watt, 2010).

Further complications may lead to post-transplant metabolic syndrome (MS) comprising hypertension, dyslipidemia, increased fat mass/obesity, and glucose intolerance, combined with other metabolic side effects derived from glucocorticoid and calcineurin inhibitor immunosuppression, which ultimately attenuates allograft and patient survival.

Similarly, liver disease is one of the leading causes of death in long-term kidney transplant recipients. In addition, chronic hepatitis, cirrhosis, and hepatocellular

carcinoma are well known liver complications of hepatitis C virus, especially after kidney transplantation (Watt, 2010).

In liver transplant recipients, up to 28% of deaths have been reported as being due to hepatic causes, while recurrent liver disease or chronic rejection account for up to 42% (Watt, 2010).

In lung transplant recipients, the most frequent metabolic complications include arterial hypertension, chronic renal insufficiency, hyperlipidaemia, diabetes, and osteoporosis (Knoop, 2010).

Studies in the literature emphasize the impact of major nutritional risk factors, such as malnutrition and other associated or independent metabolic complications, on the results of renal transplantation. Obesity, which may be either pre-existing or developing after transplantation, can lead to adverse health effects, such as poor wound healing or increased risk of CVD. Hypercholesterolemia and hypertrigliceridemia, which are risk factors for cardiovascular disease, are common post-renal transplantation complications (Martins, 2004).

Multiple factors related to the underlying disease and postoperative period and their complications, including the etiology and functional stage of liver disease and surgical complications, among others, directly contribute to malnutrition in patients. Malnutrition that existed prior to transplant has been associated with an increased risk of infection, delayed wound healing, and muscle weakness. Preoperative protein-calorie malnutrition (PCM) has been associated with an increased need for intraoperative transfusion of blood derivatives, prolonged length of stay in the intensive care unit and hospital, and a higher

cost of liver transplantation. During the postoperative period, PCM may contribute to the occurrence of infections, rejection episodes, and metabolic alterations, thus influencing the quality of life of these patients.

1.3.4 Cardiovascular and Circulatory Diseases

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality, particularly in kidney transplant recipients, where such malignancies account for up to 40% of deaths. In most transplants, the contribution of CVD to post-transplant mortality reflects to some extent the incidence of cardiac disease in the general population, but is more relevant among uremic patients (Peterson, 2005), with up to 52% of lung recipients being diagnosed with CVD at 1 year post-transplant, and approximately 86% of recipients at 5 years (Lyu, 2008).

The increased risk of CVD in patients with chronic kidney disease may be attributed to the presence of both traditional risk factors such as smoking, dyslipedemia, hypertension, and diabetes, and factors related to kidney dysfunction, such as high levels of lipoprotein A, hyperhomocysteinemia, and the increased calcium-phosporus product (Petersen, 2007).

Hypertension is another significant risk factor, higher blood pressures having been observed among patients whose allografts failed the most rapidly. Previous studies have demonstrated that systolic blood pressure, diastolic blood pressure, and mean arterial blood pressures at 1 year post-transplantation are statistically and clinically significant

predictors of long-term allograft survival independent of baseline allograft function (Mage, 2000).

Although there are robust data on the frequency of risk factors and their contributions to cardiovascular disease, few studies have demonstrated the benefit of modifying these risk factors to reduce CVD (Shirali, 2008). Since previous studies of the relationship between hypertension and organ failure have not been able to control for baseline function, the question of whether elevations in blood pressure are a cause of or a result of progressive organ dysfunction remains unanswered (Mange, 2008).

Further complicating the evaluation of the role of hypertension as a cause of progressive allograft dysfunction is the potential effect of certain classes of antihypertensive agents on renal function independent of their effect on blood pressure. For example, calcium channel blockers have been shown to limit the renal arteriolar vasoconstriction induced by cyclosporine, and angiotensin-converting enzyme inhibitors have been shown to reduce the rate of progression of renal failure in native kidney disease, possibly by decreasing intraglomerular hypertension (Mange, 2000).

1.3.5 Respiratory Diseases

Underlying lung disease has been acknowledged in the literature as a significant predictor of death (da Silva, 2009). Respiratory complications are commonly associated with respiratory tract infections and sepsis, as outlined in Section 1.3.1.

Because of the augmented immunosuppression, the likelihood of developing a pulmonary infection is particularly high in the first half-year post-transplantation. Bacterial pneumonia and opportunistic infections with organisms such as cytomegaloviruses and

Aspergillus organisms account for most of the serious infections after transplantation. Similarly, community-acquired respiratory viral infections, such as those caused by respiratory syncytial virus, influenza, parainfluenza, or adenovirus, are increasingly recognized as causes of severe pneumonia in lung transplant recipients (Matar, 1999). The highest incidence of respiratory infections, 21%, was reported in lung studies (Wendt, 1997).

In recent years, bronchiolitis obliterans syndrome (BOS) has been a common development, leading to additional infectious complications. Pathologically, BOS is characterised by mononuclear cell infiltration, followed by the disturbance of the respiratory epithelium and progressive accumulation of fibroblasts and fibrous connective tissue in the airways (Czebel, 2006). In patients with BOS, obliteration of the small airways, development of bronchiectasis and the enhanced immunosuppression—which is believed to slow down the obliterative process—are additional risk factors for infection. Death of BOS patients is usually related to respiratory failure due to recurrent respiratory tract infections or sepsis (Czebe, 2006).

1.3.6 Genitourinary Diseases

Renal dysfunction is another common long-term complication. By six months post-transplantation, 91% of lung transplant recipients have shown a degree of renal decline from their baseline pre-transplant level. The subsequent development of chronic renal failure increases the risk of death by four- to five-fold in these patients (Liu, 2008).

The most common cause of renal failure is calcineurin inhibitor nephrotoxicity, which is exacerbated by the use of nonsteroidal anti-inflammatory drugs. Such medication is used

to treat and prevent infection; however, it may impair renal function, particularly in recipients who have pre-existing kidney conditions. Other factors which worsen the development of chronic renal failure, and which are caused partly by calcineurin inhibitor use, include hypertension, hyperlipidemia, and diabetes.

In particular, urinary tract infections (UTI) have been reported to occur with frequencies ranging from 30% to 60% in kidney transplant recipients during the first year post-transplantation (Sorto, 2010).

Risk factors associated with the development of genitourinary diseases include female sex, age, alterations in the anatomy of the urinary tract, original kidney disease, surgical manipulation during transplantation, as well as the dose, intensity, and duration of immunosuppression (Sorto, 2010).

1.4 Organ-Specific Transplantations

1.4.1 Kidney Transplantation

Kidney is the most commonly replaced organ worldwide, with over 12,000 transplants performed in Canada between 1981 and 1998. The high demand for kidney transplants has in turn led to organ shortage and waiting times have increased (CIHI, 2010).

One of the primary causes of chronic renal failure among kidney transplant recipients is the development of chronic rejection. Age, sex, ethnicity (i.e., South Asian vs. white) primary renal diagnosis and donor-organ source are all important predictors of graft failure and, ultimately, death (Schaubel, 2002). In addition, time since transplantation, diabetes mellitus, geographic position of the transplant centre, and era in which the

transplant was performed—which is related to the immunosuppressive regimen prescribed—have also been acknowledged in literature as risk factors (Briggs, 2001).

Also of concern, several studies have reported increased cancer incidence rates among organ transplant recipients (Villeneuve, 2007). The standardized incidence ratio found for this cohort was 2.5-fold greater than that for the general population (Villeneuve, 2007).

As reported by Schaubel at al. (2002), between 1981 and 1998 a significant decrease over time occurred in adjusted relative risks for death and graft failure among Canadian renal transplant patients; the decrease continued to the end of 1998, likely because of refinement in patient management. The greatest decrement occurred in 1985, which corresponds to the implementation of cyclosporine therapy (Schaubel, 2002). Survival rates are up to 95% after one year, and up to 80% after five years (Organ Procurement and Transplant Network, 2009).

1.4.2 Heart Transplantation

Between 1981 and 1998, over 2,000 heart transplants were performed in Canada (CIHI, 2010). Due to the limited number of donor hearts, the costs of cardiac transplantation, as well as the associated long-term medical follow-up and inherent morbidity and mortality associated with procedures, this application is relatively limited (Bource, 1997).

The risk of *de novo* malignancies in heart transplant is reported to range from 3% to 25%. The occurrence of cancer after heart transplantation is a well-described consequence of immunosupression, with a reported incidence of 1% to 16% (El-Hamamsy, 2005). One study shows up to 21% of heart recipients developed neoplasms, the most common type

being skin (42%), lung (12%), prostate (9%) and genitourinary (9%). Overall, two-thirds of cancers in heart post-transplantation occur in the genitourinary, digestive, and respiratory systems (Sheil, 1997).

Despite many advances in transplantation medicine, studies on risk factors that influence morbidity and mortality in the recipient after cardiac transplantation are limited by their relatively small sample size, and in most cases, by the fact that they were done at a single health center (Bource, 1997).

Early graft failure (during the first month) rejection, and infection, account for over 60% of deaths during the first year, whereas after the first year they account for less than 25% of mortality. In their place, allograft coronary artery disease and malignancy become increasingly prominent causes of death—about 10% during the first year compared with nearly 50% in subsequent years.

The highest risk of death is during the first month after transplantation, and by three months, the risk is expected to fall to a low level. The 1-year and 5-year survival rates in the United States vary from 70-90% (Meerdnik, 2001) to 65-75%, respectively (Myers, 2003).

1.4.3 Liver Transplantation

In Canada, liver is the second-most commonly transplanted organ, with nearly 3,000 transplants having been performed between 1981 and 1996. The rate of *de novo* cancers after this type of transplantation has been reported at 3% to 26%. This variation may be

attributed to the length of follow-up, to different ways of reporting, and to geographic variations in *de novo* malignancies (Jain, 2008).

Non-melanoma, non-Kaposi's skin cancers (squamous cell cancer and basal cell carcinoma) are the most common type of *de novo* malignancies in the post-transplant population, showing up to 70 times greater incidence than in non-transplant populations (Jain, 2008). In particular, the standardized incidence ratio reported for this cohort was 2.5-fold greater than that for the general Canadian population (Jiang, 2008). Risk factors that may affect patient outcome include older age in donor and recipient, sex mismatching, and prolonged and acute and hepatic conditions (Quintineri, 2006). Although older age has been established as a significant risk factor, it is not considered a contraindication for liver transplantation; however, age-related morbidity may be a cause of mortality (Herrero, 2003).

In the current transplant era, the overall 1-year and 5-year survival rates after a liver transplant are 85% and 68%, respectively, with a 10-year survival rate close to 50% (Watt, 2010).

1.4.4 Lung, Heart-Lung and Bilateral Lung Transplantations

Single lung, bilateral lung, and heart-lung transplantations comprise just over 600 transplantations performed in Canada between 1981 and 1998 (CIHI, 2010).

The lung as an allograft seems particularly prone to infection. Besides the generalized immunosuppressive effects of the anti-rejection drugs, lung defences are breached at several levels after transplantation (Trulock, 2001). In particular, Gram-negative

pneumonia is the most common cause of death during the first 30 days after lung transplantation. Chronic rejection and alveolar damage are also highly prevalent and have shown to lead to prolonged respiratory insufficiency and death (Reichert, 1999). Other common morbidities include circulatory diseases, renal dysfunction, and skin diseases.

Similarly, respiratory diseases occur in 43% of recipients who survived at least 90 days post-transplantation. Hypertension and renal dysfunction are also recognized as sources of morbidity, while respiratory and circulatory diseases are minor contributors to mortality (Trulock, 2005).

Compared with the general population, a 26-fold risk of developing lymphoproliferative disorders after cardio-pulmonary transplantation has been reported (*Otto*, 2004). Cancer is a more common cause of death among patients who had single rather than among those who had bilateral lung transplantation (Thabut, 2009).

Sex, age, and type of transplant (single vs. bilateral) have been reported as significant risk factors in patient outcome (Speich, 2004, Starnes, 2004).

Life expectancy after lung transplantation has improved in recent years, but it is still lower than in patients with other solid organ transplantations (Gottlieb, 2004).

Mortality associated with lung transplant is appreciable, with 1-, 3-, and 5-year survival rates of approximately 76%, 60%, and 50%, respectively (Lynch, 2006). Survival rates for single and bilateral lung transplant recipients are similar throughout the first year; however, it has been established that single lung transplantation confers short-term survival benefit but long-term harm, whereas bilateral lung transplantation confers short-term harm but long-term survival (Thabut, 2009).

1.5 Information Gaps

Although a myriad of studies have been aimed at elucidating the associations between organ transplants and various outcomes, most of them have been narrow in focus, restricted to a partial population, using single-clinic data and with relatively short follow-up periods. Thus, there is a need for a detailed study of adverse health outcomes for the most common solid organ transplants, with a particular focus on cancer, where an adequate sample size is available for long term follow-up.

1.6 Objectives

The overall objective of this study is to conduct a detailed examination of adverse health outcomes among Canadian organ transplant recipients, with an emphasis on cancer incidence and mortality.

More specifically, the objectives of this study are as follows:

1. To examine post-transplant mortality in organ replaced patients in comparison to the general Canadian population.
2. To assess the risks of developing cancer, overall and site-specific, in transplant recipients by type in comparison to the general Canadian population.
3. To determine the impact of risk factors on the association between organ transplant and cancer development.

2. MATERIALS

2.1 CORR Database

The Canadian Organ Replacement Register (CORR) is a population-based, nation-wide organ failure replacement registry, which contains information on virtually all Canadian patients who have undergone organ transplantation (CIHI, 1999). The CORR was initiated in 1981, when the End Stage Renal Disease (ESRD) Registry was moved from Statistics Canada to the Canadian Institute for Health Information and extrapolated to include organ transplant recipients.

Baseline demographics collected include date of birth, sex, province of residence, race, co-morbid conditions, and underlying diseases leading to organ failure. Data from CORR may be used to analyze and report on the outcomes of vital organ transplantation. In addition, the register could provide statistics which may be used to assess long-term trends for organ transplantation.

2.2 Canadian Mortality Database

The Canadian Mortality Data Base (CMDB) is a file that contains all death records of Canadians, with computerized records existing as of 1950. The registration of all deaths is required by law according to the Provincial and territorial Vital Statistics Acts (or equivalent legislation), whereby the burial of a human body is not permitted without a death certificate (Statistics Canada, 2009).

The CMDB contains death events sourced from death certificates reported by the provincial and territorial death registries and are organized in the national Vital Statistics database.

In addition to the registration of death, this database captures other statistical data items such as age, sex, marital status, place of residence and birthplace of the deceased, date of death, province or territory of occurrence of death, place of accident (for most non-transport accidental deaths), underlying cause of death classified to the "World Health Organization International Statistical Classification of Disease (ICD) and Related Health Problems", and autopsy records (whether one was held, and if so, whether the results of it were taken into account in establishing the cause of death) (Statistics Canada, 2009).

Under-coverage is thought to be minimal, and is being monitored. This may occur as a result of late registration, and is known to be much less common than that observed in birth registration. Other late or missing registrations may occur with unidentified bodies, or for Canadians who die outside of Canada. Under-coverage may also occur as a result of deaths of serving members of the Canadian military, as they are not registered by the provinces and territories. Over-coverage is minimal. Deaths of non-residents of Canada are registered but are excluded from most tabulations. Duplicate death registrations are identified as part of the regular processing operations on each provincial and territorial subset, as well as by additional inter-provincial checks (Statistics Canada, 2009).

2.3 Canadian Cancer Registry Database

The National Cancer Incidence Reporting System (NCIRS) of Statistics Canada has been collecting cancer registration data from each provincial/territorial cancer registry

annually since 1969. This includes primary sites of cancer occurring among residents. In 1992, the Canadian Cancer Registry Database (CCRDB) replaced the NCIRS. The standard record layout and definitions were established using the CCRDB data dictionary. Data items for each record include age, sex, date of birth, postal code, ICD-9 code, method of diagnosis, date of diagnosis, ICD-O-topography, ICD-O-Morphology, ICD-O-behaviour, Laterality and other tumour-related information. Approximately 85% of records are microscopically confirmed, and the most recent data for all provinces is available as of 2007.

On average, about 145,000 new cancer tumour records are registered in the Canadian Cancer Registry (CCR), a patient-oriented database which is housed and maintained at Statistics Canada. Each provincial and territorial cancer registry has the ability to add, update, and delete records. The CCR can be updated with new records or changes to previous records, as part of regular submissions from the registries to Statistics Canada. The following three software modules perform the tasks of building and maintaining the data in the CCR database: Core Edit, Internal Record Linkage, and Death Clearance. An internal record linkage and a national death clearance of cancer tumours diagnosed since 1992 are performed annually (Statistics Canada, 2009).

3. METHODS

3.1 Study Population

The study population included in this study consisted of selected solid organ replaced patients who were registered in the CORR database between January 1, 1981 and December 31, 1998. Analysis was restricted to patients who did not have any pre-existing records of cancer incidence.

3.2 Study Design

3.2.1 Data Linkage

Data linkage refers to the process of linking together records pertaining to the same entity applying either a deterministic link of one unique identifier or probabilistic link from the weight of several identifiers, as outlined in detail in Section 3.3.1.

Canada is among the leading counties with a well-established national health information system, which makes record linkage a pragmatic avenue for research. The United States, Australia and some EU countries, such as the United Kingdom and Italy are some of the other countries using similar technologies (Ghbobrial, 2002, Kinchen, 2001, Stewart, 2009).

This retrospective cohort follow-up study was made possible through a series of probabilistic linkages, which were completed in order to create a data set which would comprise records of transplants recipients and associated cancer and/or mortality. The initial linkage performed in this study was between the CORR database (1981-1998) to existing taxation files from Statistics Canada, in order to confirm vital statistics of

patients, whereby an individual who was reported as being alive during a fiscal year, would have inherently completed an annual tax form in Canada. Subsequent linkages were performed between the CORR database (1981-1998) to CMDB, NCIRS and CCRDB.

3.2.1.1 Mortality Linkage

Mortality of the cohort was determined through linkage of the CORR database to the Canadian Mortality database using a probabilistic procedure referred to as the generalized record linkage system (GRLS). GRLS compared common fields in the two files to be linked, referred to as linkage keys and included variables such as first name, last name, birth date, sex, province of residence. GRLS then assigned weights to the resulting links and calculated a total weight. Links with a sufficiently high weight were accepted as a match.

This generalized software is based upon the Fellegi-Sunter model for carrying out record linkage and can be thought of as a two-stage approach. The first stage involves selecting "pockets" of records which were matched. For this particular linkage, three pockets were used as follows: 1) birth date; 2) death date; and 3) a phonetic NYSIIS version of surname and sex code. The second stage consisted of establishing comparison rules using variables common to both files for each pocket. These rules were used to generate various outcome weights depending on the degree of similarity between variables. For example, agreement of a surname like SMITH would have lower weight than agreement of a name like QUIGLEY. The various variables common to the two records were compared and the weights were summed. Threshold values were set for the acceptance

and rejection of linkages. Some manual resolutions were performed in order to select these values and to eliminate false linkages.

Completeness of the variables in CORR which were used for linkage were as follows: patient's date of birth (100%); patient's surname (100%), patient's given name (100%), patient's country of residence (81%); patient's province/territory of residence (86%), patient's city of residence (72%). The probability of correctly identifying deceased and alive subjects from record linkage to CMDB was 98% and close to 100%, respectively.

With regards to the transplantation procedure itself, analyses of the CORR database suggest that there is minimal (<4%) underreporting of kidney transplants within CORR. In addition, CORR performs active follow-up surveillance of patients, and approximately 1% of these have been lost to follow-up.

Although it is possible that some deaths in the CMDB may have been missed, particularly for those who died outside the country, Canada currently receives abstracted death data from approximately 20 American states, and the number of deaths that could have been missed is small given the personal identifying information available for this cohort (Villeneuve, 2007).

In addition, a taxation file provided by Statistics Canada was used to assist in the confirmation of these patients' vital status. This file served to refine the specificity of the mortality linkage, resulting in a lower number of false positive cases. The probability of correctly identifying deceased and alive subjects from record linkage to the CMDB was 98% and close to 100%, respectively (Villeneuve, 2007).

The causes of death were adapted from the International Classification of Diseases index (World Health Organization, 1975) and exclude the causes which had no reported deaths or low cell counts.

Mortality disease categories in ICD-9 order included:

- All causes
- Infectious and parasitic
- Neoplasms
- Endocrine/nutritional/metabolic
- Circulatory
- Respiratory
- Digestive
- Genitourinary

3.2.1.2 Cancer Incidence Linkage

Cancer registration data supplied by cancer registries were compiled into CCR, which is managed by the Health Statistics Division at Statistics Canada and is estimated to capture at least 95% of all incident cancer cases in Canada (Villeneuve, 2007). The CCR contains information on all Canadian residents, dead and alive, who have been diagnosed with cancer, excluding those with squamous and basal cell skin cancer. It also excludes patients who were diagnosed outside the country (Villeneuve, 2007). The linkage with the CORR database was done using personal identifying information which included surname, surname at birth, given names, birth date, social insurance number, and place of

residence. Given the high quality and completeness of the CCR, and the similarity in record linkage methodology used, it is reasonable to assume that the record linkage to the CCR was nearly as accurate as the record linkage to the CMDB, and that overall bias on the presented standardized incidence ratios should be minimal.

Further, each province and territory has a Cancer Act and a legislated responsibility for cancer collection, and the reporting of primary malignant cancers is in theory complete. There has been no evaluation of the accuracy of ascertaining incident cancers by linking CORR data to the CCR.

The cohort and cancer incidence data were linked before transplant in order to exclude patients who had been previously diagnosed with cancer, thus eliminating the potential residual effect of such cancers.

3.3 Ascertainment of Health Outcomes

This cohort study adopted a record linkage follow-up approach, whereby adverse health outcomes were determined using data linkage.

The CORR database was used as the exposure file. CORR records starting with 1981 until 1998 were included, with some exceptions, as outlined in Section 3.2.2. The CMDB, and the CCR served as outcome files. These well-established Canadian databases were used to generate statistics pertinent to organ transplant mortality and cancer incidence in Canada (CIHI, 2009).

3.3.1 Follow-up Process

In order to study mortality and cancer incidence of the CORR cohort, all kidney, heart, liver, bilateral lung, lung and heart-lung organ transplant recipients were included and follow-up was initiated from the date of the transplant operation. Only patients who were alive 30 days post-transplantation were included in the cancer analyses as well as the mortality analyses, unless otherwise specified. This design was adopted in order to reduce the residual effect of other health factors pre-dating transplantation, which might have had an immediate effect during the post-operative period.

In order to obtain an accurate estimation of person–years of follow-up, the date of event occurrence (i.e., death or cancer incidence) was used to determine the last day of follow-up. Where no link to CMDB and/or CCR was found, patients were assumed to be alive and cancer free, where applicable, at the last date of follow-up (i.e., date of death or December 31, 1998).

Patients with an apparent erroneous date of death (i.e., where death date appears before transplantation date, or where patients who were reported to be dead had completed an annual tax form) were eliminated from the study. In cases where there were multiple cancers, the follow-up period for cancer patients was terminated after the first occurring cancer. Moreover, patients with non-melanoma skin cancer were removed from the analysis due to poor reporting rates in the CCR.

In the mortality analysis, patients with no recorded cause of death were also excluded.

Lastly, patients with no recorded sex were excluded from the study.

3.3.2 Study Variables

The exposure of interest in this study was solid organ transplantation of various types, namely kidney, heart, liver, as well dual transplants, such as bilateral lung, single lung and heart-lung.

In the mortality analysis, the outcomes of interest were mortality due to all causes, infectious and parasitic diseases, neoplasms, endocrine/nutritional/metabolic, circulatory, respiratory, digestive and genitourinary diseases.

In the cancer analysis, the outcomes of interest were all cancers and cancers at the most common sites, such as kidney, lung, colorectal, and Non-Hodgkin's lymphoma.

The predictor variables of interest were of demographic and clinical nature, and included age, sex, race, calendar period, time since surgery, diabetes and smoking. Categorical analysis and logistic modeling were applied to adjust for potential confounding effects.

Due to limited clinical data available in CORR, only diabetes was selected in this analysis; however, the effect of this variable must be interpreted with caution, since several patients had a missing diabetes status.

A list of potential predictor variables from the CORR data dictionary which were considered for analysis is included in Appendix 4.

The general Canadian population was chosen as a control group in order to quantify the burden of the transplant population, relative to non-transplant patients. The use of a patient control group was circumvented for practicality purposes, in order to avoid costs and time consumptions.

3.4 Data Analysis

Separate analyses were conducted for each objective listed in Section 1.6 using SAS (V. 9.1, Cary NC).

3.4.1 Basic Statistics

Descriptive statistics were prepared for mortality, and cancer incidence and covariates (i.e., predictor variable) and were included in Appendix 4. Frequency tables were computed for categorical variables and grouped continuous variables.

Person–years of follow-up and incident cases of cancer were tabulated across strata defined by the following: attained age (<40, 40<60, ≥60); sex (male, female); calendar period of follow-up (1983 - 1990, 1991 - 1994, 1995 - 1998) and year of transplant (1981 – 1984, 1985 – 1988, 1989 – 1993, 1994 – 1998). In the mortality analysis, follow-up was tabulated by 0 - 3 months, 3 months - 2 years, 2 – 5 years, 5 – 10 years, and ≥10 years. Attained age, calendar period, and time since surgery were time-dependent variables as their values changed over follow-up. These tabulations served to adjust for differences in the distribution of the aforementioned variables between the two populations (transplant vs. general Canadian population) as well as changes in cancer incidence over time.

With regards to variable categorization, several alternatives were used and/or considered. Ultimately, categories were set based on sample size (e.g., year of transplant, calendar period of follow-up), and where applicable, efforts were made to create categories which were comparable to those observed in literature (i.e, age, year of transplant, calendar period of follow-up).

A 30-day period immediately post-transplantation was excluded from the follow-up in order to eliminate cases of cancer prevalent at the time of transplantation. These cases were also removed from Standardized Mortality Ratio analysis. This arbitrary cut-off point has been previously observed in literature (Villeneuve, 2007, Jiang, 2008) and also serves to eliminate deaths which may attributed to early graft rejection, bacterial infections related to the transplantation procedure, and also to eliminate au residual effects which may predate transplantation.

Follow-up extended until the earliest of: (i) date of cancer diagnosis, (ii) date of death, or (iii) December 31, 1998. The DATAB module in the Epicure software program housed by the Public Health Agency of Canada was used to tabulate these person-years. Follow-up was terminated immediately following the first incident cancer in order to eliminate additional analyses related to patient management and the occurrence of metastasis, which are outside the scope of this study.

3.4.2 Standardized Ratio Comparison

SMR

Standardized mortality ratios (SMRs) in organ-replaced patients relative to the general Canadian population were examined using data obtained through the linkage of CORR with CMDB, as outlined in Section 3.3.1.

SMR represents the ratio of the observed-to-expected number of deaths due to a selected cause and was calculated using the formula illustrated in Table 3.4.2.A, whereby the observed number of deaths was divided by the expected number of deaths, which was obtained by multiplying the mean value of death rates per 100,000 people to the person-

years of observation. Death rates for the general Canadian population were obtained using the Orius software, a program designed and housed by the Public Health Agency of Canada, which was used to generate age-sex-period-standardized statistics in Canada per 100,000.

Table 3.4.2.A Calculation of SMR by age and sex

Age group (year)	**Mean value of death rates per 100,000 (a_i) 1981-1997***	**Person-years of observation (n_i)**	**Expected no. of deaths ($e = a_i n_i /100.000$)**	**Observed no. of deaths (r_i)**	**SMR (# of observed deaths/ # of expected deaths)**
Male					
0-14	a_1	n_1	e_1	r_1	r_1 / e_1
15-44	a_2	n_2	e_2	r_2	r_2 / e_3
45-64	a_3	n_3	e_3	r_3	r_3 / e_3
65+	a_4	n_4	e_4	r_4	r_4 / e_4
Total		$\sum n_i$	$\sum e_i$	$\sum r_i$	$\sum r_i / \sum e_i$
Female					
0-14	a_1	n_1	e_1	r_1	r_1 / e_1
15-44	a_2	n_2	e_2	r_2	r_2 / e_3
45-64	a_3	n_3	e_3	r_3	r_3 / e_3
65+	a_4	n_4	e_4	r_4	r_4 / e_4
Total		$\sum n_i$	$\sum e_i$	$\sum r_i$	$\sum r_i / \sum e_i$

Person-Years Calculation

Age-specific person years (PYs) at risk for each study population were calculated for each person at risk within a specified age group for each year from 1981 to 1998 and summed to obtain the total number of PYs. For each year, all transplant patients registered in the CORR data set as of December 31 of the previous year were assigned as having contributed one PY to their respective age group. Each newly registered case in the current year contributed with half a PY, and each death or lost-to-follow-up resulted in half a year being deducted from the total PY per age category. For example, in

December 1995, there were 14,609 organ-replaced patients in CORR. In 1996, there were 407 newly registered cases, 4,641 deaths and 53 patients lost-to-follow-up. Therefore, a total of (14,609 + (407 x 0.5) – (4,641 x 0.5) – (53 x 0.5) = 12,465.5 PYs were added to total PYs of the CORR cohort and matched with the corresponding sex and age categories.

Confidence Interval (CI) calculation for SMRs

Consequently, 95% confidence intervals were constructed assuming that the observed causes follow a Poisson distribution, which is a discrete probability distribution that expresses the probability of a number of events occurring in a fixed period of time, when these events occur with a known average rate and independently of the time elapsed since the last event (Breslow, 1987).

Exact confidence intervals for standardised mortality (event) ratios were calculated using the Poisson and chi-square methods (Dobson, 1991):

$$SMR = O/E$$

$$E = \sum n_i R_i$$

$$LL = \frac{(X^2_{\alpha/2,\ 2\alpha})}{2E}$$

$$UL = \frac{(X^2_{1-\alpha/2,\ 2(\alpha+1)})}{2E}$$

where LL and UL are lower and upper confidence limits respectively for the SMR, χ^2,α is the (100*α)th chi-square centile with ν degrees of freedom, O is the number of observed

deaths, E is the number of expected deaths, n_i is the person-time for the ith study group stratum and Ri is the reference population rate for the ith stratum.

PMR

A proportionate mortality ratio (PMR) analysis was calculated for the purpose of comparing proportionate mortality between the study cohort and the general Canadian population. In this analysis, the observed proportion of all deaths and a specific cause of death (infectious and parasitic, neoplasms, endocrine/nutritional/metabolic, circulatory, respiratory, digestive and genitourinary diseases) were compared with the corresponding proportion of these causes of deaths in the Canadian population obtained through a linkage with CMDB. PMRs were adjusted for the potentially confounding effects of age and sex and calendar period and were calculated using the procedures by Mantel and Haenszel (1959). A chi-square test was used to evaluate statistical significance.

As outlined in Table 3.4.2.B below, PMR was calculated by dividing the number of deaths from 1981-1998 due to a specific cause by the number of expected specific deaths, which was obtained by multiplying the number of all deaths from 1981-1998 by the number of specific deaths in the general Canadian population from 1981-1998 and

divided by the number of all deaths in general Canadian population from 1981-1998.

Table 3.4.2.B Calculation of PMR

# of deaths from 1981-1998 due to a specific cause	**# of all deaths from 1981-1998**	**# of specific deaths in general Canadian population 1981-1998**	**# of all deaths in general Canadian population 1981-1998**	**Proportion of specific deaths in all general Canadian population**	**Expected specific deaths ($e_{1)}$**	**PMR**
r_1	t_1	R_1	T_1	R_1/T_1	t_1*R_1/T_1	r_1/ e_1

SIR

The risks of developing cancer, overall and site-specific (e.g., kidney, liver, NHL, colorectal, and lung) in transplant recipients by organ type were compared to the general Canadian population, using the standardized incidence ratio (SIR). SIR is the ratio of the observed/expected number of incident cancers.

Canadian cancer incidence rates for these strata were multiplied by the person-years of follow-up to calculate the expected number of incident cases.

As with the SMR, the 95% CI was constructed under the assumption that the observed number of incident cases follows a Poisson distribution. SIRs were also adjusted for age and sex.

Stratified analyses were conducted to examine variations in categories of follow-up interval, transplant date, sex, and age at transplantation for all cancer sites.

3.4.3 Cox Proportional Hazards Model

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. The Cox proportional hazards model is a regression model which was used to analyze the time varying variables, such as age at transplant and follow-up interval. A key difference between logistic regression and Cox regression models is that Cox regression aims to estimate the hazard ratio, while logistic regression aims to estimate the odds ratio. The two are similar in that Cox regression is like the multiple regression except that the dependent variable is a hazard rate, and the outcome is shown as a function of time (Cox, 1972).

Through the Cox model, one can estimate the risk-factor-adjusted multiplicative effect of a patient characteristic without making strong assumptions about the actual underlying failure time distribution. In situations where the degree of relative importance of a risk factor over time is of interest, the Cox model can be adapted using time-dependent covariates (Statistics Canada, 2000).

In this study, age, sex, transplant date and follow-up interval variables were used to study the independent effects on the risk of developing cancer post-transplantation. The key assumption in the Cox proportional hazards model is constancy of covariate effects over time. This was examined in several ways, including fitting time-dependent effects and covariate-by-time interaction terms, and by examining residual plots.

The Cox model is robust in that it requires no particular probability distribution like Exponential, Weibull and Gompertz models to represent survival times. The model must meet the requirement that for any two individuals' hazards, the ratio of the hazards is constant (proportional) over time.

3.4.4 Logistic Regression Model

The association between organ replacement and mortality was assessed using logistic regression, which was used to determine the probability of occurrence of an event, (e.g., cause of death), by fitting data to a logit function (Agresti, 2007). This is a generalized linear model used for binomial regression, which makes use of several predictor variables, such as sex, race, smoking status, diabetes, age at surgery, and year of surgery to create generalized linear model for binomial regression. All variables included in this model were treated as categorical in order to avoid the assumption of linearity. Variables

employed in this model included age at surgery, year of surgery, sex, race, diabetes and smoking status. To initiate a logistic regression analysis, univariate models for each covariate were built to estimate unadjusted covariate effects. Unadjusted covariate effects were used for comparison with adjusted results to infer the direction and strength of confounding. In addition, a full model which included all covariates of interest, was fitted. Covariates which showed to be non-significant were removed in a backward step-wise fashion, provided that such removal did not bias the remaining covariates. A P-value of 0.05 was considered to indicate statistical significance. Interaction terms were examined after finalizing the inclusion of covariates. Once the final model was established, the adherence to its underlying assumptions was checked to ensure validity.

Although the COX model is preferred over the logistic regression model as it provides time dependent information, the hazard ratio may be biased when the proportional hazard assumption does not hold. For this reason, the logistic regression was utilized in the mortality analysis.

3.4.5 Cumulative Incidence

Well established competing risk methods were used to estimate the cumulative incidence of developing certain cancers or of dying post-transplantation. These are based on formulae by Gooley *et al.*. (1999), whereby the cumulative incidence function (CIF) is used to characterize the time-dependent, marginal probability of the outcome, represented here by cancer or mortality post-transplantation. Cumulative incidence was interpreted as the proportion of transplant recipients who developed cancer or died post-transplantation, a number which increases over time. The CIF for cancer or death is defined as the

integration over time of the product of the annual cancer or death rate and the probability of survival. This method is different than Kaplan–Meier failure time model in that individuals who die or develop cancer are no longer at risk for dying or developing cancer.

3.4.6 Population-Attributable Risk

Population-attributable risk (PAR) was used to determine the portion of the incidence of a disease in the population (exposed and non-exposed) that is due to exposure (Fleiss, 1979). In this study, PAR was employed to draw a comparison of the incident number of cancer cases or deaths when exposed to organ transplantation, under a counterfactual pattern, as expected in the general Canadian population (non-exposed population). As such, PAR is the proportion of cancer or deaths in the population that would be eliminated if exposure were eliminated.

Since CORR is a population-based register, the following formula was used:

$$\text{Cumulative Incidence} = \frac{\text{Number of exposed cases in study group X ARe}}{\text{Incidence in total population}}$$

where ARe is the attributable risk in the exposed, which is calculated using:

$$\text{ARe} = \frac{\text{(Standardized Mortality Rate* – 1)}}{\text{Standardized Mortality Ratio}}$$

*Standardized Incidence Rates were used in the cancer analysis

As stated by Gordis (2004), this is the equivalent of:

$$\text{Cumulative Incidence} = \frac{\text{(Incidence in total population) – (Incidence in non-exposed group)}}{\text{Incidence in total population}} \times 100$$

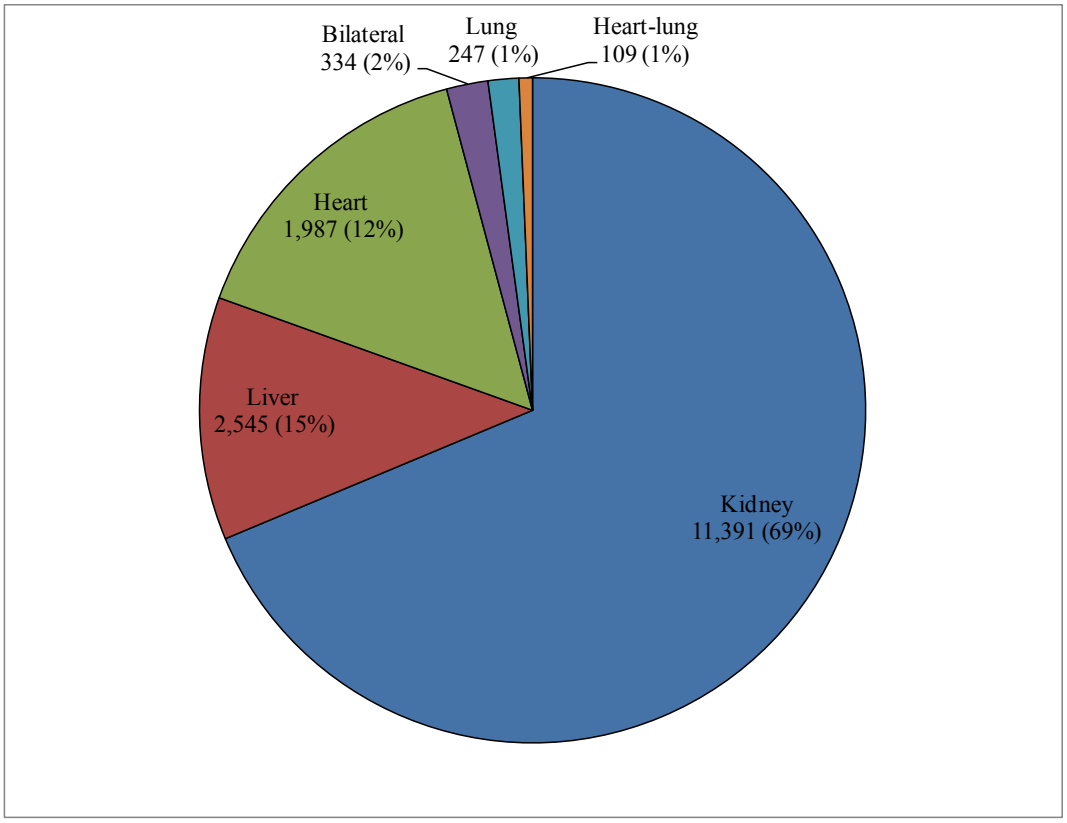
where incidence in total population refers to the total number of estimated new cases of cancer or deaths in Canada between 1981 and 1998, as reported in the Orius software, which is housed within the Public Health Agency of Canada.

4. RESULTS

4.1 Organ Replacement Statistics

Between January 1, 1981 and December 31, 1998, there was a total of 16,613 kidney, liver, heart, lung, bilateral lung and heart-lung transplants were performed in Canada. As depicted in Figure 4.1.A, the majority of these were kidney transplants, representing 11,391 (68.4%) cases of the entire aforementioned population. Liver and heart were the second and third most common transplants, with 2,545 (15.3%) and 1,987 (11.9%) cases, respectively. Bilateral lung, single lung, and heart-lung transplantations were much less commonly performed, with 334, 247 and 109 transplantations, and accounted for 1-2% each.

Figure 4.1.A Selected transplants performed in Canada between January 1, 1981 and December 31, 1998



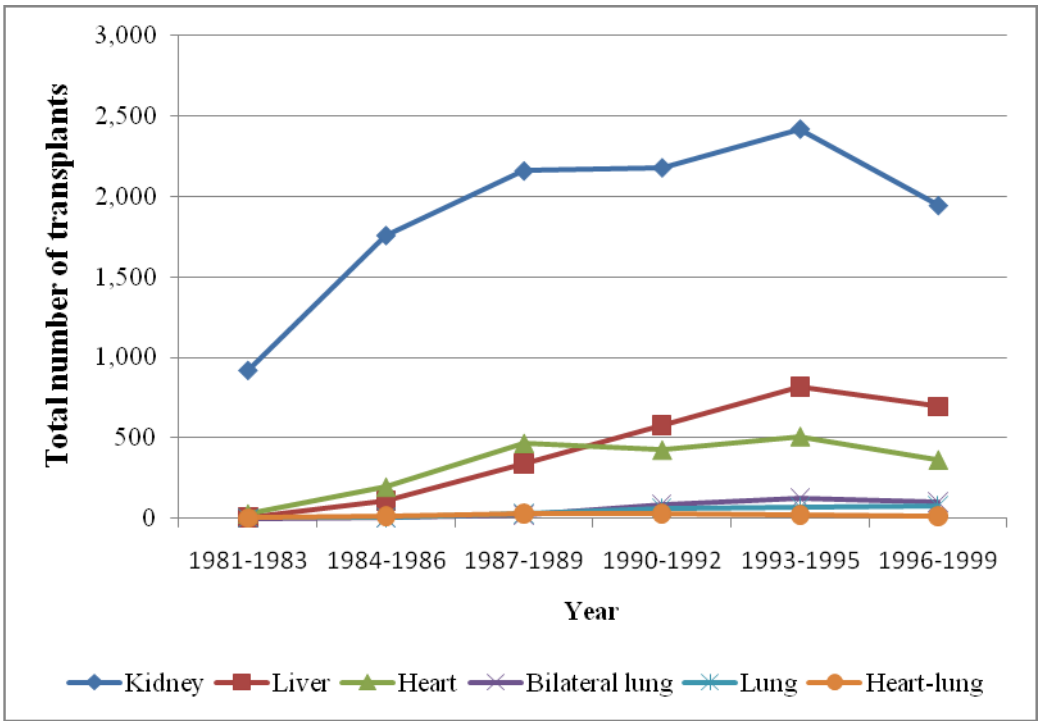
As shown in Table 4.1.A, the total number of transplants increased between 1981 and 1995, and decreased between 1996 and 1998 for all organs, with the exception of the heart. Despite the decrease in the number of procedures, the number of patients awaiting transplantation has consistently increased over the years for all types of solid organ replacement, with the exception of heart transplantation, which experienced a drop between 1996 and 1998 (CIHI, 2008).

With regards to the total number of new transplants for all solid organs, the lowest number was reported in 1981, while the highest was reported in 1997 (Figure 4.1.B). Overall, this difference is 7.5-fold greater, over the span of 16 years. Notably, there was a drop in the number of transplants in 1998, which may likely be attributed to incomplete registration in the last year of this study.

Table 4.1.A Selected transplants performed in Canada between January 1, 1981 and December 31, 1998

Transplant	**1981-1983**	**1984-1986**	**1987-1989**	**1990-1992**	**1993-1995**	**1996-1998**	**Total**
Kidney	922	1,760	2,161	2,181	2,421	1,946	11,391
Heart	27	194	467	425	510	364	1,987
Liver	3	108	341	579	819	695	2,545
Bilateral lung	0	1	22	87	124	100	334
Lung	1	6	30	63	70	77	247
Heart-lung	1	13	29	30	22	14	109
Total	954	2,082	3,050	3,365	3,966	3,196	16,613

Figure 4.1.B Selected solid organ transplants performed in Canada between January 1, 1981 and December 31, 1998



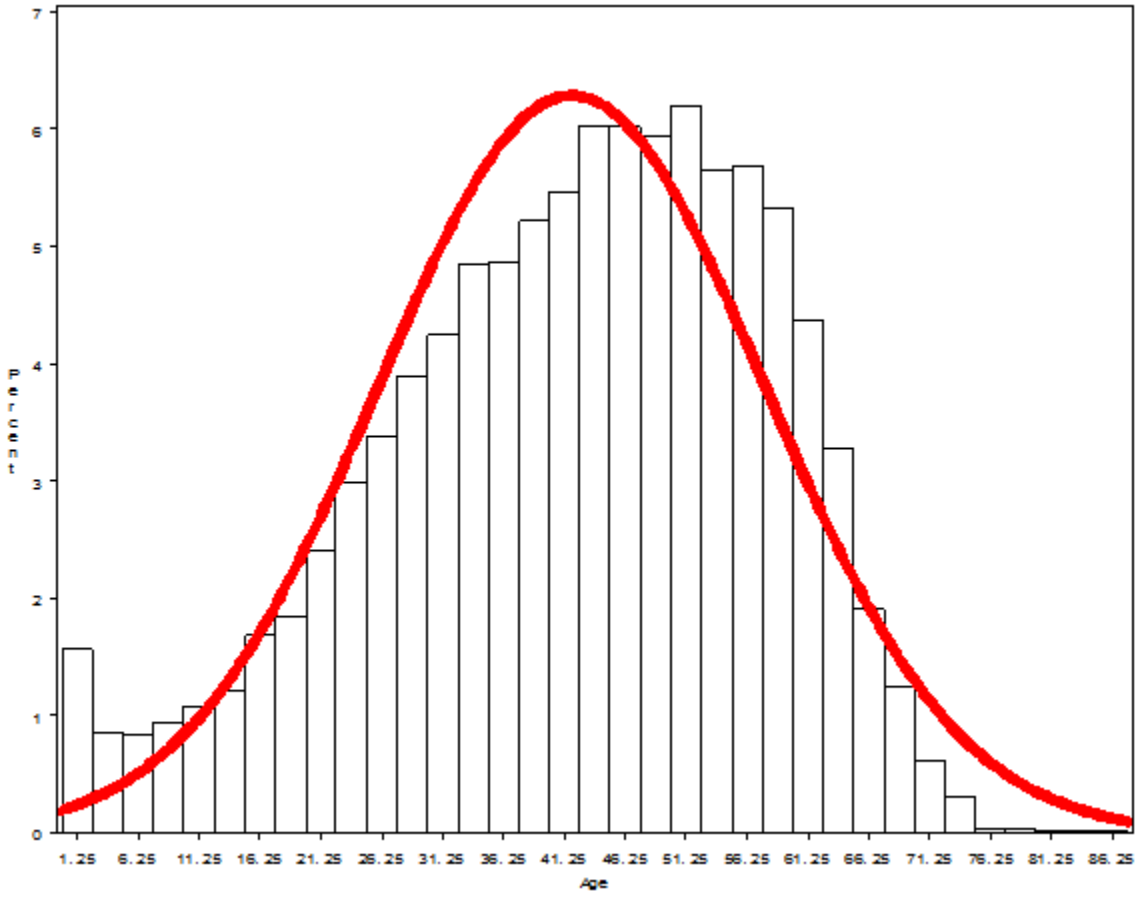
4.1.1 Demographics

Of the 16,613 organ transplant recipients, the mean age at initial transplantation was 41.8 and the age range was between 0 and 87.4 years. The largest proportion of patients were between the ages of 40 – 60 (46.7%), while the least common age groups were between 0 – 18 and over 60, with proportions of 8.6% and 11.9%, respectively (Table 4.1.1.A). The age distribution of organ transplant recipients in Canada appears slightly skewed to the right from a normal distribution (Figure 4.1.1.A).

Table 4.1.1.A Age of organ transplant recipients in Canada between January 1, 1981 and December 31, 1998

Age (years)	Frequency	Percentage (%)
≤18	1,411	8.6
19<40	5,401	32.8
40<60	7,702	46.7
≥60	1,967	11.9
Total	16,613	

Figure 4.1.1.A Age distribution amongst organ transplant recipients in Canada between January 1, 1981 and December 31, 1998



As shown in Table 4.1.1.B, 4,839 (29.1%) patients were from Ontario, 2,896 (17.4%) were from Quebec, and nearly 10% were from the Maritimes (i.e., New Brunswick, Newfoundland, Nova Scotia, Prince Edward Island), while 20.9% had missing records.

Table 4.1.1.B Organ transplant recipients by province in Canada between January 1, 1981 and December 31, 1998

Province	Number of Patients	Percentage (%)
Alberta	1,498	9.0
British Colombia	1,612	9.7
Manitoba	629	3.8
New Brunswick	314	1.9
Newfoundland	297	1.8
Nova Scotia	534	3.2
Northwest Territories	11	0.1
Ontario	4,839	29.1
Prince Edward Island	78	0.5
Quebec	2,896	17.4
Saskatchewan	427	2.6
Yukon Territories	12	0.1
Missing	3,466	20.9
Total	16,613	

The majority of patients were male (63.4%) and of Caucasian origin (70.0%), as shown in Tables 4.1.1.C and 4.1.1.D.

Table 4.1.1.C Organ transplant recipients by sex in Canada between January 1, 1981 and December 31, 1998

Sex	Frequency	Percentage (%)
Female	6,041	36.4
Male	10,538	63.4
Missing	34	0.2
Total	16,613	

Table 4.1.1.D Organ transplant recipients by race in Canada between January 1, 1981 and December 31, 1998

Race	Frequency	Percentage (%)
Caucasian	11,622	70.0
Oriental	597	3.6
Black	278	1.7
North American Indian and Inuit	464	2.8
Asian Indian	289	1.7
Latin American	26	0.2
Missing	3,179	19.1
Other	158	1.0
Total	16,613	

As outlined in Table 4.1.1.F, the major causes of death were most commonly attributed to diseases of the circulatory system (1,548), genitourinary system (649), neoplasms (625), endocrine, nutritional, metabolic systems (556), digestive system (538), infectious and parasitic (338) and of the respiratory system (286). The least commonly reported causes of deaths were due to diseases of the skin/subcutaneous tissues (8), mental (5), and perinatal (2).

Table 4.1.1.F Major causes of death in selected organ transplant recipients in Canada between 1981 and 1998

Cause of death	Kidney		Heart		Liver		Lung		Heart-lung		Bilateral lung		Total
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	
Circulatory system	865	29.0	536	67.6	83	9.6	14	11.4	31	40.3	19	11.4	1,548
Genitourinary	608	20.4	18	2.3	18	2.1	3	2.2	-	-	2	1.2	649
Neoplasms	379	12.7	92	11.6	126	14.6	13	9.7	2	2.6	13	7.8	625
Endocrine, nutritional, metabolic	441	14.8	12	1.5	34	3.9	8	6.0	4	5.2	57	34.1	556
Digestive system	176	5.9	22	2.8	332	38.5	4	3.0	2	2.6	2	1.2	538
Infectious and parasitic	129	4.3	25	3.2	163	18.9	13	9.7	1	1.3	5	3.0	336
Respiratory system	102	3.4	15	1.9	22	2.6	73	54.5	14	18.2	60	35.9	286
Accidents/poisonings/violence	95	3.2	28	3.5	28	3.2	1	0.8	6	7.8	3	1.8	161
Congenital	71	2.4	33	4.2	22	2.6	-	-	14	18.2	4	2.4	144
Symptoms/ill defined	32	1.1	8	1.0	6	0.7	4	3.0	2	2.6	-	-	52
Blood	27	0.9	-		12	1.4	-	-	-	-	-	-	39
Nervous system/sense organs	19	0.6	3	0.4	12	1.4	1	0.8	1	1.3	-	-	36
Musculoskeletal	25	0.8	1	0.1	1	0.1	-	-	-	-	2	1.2	29
Skin/subcutaneous tissues	8	0.3	-	-	-	-	-	-	-	-	-	-	8
Mental	3	0.1	-		2	0.2	-	-	-	-	-	-	5
Perinatal	-	-	-	-	2	0.2	-	-	-	-	-	-	2
Complications of pregnancy	-	-	-	-	-	-	-	-	-	-	-	-	0
Total	2,980		793		863		134		77		167		5,014

4.1.2 Study Exclusions

In the mortality analysis, particularly for the purpose of SMR calculations, 118 patients were removed, since their death date was during the 30 days post-transplantation. In addition, five patients were removed, since their death data appeared to be prior to their transplantation date. Lastly, three individuals did not have a recorded sex.

In the cancer analysis, 705 patients were removed, since they were reported to have had an incident cancer in the first 30 days post-transplantation. In addition, 113 non-melanoma skin cancer patients were removed from the analysis due to poor registry in the CCR, while 34 cancer patients were excluded since they did not have a reported sex. An additional four patients were removed since their last date of follow-up appeared to be before transplantation date.

4.2 Mortality

4.2.1 Standardized Mortality Ratio

Standardized mortality ratios (SMRs) for the most common causes of death observed in organ transplants recipients were presented in Tables 4.2.1.A – F, in order of ICD-9 coding. As observed, SMRs were greatly increased for all organ transplants in this study. SMRs due to all causes of death varied between 7.6 (95% CI = 7.4, 7.9) in kidney transplant recipients to 11.8 (95% CI = 10.9, 12.8) in liver transplant recipients.

For less common transplants (e.g., lung, bilateral lung and heart-lung) where results appear to be less reliable due to the small number of procedures performed over the 17 years of observation in this study, SMRs due to all causes of death ranged from 30.8 - 100.0, with the lowest being in lung transplants (SMR = 30.8, 95% CI = 25.4, 37.0),

closely followed by bilateral lung transplants (SMR = 34.1, 95% = 28.4, 40.5), while the highest was observed in bilateral lung transplants (SMR = 100.0, 95% CI = 4.2, 131.8).

With regards to SMRs for specific causes of death, genitourinary diseases were consistently higher than all other causes of death for most types of transplants. In particular, the SMR for genitourinary diseases was highest among kidney transplant patients (SMR = 158.3, 95% CI = 145.6, 171.9) and significantly lower in liver, with an SMR of 30 (95% CI = 16.5, 45.4), and in heart recipients, with an SMR of 28.3 (95% CI = 16.5, 45.4). SMRs in less commonly performed transplants were up to 100.0 in lung recipients (95% CI = 20.1, 292.2) and as low as 33.3 in bilateral lung transplants (95% CI = 0.4, 185.5). No genitourinary deaths were observed in heart-lung transplants.

SMRs where infections and parasitic diseases were listed as the cause of death were also high, particularly in liver transplants, with an SMR of 119.0 (95% CI = 98.6, 142.4), as well as in heart (SMR = 19.2, 95% CI = 12.1, 28.8) and kidney transplants (SMR = 15.4, 95% = 12.9, 18.3). In less commonly performed transplants, these ratios ranged from 40.0 (95% CI = 10.8, 102.4) in bilateral lung transplants to 120.00 (95% = 25.4, 37.0) in single lung transplants.

Endocrine, nutritional and metabolic diseases as a cause of death were higher in kidney transplant recipients, with an SMR of 38.7 (95% = 35.1, 42.6) and in liver transplant recipients, with an SMR of 15.3 (95% CI = 10.0, 22.4).

Similarly, digestive diseases were seen in higher proportions in kidney and liver transplant recipients, with an SMR of 95.9 (95% CI = 98.6, 142.4) and 10.4 (95% = 8.9, 12.2), respectively.

Circulatory diseases as a cause of death were commonly observed in heart transplant recipients with an SMR of 16.9 (95% CI = 15.2, 18.8), while respiratory diseases were highest in lung-associated transplants and ranged from an SMR of 225.0 (95% CI = 164.1, 301.1) up to 500.0 (95% CI = 234.9, 919.6).

Notably, neoplasms had some of the lowest SMRs, with values between 2.7 (95% CI = 2.5, 3.0) in kidney to 5.5 (95% CI = 4.5, 6.6) in liver.

Table 4.2.1 Standardized mortality ratios (SMRs) for major causes of death for various organ transplants between January 1, 1981 and December 31, 1998

A) Kidney transplant

Major causes of death	**Obs. Deaths**	**Exp. Deaths**	**SMR**	**95% CI**
All causes	2871	376.8	7.6	(7.4, 7.9)
Infections and parasitic	128	8.3	15.4	(12.9, 18.3)
Neoplasms	379	138.7	2.7	(2.5, 3.0)
Endocrine/nutritional/metabolic	426	11.0	38.7	(35.1, 42.6)
Circulatory	844	113.6	7.4	(6.9, 7.9)
Respiratory	98	20.1	4.9	(4.0, 5.9)
Digestive	164	15.7	10.4	(8.9, 12.2)
Genitourinary	570	3.6	158.3	(145.6, 171.9)

B) Heart transplant

Major causes of death	Obs. Deaths	Exp. Deaths	SMR	95% CI
All causes	582	67.2	8.7	(7.9,9.3)
Infections and parasitic	23	1.2	19.2	(12.1, 28.8)
Neoplasms	91	25.9	3.5	(2.8, 4.3)
Endocrine/nutritional/metabolic	11	2.0	5.5	(2.7, 9.8)
Circulatory	362	21.4	16.9	(15.2, 18.8)
Respiratory	14	3.2	4.4	(2.4, 7.3)
Digestive	22	3.0	7.3	(4.6, 11.1)
Genitourinary	17	0.6	28.3	(16.5, 45.4)

C) Liver transplant

Major causes of death	Obs. Deaths	Exp. Deaths	SMR	95% CI
All causes	634	53.7	11.8	(10.9, 12.8)
Infections and parasitic	119	1.0	119.0	(98.6, 142.4)
Neoplasms	118	21.5	5.5	(4.5, 6.6)
Endocrine/nutritional/metabolic	26	1.7	15.3	(10.0, 22.4)
Circulatory	69	15.5	4.4	(3.5, 5.6)
Respiratory	22	2.9	7.6	(4.8, 11.5)
Digestive	211	2.2	95.9	(83.4, 109.8)
Genitourinary	15	0.5	30.0	(16.7, 49.5)

D) Bilateral lung transplant

Major causes of death	Obs. Deaths	Exp. Deaths	SMR	95% CI
All causes	126	3.7	34.1	(28.4, 40.5)
Infections and parasitic	4	0.1	40.0	(10.8, 102.4)
Neoplasms	13	1.4	9.3	(4.9, 15.9)
Endocrine/nutritional/metabolic	44	0.1	440.0	(319.7, 590.7)
Circulatory	11	1.0	11.0	(5.5, 19.7)
Respiratory	45	0.2	225.0	(164.1, 301.1)
Digestive	2	0.2	10.0	(1.1, 36.1)
Genitourinary	1	0.03	33.3	(0.4, 185.5)

E) Lung transplant

Major causes of death	Obs. Deaths	Exp. Deaths	SMR	95% CI
All causes	114	3.7	30.8	(25.4, 37.0)
Infections and parasitic	12	0.1	120.0	(61.9, 209.6)
Neoplasms	13	1.6	8.1	(4.3, 13.9)
Endocrine/nutritional/metabolic	5	0.1	50.0	(16.1, 116.7)
Circulatory	11	1.0	11.0	(5.5, 19.7)
Respiratory	61	0.2	305.0	(233.3, 391.8)
Digestive	4	0.2	20.0	(5.4, 51.2)
Genitourinary	3	0.03	100.0	(20.1, 292.2)

F) Heart and lung transplant

Major causes of death	Obs. Deaths	Exp. Deaths	SMR	95% CI
All causes	50	0.5	100.0	(4.2, 131.8)
Infections and parasitic	1	0.02	50.0	(0.6, 278.2)
Neoplasms	2	0.2	10.0	(1.1, 36.1)
Endocrine/nutritional/metabolic	3	0.01	300.0	(60.3, 876.5)
Circulatory	20	0.10	200.0	(122.1, 308.9)
Respiratory	10	0.02	500.0	(239.4, 919.6)
Digestive	1	0.02	50.0	(0.6, 278.2)
Genitourinary	-	0.004	-	-

*Individuals were followed up from 30 days after the date of their renal transplant until the earliest date associated with diagnosis of an incident cancer, death or December 31, 1998

4.2.2 Proportionate Mortality Ratio

Proportionate mortality ratios (PMRs) with 95% confidence intervals were calculated for intervals of 0 – 3 months, 3 months – 2 years, 2 – 5 years, 5 – 10 years, >10 years for all organ transplants, as outlined in Table 4.2.2.A – C.

In kidney transplant recipients, PMRs were highest in genitourinary diseases; however, these values decreased over time from 42.8 (95% = 34.5, 30.0) at 0 - 3 months to 21.5 after 10 years of follow-up. Endocrine, nutritional and metabolic diseases had the second highest PMRs, with values fluctuating between 5.4 (95% CI = 3.8, 7.4) from 0 – 3 months, to 5.8 (95% CI = 4.6, 7.3) at 3 months - 2 years, and down to 4.7 (95% = 1.6, 3.6) after 10 years. Infections and parasitic causes of death had the second highest PMRs, which were 3.4 (95% CI = 2.2, 5.1) in the first 0 – 3 months post-transplantation and slowly decreased over time to 1.1 (95% CI = 0.6, 1.8) after 10 years of follow-up.

Neoplasms had the lowest PMRs, ranging from 0.1 (95% CI = 0.001, 0.2) in the first 0 – 3 months, which increased to 0.4 after 2 – 10 years, followed by a decrease to 0.3 (95% CI = 0.2, 4.3) after 10 years of follow-up.

PMRs in heart transplant recipients were highest due to circulatory diseases and decreased over time from 3.4 (95% = 3.0, 3.9) in the first 0 – 3 months post-transplantation to 2.2 (95% = 1.6, 3.0) after 10 years of follow-up. Genitourinary diseases had the second highest PMRs over time and increased from 1.2 (95% = 0.1, 4.2) in the first 0 – 3 months post-transplantation to 8.3 (95% CI = 2.7, 19.4) after 10 years of follow-up. Similar to kidney transplants, neoplasms had amongst the lowest PMRs, which ranged from 0.01 (95% CI = 0.0001, 0.1) at 0 – 3 months post-transplantation to 0.6 (95% CI = 0.4, 0.9) to 0.5 (95% CI = 0.4, 0.7) at 2 – 5 and 5 – 10 years post-transplantation, respectively. The PMR in these transplant recipients shows a slight decrease after 10 years of follow-up to 0.4 (95% CI = 0.2, 0.8).

In liver transplants, the highest PMRs were observed in deaths due to digestive diseases, which were highest in the first 0 – 3 months post-transplantation (PMR = 14.2, 95% CI = 12.2, 16.4) which decreased to 6.9 (95% CI = 4.9, 9.5) after 2 - 5 years and started drastically increasing again after 10 years of follow-up, with a PMR of 15.0 (95% CI = 5.4, 32.7). Infections and parasitic diseases as a cause of death led to the third highest PMRs, ranging from 7.1 (95% = 5.4, 9.0) in the first 0 – 3 months to 3.3 (95% CI = 1.8, 4.9) after >10 years of follow-up. As with all other organ transplants, neoplasms had amongst the lowest PMRs which were lowest in the first 0 – 3 months post-transplantation (PMR = 0.2, 95% CI = 0.1, 0.2), to 0.7 in the 3 months – 5 years range, and down to 0.4 from 5 years post-transplantation onwards.

Table 4.2.2 Proportionate mortality ratios (PMRs) for the most common causes of death, as observed between January 1, 1981 and December 31, 1998 for selected transplants in Canada

A) Kidney transplant

Cause of death	Follow-up intervals																			
	0 – 3 months				3 months – 2 years				2 – 5 years				5 – 10 years				>10 years			
	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI
All causes	292	292	1.0	0.9, 1.1	485	485	1.0	0.9, 1.1	749	749	1.0	0.9, 1.1	1022	1022	1.0	0.9, 1.1	432	432	1.0	0.9, 1.1
Infections and parasitic	25	7.3	3.4	2.2, 5.1	31	13.9	2.2	1.5, 3.2	25	23.1	1.1	0.7, 1.6	33	30.5	1.1	0.7, 1.5	15	13.7	1.1	0.6, 1.8
Neoplasms	8	92.2	0.1	0.001, 0.2	53	161.5	0.3	0.2, 0.4	115	260.7	0.4	0.4, 0.5	152	378.3	0.4	0.3, 0.5	51	155.4	0.3	0.2, 4.3
Endocrine/nutritional/ metabolic	38	7.0	5.4	3.8, 7.4	73	12.5	5.8	4.6, 7.3	110	20.1	5.5	4.5, 6.6	160	29.2	5.5	4.6, 6.4	60	12.8	4.7	1.6, 3.6
Circulatory	56	70.2	0.8	0.6, 1.0	124	117.4	1.0	0.9, 1.2	232	189.1	1.2	1.1, 1.4	304	262.8	1.2	1.0, 1.3	149	106.8	1.4	1.2, 1.6
Respiratory	10	10.5	1.0	0.4, 1.8	14	18.6	0.8	0.4, 1.3	24	31.3	0.8	0.5, 1.1	39	46.6	0.8	0.6, 1.1	15	18.9	0.8	0.4, 1.3
Digestive	24	11.8	2.0	1.3, 3.0	28	19.3	1.4	1.0, 2.1	39	30.2	1.3	0.9, 1.8	64	41.0	1.6	1.2, 2.0	21	17.2	1.2	0.8, 1.9
Genitourinary	90	2.1	42.8	34.5, 52.7	108	3.6	30.0	24.6, 36.2	129	6.1	21.1	17.6, 25.1	197	9.1	21.6	18.7, 24.9	84	3.9	21.5	17.2, 26.7

B) Heart transplant

Cause of death	Follow-up intervals																			
	0 – 3 months				3 months – 2 years				2 – 5 years				5 – 10 years				>10 years			
	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI
All causes	277	277	1.0	0.9, 1.1	153	153	1.0	0.8, 1.2	130	130	1.0	0.8, 1.2	174	174	1.0	0.8,1.2	59	59	1.0	0.8, 1.3
Infections and parasitic	5	8.7	0.6	0.2, 1.3	10	4.2	2.4	1.1, 4.4	5	3.7	1.4	0.4, 3.2	5	4.1	1.2	0.4, 2.8	-	1.4	-	-
Neoplasms	1	84.5	0.01	0.0, 0.1	19	49.7	0.4	0.2, 0.6	28	44.4	0.6	0.4, 0.9	34	64.8	0.5	0.4, 0.7	10	23.1	0.4	0.2, 0.8
Endocrine/nutritional/ metabolic	1	6.7	0.1	0.0, 0.8	1	3.8	0.3	0.0, 1.5	4	3.4	1.2	0.3, 3.0	5	5.2	0.9	0.3, 2.2	1	1.9	0.5	0.001, 2.9
Circulatory	224	65.6	3.4	3.0, 3.9	93	40.2	2.3	1.9, 2.8	78	33.5	2.3	1.8, 2.9	102	48.4	2.1	1.7, 2.6	39	17.7	2.2	1.6, 3.0
Respiratory	3	8.6	0.3	0.1, 1.0	5	5.4	0.9	0.3, 2.2	1	4.9	0.2	0.0, 1.1	6	7.4	0.8	0.3, 1.8	-	2.9	-	-
Digestive	4	11.5	0.3	0.1, 0.9	6	6.4	0.9	0.3, 2.0	3	5.3	0.6	0.1, 1.6	8	7.3	1.1	0.5, 2.2	1	2.5	0.4	0.0, 2.2
Genitourinary	2	1.7	1.2	0.1, 4.2	2	1.1	1.8	0.2, 6.6	2	0.9	2.2	0.2, 8.0	7	1.4	5.0	2.0, 10.3	5	0.6	8.3	2.7, 19.4

C) Liver transplant

Cause of death	Follow-up intervals																			
	0 – 3 months				3 months – 2 years				2 – 5 years				5 – 10 years				>10 years			
	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI
All causes	367	367	1.0	0.9, 1.1	229	229	1.0	0.9, 1.1	142	142	1.0	0.8, 1.2	112	112	1.0	0.8, 1.2	13	13	1.0	0.5, 1.7
Infections and parasitic	65	9.2	7.1	5.4, 9.0	59	7.7	7.7	5.8, 9.9	24	3.7	6.5	4.2, 9.6	12	2.9	4.1	2.1, 7.2	3	0.3	3.3	1.8, 4.9
Neoplasms	18	119.2	0.2	0.1, 0.2	52	75.1	0.7	0.5, 0.9	37	52.8	0.7	0.5, 1.0	17	43.1	0.4	0.2, 0.6	2	5.0	0.4	0.001, 1.4
Endocrine/nutritional/ Metabolic	13	9.2	1.4	0.8, 2.4	6	6.1	1.0	0.4, 2.1	8	4.1	2.0	0.8, 3.8	7	3.4	2.1	0.8, 4.2	-	0.4	-	-
Circulatory	26	70.0	0.4	0.2, 0.5	9	50.2	0.2	0.1, 0.3	21	33.1	0.6	0.4, 1.0	27	26.0	1.0	0.7, 1.5	-	2.8	-	-
Respiratory	6	12.7	0.5	0.2, 1.0	6	8.5	0.7	0.2, 1.5	4	5.9	0.7	0.2, 1.7	4	5.1	0.8	0.2, 2.0	2	0.6	3.3	0.4, 12.0
Digestive	184	13.0	14.2	12.2, 16.4	73	8.6	8.4	6.6, 10.7	38	5.5	6.9	4.9, 9.5	31	4.3	7.2	4.9, 10.2	6	0.4	15.0	5.4, 32.7
Genitourinary	9	2.5	3.6	1.6, 6.8	2	1.7	1.2	0.1, 4.2	3	1.2	2.5	0.5, 7.3	4	1.0	4.0	1.1, 10.2	-	0.1	-	-

PMRs for less commonly performed transplants such as lung, bilateral lung and heart-lung were included in Appendix 5. Due to low sample sizes per stratum, these results appear to be less reliable.

4.3 Cancer Incidence

4.3.1 Standardized Incidence Ratio

Standardized incidence ratios (SIRs) with 95% confidence intervals were calculated for five of the more commonly reported cancers, such as kidney, liver, NHL, colorectal and lung. As illustrated in Table 4.3.1.A - E, SIRs due to all cancers were lowest in kidney and liver transplants (SIR = 2.5, 95% CI = 2.3, 2.7 and 2.1, 3.0), while heart transplant SIRs were slightly higher (SIR = 3.6, 95% CI = 2.0, 5.8).

SIRs for all cancers were highest in heart and lung transplantations (SIR = 10.0, 95% CI = 2.3, 2.7) Bilateral lung and heart transplants had the second and third highest SIRs for all cancers, with 5.6 (95% CI = 3.4, 8.6) and 3.6 (95% CI = 2.0, 5.8), respectively.

For each type of transplant, the organ which was being replaced appeared to host cancers at much higher rates than those encountered in the general Canadian population. In particular, liver transplant recipients had an SIR of 52.5 (95% CI = 52.5, 21.1) for liver cancer, while kidney transplant recipients had an SIR of 7.0 (95% CI = 5.4, 8.7) for kidney cancer. NHL had particularly increased SIRs relative to all other types of cancers, and in particular in bilateral lung transplants, where SIR was 40.0 (95% CI = 17.2, 78.8), as well as in heart recipients (SIR = 30.0, 95% CI = 11.0, 65.2), and in lung recipients (SIR = 22.7, 95% CI = 17.2, 29.3).

Lung cancer had an elevated SIR in heart transplant recipients (SIR = 11.4, 95% CI = 4.9, 22.5), while colorectal cancer had an SIR in kidney transplant recipients (SIR=10.0, 95% CI = 3.2, 23.3).

No SIRs were reported for heart-lung transplantations due to low cell counts, where a total 7 cancers were observed.

Table 4.3.1 Standardized cancer incidence ratios (SIRs) for major types of cancer (non-stratified) for various organ transplants between January 1, 1981 and December 31, 1998.

A) Kidney transplant

Cancer Site	**ICD-9**	**O**	**E**	**SIR**	**95% CI**
All cancers		773	312.3	2.5	(2.3, 2.7)
Kidney	189	71	10.2	7.0	(5.4, 8.7)
Liver	155	5	2.8	1.8	(0.6, 4.2)
NHL	200, 202	25	14.1	1.8	(1.1, 2.6)
Colorectal	153, 154	51	37.6	1.4	(1.0, 1.8)
Lung	162	108	51.4	2.1	(1.7, 2.5)

B) Heart transplant

Cancer Site	**ICD-9**	**O**	**E**	**SIR**	**95% CI**
All cancers		16	4.5	3.6	(2.0, 5.8)
Kidney	189	-	0.1	-	-
Liver	155	-	0.03	-	-
NHL	200, 202	6	0.2	30.0	(11.0, 65.2)
Colorectal	153, 154	1	0.5	2.0	(0.02, 11.1)
Lung	162	8	0.7	11.4	(4.9, 22.5)

C) Liver transplant

Cancer Site	ICD-9	O	E	SIR	95% CI
All cancers		113	44.7	2.5	(2.1, 3.0)
Kidney	189	4	1.4	2.9	(0.8, 3.0)
Liver	155	21	0.4	52.5	(32.5, 80.3)
NHL	200, 202	40	1.9	21.1	(15.0, 28.6)
Colorectal	153, 154	14	5.3	2.6	(1.4, 4.4)
Lung	162	10	7.0	1.4	(0.7, 2.6)

D) Bilateral lung transplant

Cancer Site	ICD-9	O	E	SIR	95% CI
All cancers		20	3.6	5.6	(3.4, 8.6)
Kidney	189	-	0.1	-	-
Liver	155	-	0.03	-	-
NHL	200, 202	8	0.2	40.0	(17.2, 78.8)
Colorectal	153, 154	1	0.4	2.5	(0.03, 13.9)
Lung	162	2	0.5	4.0	(0.4, 14.4)

E) Lung transplant

Cancer Site	ICD-9	O	E	SIR	95% CI
All cancers		159	58.1	2.7	(2.3, 3.2)
Kidney	189	61	2.2	27.7	(21.2, 35.6)
Liver	155	1	0.6	1.7	(0.0, 9.2)
NHL	200, 202	59	2.6	22.7	(17.2, 29.3)
Colorectal	153, 154	5	0.5	10.0	(3.2, 23.3)
Lung	162	22	11.0	2.0	(1.3, 3.0)

*Individuals were followed up from 30 days after the date of their renal transplant until the earliest date associated with diagnosis of an incident cancer, death or December 31, 2006.

4.3.2 Stratified Standardized Incidence Ratio

Findings from the stratified analysis of SIRs by follow-up interval, transplantation date, sex, and age at surgery were presented in Table 4.3.2A.

Due low sample sizes for each stratum (e.g., follow-up date, transplantation date, etc), only kidney transplants allowed for stratified SIR analysis. Analyses for other organs were presented in Appendix 6.

Amongst specific cancers, SIRs were much higher in NHL and kidney cancer, while colorectal and lung cancer SIRs were close to 1.0, indicating that these types of cancers were similar to those observed the Canadian general population.

SIRs were highest amongst patients with less than a year (and at least 30 days) of follow-up, both for all cancers and for NHL. The SIR for all cancers in this stratum was 2.9 (95% CI = 2.4, 3.6). The highest SIR was observed in NHL (SIR = 28.8, 95% CI = 21.0, 38.3), followed by kidney cancer (SIR = 8.2, 95% CI = 3.8, 15.5). These values consistently decreased with time, and after 10 years of follow-up, the SIR for NHL was 5.7 (95% CI = 2.9, 10.0), while that for kidney cancer dropped to 6.0 (95% CI = 2.7, 11.4).

With regards to transplant date, no major variations were observed between 1981 – 1998, and SIRs ranged between 2.1 (95% CI = 1.8, 2.5) to 2.9 (95% CI = 1.9, 3.4) from 1981 to 1998. In NHL, the highest SIR was found between 1996 and 1998 (SIR = 18.9, 95% CI = 11.0, 30.2), while the second highest was from 1987 to 1989 (SIR = 11.5, 95% CI = 8.2, 15.7). For kidney cancer, the highest SIR was observed between 1993 and 1995 (SIR = 12.7, 95% CI = 7.6, 19.8), followed by 1987 – 1989 (SIR = 7.6, 95% CI = 1.9, 3.4).

In addition, SIRs were slightly higher in males than in females for all cancers (SIR = 2.6, 95% CI = 1.9, 2.8 in males vs. SIR = 2.3, 95% CI = 2.0, 2.6 in females). This trend was reversed in NHL and kidney cancer. In particular, the SIR for NHL was 10.0 (95% CI = 7.2, 13.5) for females and 8.3 (95% CI = 6.6, 10.3) males. For kidney cancer, the SIR for males was 6.2 (95% CI = 4.5, 8.2), while the SIR for females was 9.6 (95% CI = 6.1, 41.4)

Lastly, SIRs by age at surgery were highest among younger transplant patients and were inversely related to age at surgery. More specifically, for all cancers, SIR was 6.1 (95% CI = 2.4, 2.8) under the age of 35 and consistently decreased to 1.9 (95% CI = 1.6, 2.2) in patients over the age of 60. The highest SIRs were observed in NHL in patients under the age of 35 (SIR=27.2, 95% CI = 20.1, 36.0), which dropped to 4.2 (95% CI = 2.3, 7.1). In kidney cancer, SIR was 25.0 (95% CI = 14.0, 41.2) for patients under the age of 35 and dropped to 3.9 (95% CI = 2.0, 7.0) in those over the age of 60.

Table 4.3.2 Standardized incidence ratios (SIRs) for selected cancer sites among those who received a transplant, by follow-up interval, transplant date, and age at transplant, as observed between January 1, 1981 and December 31, 1998 for selected transplants in Canada

A) Kidney transplant

	All Cancers				Kidney				NHL				Colorectal				Lung			
Characteristic	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**
Follow-up interval																				
30 d < 1 y	102	34.6	2.9	(2.4, 3.6)	9	1.1	8.2	(3.8,15.5)	46	1.6	28.8	(21.0, 38.3)	5	4.1	1.2	(0.4, 2.8)	10	5.8	1.7	(0.8, 3.2)
1 < 5 y	312	130.1	2.4	(2.1, 2.7)	31	4.3	7.2	(4.9,10.2)	34	5.9	5.8	(4.0,8.1)	21	15.7	1.3	(0.8, 2.0)	54	21.7	2.5	(1.9, 3.2)
5 < 10 y	266	102.5	2.6	(2.3, 2.9)	22	3.3	6.7	(4.2,10.1)	33	4.6	7.2	(4.9,10.1)	21	12.4	1.7	(1.0, 2.6)	29	16.8	1.7	(1.2, 2.5)
≥10y	93	45.1	2.1	(1.7, 2.5)	9	1.5	6.0	(2.7,11.4)	12	2.1	5.7	(2.9,10.0)	4	5.4	0.7	(0.2, 1.9)	15	7.1	2.1	(1.2, 3.5)
Transplant date																				
1981 - 1983	82	32.7	2.5	(2.0, 3.1)	7	1.1	6.4	(2.5,13.1)	7	1.6	4.4	(1.8, 9.0)	5	3.8	1.3	(0.4, 3.1)	12	5.3	2.3	(1.2, 4.0)
1984 - 1986	146	69.6	2.1	(1.8, 2.5)	11	2.3	4.8	(2.4,8.6)	16	3.1	5.2	(2.9, 8.4)	8	8.4	1.0	(0.4, 1.9)	22	11.8	1.9	(1.2, 2.8)
1987 - 1989	208	77.1	2.7	(2.3, 3.1)	19	2.5	7.6	(4.6,11.9)	39	3.4	11.5	(8.2, 15.7)	15	9.4	1.6	(0.9, 2.6)	26	12.9	2.0	(1.3, 3.0)
1990 - 1992	150	66.1	2.3	(2.6, 2.7)	9	2.1	4.3	(2.0,8.1)	24	2.9	8.3	(5.3, 12.3)	8	8	1.0	(0.4, 2.0)	22	10.8	2.0	(1.3, 3.1)
1993 - 1995	136	46.6	2.9	(1.9, 3.4)	19	1.5	12.7	(7.6,19.8)	22	2.2	10.0	(6.3, 15.1)	9	5.6	1.6	(0.7, 3.0)	17	7.4	2.3	(1.3, 3.7)
1996 - 1998	51	20.1	2.5	(2.4, 3.3)	6	0.7	8.6	(3.1,18.6)	17	0.9	18.9	(11.0, 30.2)	6	2.4	2.5	(0.9, 5.4)	9	3.2	2.8	(1.3, 5.3)
Sex																				
Male	516	200.7	2.6	(1.9, 2.8)	48	7.8	6.2	(4.5,8.2)	83	10	8.3	(6.6, 10.3)	39	26.5	1.5	(1.0, 2.0)	83	38.4	2.2	(1.7, 2.7)
Female	257	111.6	2.3	(2.0, 2.6)	23	2.4	9.6	(6.1,41.4)	42	4.2	10.0	(7.2, 13.5)	12	11.1	1.1	(0.6, 1.9)	25	13	1.9	(1.2, 2.8)
Age at surgery																				
<35	148	24.2	6.1	(2.4, 2.8)	15	0.6	25.0	(14.0,41.2)	49	1.8	27.2	(20.1, 36.0)	4	1.4	2.8	(0.8, 7.3)	4	1.2	3.3	(0.9, 8.5)
35≥y<50	225	83.8	2.7	(5.1, 7.1)	21	3.2	6.6	(4.1,10.0)	41	4.7	8.7	(6.2, 11.8)	11	9.2	1.2	(0.6, 2.1)	29	11.4	2.5	(1.7, 3.7)
50=<y<60	235	106.2	2.2	(2.3, 3.1)	24	3.6	6.7	(4.3,10.0)	21	4.3	4.9	(3.0, 7.5)	22	13.6	1.6	(1.0, 2.4)	45	19.7	2.3	(1.7, 3.1)
≥60	165	88.1	1.9	(1.6 2.2)	11	2.8	3.9	(2.0,7.0)	14	3.3	4.2	(2.3, 7.1)	14	13.3	1.1	(0.6, 1.8)	30	19.1	1.6	(1.1, 2.2)
Total	773	312.3	2.5	(2.3, 2.7)	71	10.2	7.0	(5.4,8.8)	125	14.1	8.9	(7.4 , 10.6)	51	37.6	1.4	(1.0, 1.8)	108	51.4	2.1	(1.7, 2.5)

*Individuals were followed up from 30 days after the date of their renal transplant until the earliest date associated with diagnosis of an incident cancer, death or December 31, 1998.

4.4 Factors Impacting Cancer Incidence

4.4.1 Cox Proportional Hazards Model

As observed in Tables 4.4.1.A - F, there was an increased risk of developing cancer for all types of transplants analysed in this study. In kidney, heart and liver transplant recipients, there was a statistically significant association between the incidence of cancer and age at transplant, whereby the greater the age, the higher the risk of developing cancer. The greatest risk was observed kidney transplant recipients over the age of 60 (HR = 6.0, 95% CI = 4.8, 7.3, P-value = <0.0001), while that observed liver and heart transplants was lower (HR = 3.4, 95% = 2.0, 5.7, P-value = <0.0001 and HR = 2.4, 95% CI = 1.3, 4.5, P-value = 0.004).

With regards to cancer risk between sexes, females had a lower risk than males in kidney transplants, where HR = 0.8, P = 0.02.

Similar trends were found in other transplants; however, these risks were not statistically significant.

In addition, no statistically significant HRs were found between NHL incidence and transplant replacement.

Table 4.4.1 Cox proportional hazards model for risk factors for developing all cancers and Non-Hodgkin's lymphoma post organ transplantation

A) Kidney transplant

Type of Cancer	Risk Factor	Patient Number	Hazard Ratio	95% CI	P-value
All Cancers	Age at transplant				
	<40	215	1	-	-
	40 to <60	393	2.6	(2.2, 3.1)	<0.0001
	≥60	165	6.0	(4.8, 7.3)	<0.0001
	Sex				
	Male	516	1	-	-
	Female	257	0.8	(0.7, 1.0)	0.02
	Calendar Period				
	1983-1990	446	1	-	-
	1991-1994	189	1.1	(1.0, 1.4)	0.1
	1995-1998	94	1.4	(1.1, 1.7)	0.02
Non-Hodkin's Lymphoma	Age at transplant				
	<40	64	1	-	-
	40 to <60	47	1.0	(0.7, 1.4)	0.8
	≥60	14	1.3	(0.7, 2.4)	0.3
	Sex				
	Male	83	1	-	-
	Female	42	0.8	(0.6, 1.2)	0.4
	Calendar Period				
	1983-1990	68	1	-	-
	1991-1994	32	1.5	(0.9, 2.3)	0.1
	1995-1998	24	2.0	(1.2, 3.4)	0.01

B) Heart transplant

Type of Cancer	Risk Factor	Patient Number	Hazard Ratio	95% CI	P-value
All Cancers	Age at transplant				
	<40	24	1	-	-
	40 to <60	116	1.9	(1.2, 3.0)	0.004
	≥60	19	2.4	(1.3, 4.5)	0.005
	Sex				
	Male	136	1	-	-
	Female	23	1.0	(0.6, 1.5)	0.9
	Calendar Period				
	1983-1990	89	1	-	-
	1991-1994	46	1.2	(0.8, 1.8)	0.3
	1995-1998	24	1.6	(0.9, 2.7)	0.08
Non-Hodkin's Lymphoma	Age at transplant				
	<40	18	1	-	-
	40 to <60	38	0.8	(0.5, 1,4)	0.5
	≥60	3	0.4	(0.1, 1.4)	0.2
	Sex				
	Male	51	1	-	-
	Female	8	0.8	(0.4, 1.6)	0.5
	Calendar Period				
	1983-1990	27	1	-	-
	1991-1994	20	1.8	(1.0, 3.4)	0.06
	1995-1998	12	2.4	(1.1, 5.2)	0.04

C) Liver transplant

Type of Cancer	Risk Factor	Patient Number	Hazard Ratio	95% CI	P-value
All Cancers	Age at transplant				
	<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				
	Male	53	1	-	-
	Female	60	0.8	(0.6, 1.2)	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-Hodkin's Lymphoma	Age at transplant				
	<40	17	1	-	-
	40 to <60	18	1.0	(0.5, 1.9)	0.9
	≥60	5	1.0	(0.4, 2.8)	0.9
	Sex				
	Male	20	1	-	-
	Female	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

D) Bilateral lung transplant

Type of Cancer	Risk Factor	Patient Number	Hazard Ratio	95% CI	P-value
All Cancers	Age at transplant				
	<40	2	1	-	-
	40 to <60	16	9.1	(2.1, 40.1)	0.004
	≥60	2	10.8	(1.4, 81.1)	0.02
	Sex				
	Male	14	1	-	-
	Female	6	0.5	(0.2, 1.4)	0.2
	Calendar Period				
	1983-1990	3	1	-	-
	1991-1994	10	1.5	(0.3, 7.3)	0.6
	1995-1998	7	1.7	(0.3, 9.3)	0.5
Non-Hodkin's Lymphoma	Age at transplant				
	<40	2	1	-	-
	40 to <60	5	2.9	(0.6, 15.1)	0.2
	≥60	1	7.3	(0.6, 89.7)	0.1
	Sex				
	Male	4	1	-	-
	Female	4	1.2	(0.3, 4.9)	0.8
	Calendar Period				
	1983-1990	1	1	-	-
	1991-1994	4	7717145	(0, -)	1.0
	1995-1998	3	7043173	(0, -)	1.0

E) Lung transplant

Type of Cancer	Risk Factor	Patient Number	Hazard Ratio	95% CI	P-value
All Cancers	Age at transplant				
	<40	3	1	-	-
	40 to <60	10	0.6	(0.2, 2.1)	0.4
	≥60	3	1.1	(0.2, 5.7)	0.9
	Sex				
	Male	11	1	-	-
	Female	5	0.3	(0.1, 1.0)	0.04
	Calendar Period				
	1983-1990	5	1	-	-
	1991-1994	6	1.0	(0.3, 3,8)	1.0
	1995-1998	5	0.8	(0.2, 3.6)	0.8
Non-Hodkin's Lymphoma	Age at transplant				
	<40	2	1	-	-
	40 to <60	4	0.4	(0.07, 2.2)	0.3
	≥60	-	0.0	-	1.0
	Sex				
	Male	3	1	-	-
	Female	3	0.6	(0.1, 3.2)	0.6
	Calendar Period				
	1983-1990	3	1	-	-
	1991-1994	2	0.6	(0.09, 3.7)	0.6
	1995-1998	1	0.3	(0.03, 3.0)	0.3

F) Heart-lung transplant

Type of Cancer	Risk Factor	Patient Number	Hazard Ratio	95% CI	P-value
All Cancers	Age at transplant				
	<40	2	1	-	-
	40 to <60	5	4.0	(0.7, 22.4)	0.1
	≥60	-	-	-	-
	Sex				
	Male	4	1	-	-
	Female	3	0.6	(0.1, 2.7)	0.5
	Calendar Period				
	1983-1990	3	1	-	-
	1991-1994	1	0.4	(0.04, 4.2)	0.5
	1995-1998	3	2.3	(0.4, 12.7)	0.3
Non-Hodkin's Lymphoma	Age at transplant				
	<40	2	1	-	-
	40 to <60	4	3.2	(0.6, 18.4)	0.2
	≥60	-	-	-	-
	Sex				
	Male	4	1	-	-
	Female	2	0.4	(0.06, 2.1)	0.3
	Calendar Period				
	1983-1990	3	1	-	-
	1991-1994	-	-	-	-
	1995-1998	3	1.7	(0.3, 8.6)	0.5

*All covariates were fit simultaneously in the same model.

4.4.2 Logistic Regression Model

The logistic regression results presented in Table 4.4.2.A indicate that the year that the surgery was performed, sex and age (with the exception of the 40 – 49 age group, P-value = 0.615) were statistically significant predictors of mortality (P-values<0.05). Notably, the age group between 40 and 49 was not a statistically significant predictor of mortality (P-value = 0.615). Notably, smoking status and diabetes were eliminated from the model, as they were not statistically significant (P-values>0.05).

Based on the odds ratios presented in Table 4.4.2.B, it can be said that there is a 4.4-fold higher risk of dying in patients who had a transplantation done between 1981 - 1990 than those who underwent the procedure from 1991 - 1998. In addition, females had a 19% lower risk of dying, while the risk of dying increased with age, where those under the age of 20 had an 85% lower risk of dying than those over the age 60. In the 50 – 60 age category, patients had a 50% lower risk of dying that those over the age of 60.

Logistic regression results for other organs did not show statistically sound results and were included in Appendix 7.

Table 4.4.2 Logistic regression model and odds ratios estimates for risk factors contributing to mortality post kidney transplantation between January 1, 1981 and December 31, 1998

A) Analysis of Maximum Likelihood Estimates

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	-1.5073	0.0550	750.0140	<.0001
Year of Surgery (1981- 1990)	0.7460	0.0452	271.8410	<.0001
Sex (Female)	-0.1060	0.0452	5.5007	0.0190
Age (<20)	-0.7764	0.1424	29.7434	<.0001
Age (30-39)	-0.6281	0.1148	29.9196	<.0001
Age (40-49)	-0.1698	0.0908	3.4960	0.0615
Age (50-59)	0.4386	0.0732	35.8985	<.0001

B) Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
Year of Surgery (1[a] vs. 2[b])		4.446	3.724	5.309
Sex	F[c] vs M[d]	0.809	0.678	0.966
Age	1[e] vs 6	0.148	0.099	0.221
Age	3[f] vs 6	0.171	0.122	0.241
Age	4[g] vs 6	0.271	0.203	0.362
Age	5[h] vs 6[i]	0.498	0.388	0.639

[a] Year of surgery = 1981 – 1990
[b] Year of surgery = 1991 – 1998
[c] Sex = Female
[d] Sex = Male
[e] Age surgery <20
[f] Age surgery = 30 to 39
[g] Age surgery = 40 to 49
[h] Age surgery = 50 to 59
[i] Age surgery ≥60

4.4.3 Cumulative Incidence

The cumulative incidence of all cancers and death among transplant recipients by time since transplantation is shown in Figures 4.4.3.A - B for kidney and heart transplant recipients.

In kidney transplant recipients, the cumulative incidence of post-transplant *de novo* cancer at 1, 5, 10 and 16 years post transplantation was approximately 4, 13, 23, and 40%, respectively. The cumulative incidence of mortality in kidney transplants for the same time intervals were 2, 3, 6, and 8%, respectively.

In heart transplant recipients, the cumulative incidence of post-transplant *de novo* cancer at 1, 5, 10 and 14 years post transplantation was approximately 10, 17, 32, and 48%,

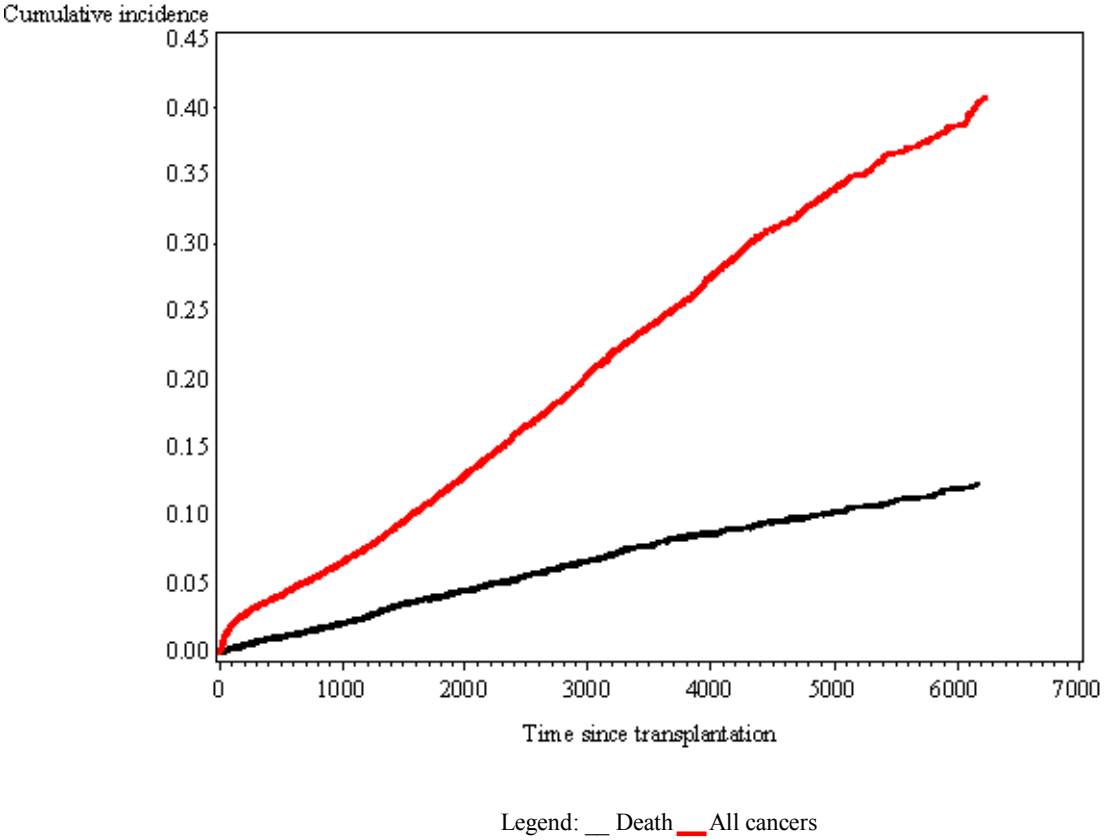
respectively. The cumulative incidence of mortality in heart transplants for the same time intervals were 2, 4, 7, and 12% respectively.

Overall, there was a higher cumulative incidence of all cancers and death in heart than in kidney transplant recipients.

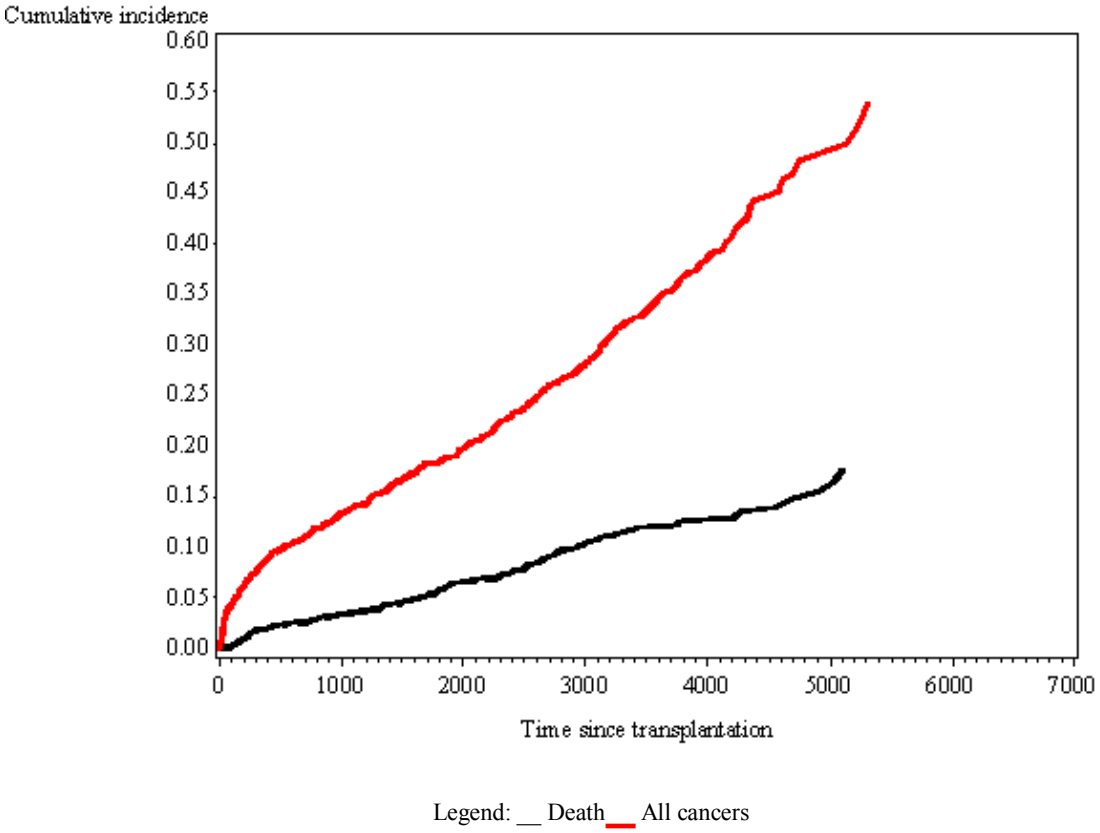
Figures for other transplants were included in Appendix 8.

Figure 4.4.3 Cumulative incidence of cancer and death among transplant recipients in Canada between 1981 and 1998, by time since transplantation

A) Kidney transplant



B) Heart transplant



4.4.4 Population-Attributable Risk

As outlined in Table 4.4.A - B, the PAR of developing cancer is highest in kidney, with a PAR of 0.247% for all cancers, while all other PARs were ≤0.1%. Similarly, mortality PARs were very low, with the highest PAR due to all causes of death being in kidney transplant recipients (0.072). Genitourinary diseases as a cause of death led to the highest PAR (1.1%).

Table 4.4.A Population-attributable risk (PAR) of developing cancer in transplant recipients in Canada between 1981 and 1998

Organ	Cancer	Observed	No. of cancer cases in Canada	ARe	PAR (%)
Kidney	All cancers	773	187,396	0.60	0.247
	Kidney	71	51,145	0.86	0.119
	Liver	5	14,325	0.44	0.016
	NHL	25	72,101	0.44	0.015
	Colorectal	51	255,730	0.29	0.006
	Lung	108	291,109	0.52	0.019
Liver	All cancers	113	187,396	0.60	0.036
	Kidney	4	51,145	0.66	0.005
	Liver	21	14,325	0.98	0.144
	NHL	40	72,101	0.95	0.053
	Colorectal	14	255,730	0.62	0.003
	Lung	10	291,109	0.29	0.001
Heart	All cancers	16	187,396	0.72	0.006
	Kidney	-	51,145	-	-
	Liver	-	14,325	-	-
	NHL	6	72,101	0.97	0.008
	Colorectal	1	255,730	0.50	0.000
	Lung	8	291,109	0.91	0.003
Bilateral lung	All cancers	20	187,396	0.82	0.009
	Kidney	-	51,145	-	-
	Liver	-	14,325	-	-
	NHL	8	72,101	0.98	0.011
	Colorectal	1	255,730	0.60	0.000
	Lung	2	291,109	0.75	0.001
Lung	All cancers	159	187,396	0.63	0.053
	Kidney	61	51,145	0.96	0.115
	Liver	1	14,325	0.41	0.003
	NHL	59	72,101	0.96	0.078
	Colorectal	5	255,730	0.90	0.002
	Lung	22	291,109	0.50	0.004

Table 4.7.B Population-attributable risk (PAR) of dying in transplant recipients in Canada between 1981 and 1998

Organ	Cause of death	Observed	No. of deaths in Canada	ARe	PAR (%)
Kidney	All causes	2,871	3,480,628	0.87	0.072
	Infections and parasitic	128	36,979		
				0.94	0.324
	Neoplasms	379	939,166	0.63	0.025
	Endocrine/nutritional/metabolic	426			
			95,267	0.97	0.436
	Circulatory	844	1,412,003	0.86	0.052
	Respiratory	98	291,150	0.80	0.027
	Digestive	164	129,706	0.90	0.114
	Genitourinary	570	53,234	0.99	1.064
Heart	All causes	582	3,480,628	0.89	0.015
	Infections and parasitic	23	36,979		
				0.95	0.059
	Neoplasms	91	939,166	0.71	0.007
	Endocrine/nutritional/metabolic	11			
			95,267	0.82	0.009
	Circulatory	362	1,412,003	0.94	0.024
	Respiratory	14	291,150	0.77	0.004
	Digestive	22	129,706	0.86	0.015
	Genitourinary	17	53,234	0.96	0.031
Liver	All causes	634	3,480,628	0.92	0.017
	Infections and parasitic	119	36,979		
				0.99	0.319
	Neoplasms	118	939,166	0.82	0.010
	Endocrine/nutritional/metabolic	26			
			95,267	0.93	0.026
	Circulatory	69	1,412,003	0.77	0.004
	Respiratory	22	291,150	0.87	0.007
	Digestive	211	129,706	0.99	0.161
	Genitourinary	15	53,234	0.97	0.027

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Table 4.7.B Population-attributable risk (PAR) of dying in transplant recipients in Canada between 1981 and 1998

Organ	Cause of death	Observed	No. of deaths in Canada	ARe	PAR (%)
Bilateral lung	All causes	126	3,480,628	0.97	0.004
	Infections and parasitic	4	36,979	0.98	0.011
	Neoplasms	13	939,166	0.89	0.001
	Endocrine/nutritional/metabolic	44	95,267	1.00	0.046
	Circulatory	11	1,412,003	0.91	0.001
	Respiratory	45	291,150	1.00	0.015
	Digestive	2	129,706	0.90	0.001
	Genitourinary	1	53,234	0.97	0.002
Lung	All causes	114	3,480,628	0.97	0.003
	Infections and parasitic	12	36,979	0.99	0.032
	Neoplasms	13	939,166	0.88	0.001
	Endocrine/nutritional/metabolic	5	95,267	0.98	0.005
	Circulatory	11	1,412,003	0.91	0.001
	Respiratory	61	291,150	1.00	0.021
	Digestive	4	129,706	0.95	0.003
	Genitourinary	3	53,234	0.99	0.006
Heart-lung	All causes	50	3,480,628	0.99	0.001
	Infections and parasitic	1	36,979	0.98	0.003
	Neoplasms	2	939,166	0.90	0.000
	Endocrine/nutritional/metabolic	3	95,267	1.00	0.003
	Circulatory	20	1,412,003	1.00	0.001
	Respiratory	10	291,150	1.00	0.003
	Digestive	1	129,706	0.98	0.001
	Genitourinary	0	53,234	0.00	0.000

5. DISCUSSION

5.1 Study Overview

This is a population-based, retrospective cohort follow-up study concerning data collected between January 1, 1981 and December 31, 1998. The objectives of this study were firstly, to examine post-transplant mortality in organ-replaced patients relative to the general Canadian population, using SMR and PMR analyses; secondly, to assess the risks of developing cancer, overall and site-specific, in transplant recipients relative to the general Canadian population, using SIR and stratified SIR analyses; and thirdly, to determine the impact of such risk factors as age, sex, and calendar period on the association between organ transplant and cancer development and mortality. Cox proportional hazards and logistic regression models were used to assess the effect of various risk factors on cancer incidence and mortality in transplant sub-populations, while cumulative incidence was used to study the patient survival pattern. Finally, PAR was used to quantify the impact of organ transplantation on cancer incidence and mortality.

Findings presented in this study were similar to those presented by Jiang (2008) and Villeneuve (2007) for liver and kidney transplants, With regards to other transplants, different analyses were conducted, and for this reason, there is very limited data was available for comparison. In addition, most studies have insufficient sample size for precisely examining risk for various causes of cancers, and very few examined the pattern of cancer risk as a function of time. Further, results may vary since many studies are based on a single-clinic experience, originating in different countries, which implies

different referral patterns, sociodemographic characteristics, treatments, and possibly different outcomes which were assessed.

5.2 Key Findings and Interpretation

5.2.1 Objective 1

5.2.1.1 SMR

Referring to the first objective, SMRs due to all causes of death ranged from 7.6 in kidney transplant recipients to 11.8 in liver transplant recipients. Comparable results were found in a Canadian study of kidney transplant recipients, which indicated that SMRs due to all causes of death between 1981 and 1986 were 4 and 8 for males and females, respectively (Silins, 1989).

Genitourinary diseases represented a major risk of death for all types of organ transplants, with an SMR as high as 158.3 in kidney transplant recipients. This condition can be attributed part to pre-existing kidney diseases, which are known to reoccur in renal transplant recipients, as well as calcineurin-inhibitor therapy, which plays an important role in the immunosuppressive regimen given to patients undergoing transplantation and which has been associated with severe renal complications (Ojo, 2003). The following conditions can also contribute to chronic renal failure post transplantation: UTIs, perioperative hemodynamic insults to the kidneys, nephrotoxic effects of other drugs, dyslipidemia, hypertension, and diabetes mellitus (Ojo, 2003).

Endocrine, nutritional and metabolic diseases as causes of death had SMRs ranging from 15.3 in liver recipients to 38.7 in kidney recipients. The increased SMRs as a result of such diseases may be attributed part to the new-onset diabetes mellitus (NODM), which

occurs in approximately 15% of liver transplant patients and 15-20% of renal transplant recipients. A renal registry analysis in the US has reported an increase of up to 87% in risk of death following onset of NODM (Watt, 2010). Diabetes after transplantation has been established as a leading risk factor for cardiovascular events, with a higher prognostic value than in the non-transplant population. Moreover, patient mortality following transplantation was found to be higher in patients with diabetes and diabetes-related complications, notably infection (Watt, 2010).

SMRs due to infectious and parasitic diseases were also relatively high, the highest being in liver (SMR = 119.0), followed by heart (SMR = 19.2), and then kidney (SMR = 15.4). While the evolution of immunosuppression for organ transplantation has reduced the incidence of acute graft rejection, it has also increased the risk of infection and virally mediated malignancies. Epidemiologic exposures can be divided into multiple categories: donor- and recipient-derived infections, community-acquired infections including those related to travel, and nosocomial infections (Fishman, 2010). It is important to note, however, that follow up of individuals in the SMR analysis started 30 days post-transplantation, and as a result, the total number of observed deaths does not include infections that may have occurred immediately after the procedure was performed.

Because of the low number of patients, which was only 100-300 per procedure, single lung, heart-lung, and bilateral lung transplantation data did not allow for complex analyses, as seen for other organs. Further, the lung is unique among all solid organ transplantations in that it is highly prone to infection, since systemic arterial blood supply is not routinely restored during engraftment. For this reason, the high rate of complications in lung transplant has been attributed primarily to ischemia of the donor bronchus (Lin, 2008). Application of effective antibiotics, aseptic operation in sputum

aspiration, and unobstructed respiratory tract drainage are important measures for controlling pulmonary infection post-transplantation (Lin, 2008).

Despite improvements in long-term survival, mortality rates among children remain substantially higher than those among children without end-stage diseases. Although not explored as a separate entity in this study, mortality in children age 14 years and under who had undergone renal transplantation was 30 times higher than among 14 and under in the general population (Groothoff, 2002).

The generally lower SMRs for neoplasms indicate taht neoplasms are not a major cause of death relative to other causes of death. Further, these findings indicate that mortality in organ transplant recipients is comparable to that observed in the general Canadian population, which in turn highlights the beneficial role of the procedure.

With regards to the magnitude of the values observed in this study, some deaths may be attributed to the age of the donor and/or recipient. The literature shows that the age of end-stage organ failure patients has steadily increased with the mean age of patients suitable for transplantation, with approximately 20% of patients in Canada being over age 50 and up to 20% of patients being under age 20 in certain transplants including liver (CIHI, 2010). Moreover, donor age has increased, and donors over 70 are being accepted. This modification of the clinical picture is inherently associated with different causes of death. Because of their age, elderly patients have a higher rate of complications and, thus, a high risk of patient death due to these events. These causes of death, however, are only indirectly related to the transplantation procedure (Moreso, 2003). In addition, elderly patients may have a higher incidence of infectious complications since they are less immunologically active, especially when they must follow a powerful immunosuppresion regimen (Moreso, 2003).

5.2.1.2 PMR

PMRs presented in this study are cohesive with earlier findings, whereby the risk of dying due to genitourinary, endocrine, nutritional and metabolic, and infectious diseases is higher than the risk from all other causes.

Among all transplants, kidney had the highest PMRs due to genitourinary diseases, which decreased over time and ranged from 42.8 at 0-3 months to 21.5 after 10 years of follow-up. PMRs followed less distinct trends for heart and liver recipients, where the magnitude of these values was significantly lower: PMR of 3.6, at 0-3 months in liver, and 1.2 in liver and 4.2 in heart transplant recipients.

Endocrine, nutritional and metabolic diseases had the second highest PMRs, with values for kidney transplant recipients ranging between 5.4 and 4.7 from 0 – 3 months to 10 years and up.

Over time, PMRs decreased for infectious and parasitic diseases in all types of transplants. The literature shows that infectious diseases are generally related to the transplantation procedure itself, and are most likely to occur immediately post-surgery (Fishman, 2010). It is therefore probable that the PMRs provided in this study would be higher if follow-up of cases were to start 30 days post-transplantation.

As previously established by Ward et al. (2009), given the nature of these diseases, infections represent a risk in early years post-transplantation, while complications due to cardiovascular, endocrine, nutritional, metabolic and digestive diseases after various transplants are a major source of concern long-term.

It is important to note that heart transplant recipients had an increased PMR for circulatory diseases. It has been reported that the role of classical cardiovascular risk

factors in transplanted patients is more pronounced than that in the general population; therefore, taking into account that heart transplant recipients have a higher incidence of cardiovascular risk factors, one would expect that the accurate management of these factors would reduce cardiovascular mortality (Moreso, 2003).

Neoplasms had the lowest PMRs, ranging from 0.1 to 0.4, providing further evidence that cancer mortality in organ transplant recipients is very similar to that observed in the general Canadian population.

Overall, PMRs for neoplasms appeared uniformly low, and lower than 1.0, while genitourinary PMRs throughout the study interval appeared to be higher than 5.0.

The contrast between the SMRs (>7.0) and PMRs (< 1.0) may be partly explained by the fact that transplant replacement patients are a vulnerable sub-population, and are subject to higher risk of dying due to all causes of mortalities. In contrast to the outcome with other diseases, low cancer mortality among organ replacement patients may be attributed to careful patient follow-up and earlier detection. Moreover, the cancer risk in the organ replaced population is lower than that in the general population, possibly due to pre-transplant cancer screening.

5.2.2 Objective 2

5.2.2.1 SIR

SIRs indicate that the number of observed cases of all cancers in heart transplant recipients is up to 3.6 times greater in transplant recipients than in the general Canadian population, while the lowest was in kidney and liver, with an SIR of 2.5. The highest SIR

for all cancers was observed in bilateral lung transplants (SIR = 5.6); however, as discussed earlier, these results were not significant and are, therefore, less reliable.

NHL and kidney cancer had among the highest SIRs for all organs, while liver cancer was particularly high for liver transplants only (SIR = 52.5). NHL is causally associated with infection by γ herpesviruses, such as the Epstein-Barr virus, which is present in a large proportion of immunodeficient cases, and for this reason it has been reported to occur at excess rates after solid organ transplantation (Van Leeuwen, 2010). In kidney transplant recipients, kidney cancer has been attributed in literature as a consequence of acquired cystic kidney disease that is present in approximately 40% of graft recipients when transplanted, and it appears after transplantation in a further 16% (Stewart, 2009). Studies show that the risk of developing kidney and urinary tract cancers in persons with end-stage kidney disease is as high prior to transplantation as it is after transplantation, indicating that the risk precedes pharmacological immunosuppression (Stewart, 2009).

On average, it is estimated that the incidence of cancer in patients who have received kidney transplants is 3 times higher the general Canadian population; however, this ratio can reach an incidence rate of between 8 and 14 times greater for kidney cancer in kidney transplant recipients (Pita-Fernandez, 2009).

Although the risk of developing the most common cancers (e.g., colon, lung, stomach, oesophagus, pancreas and ovary cancer) is higher in transplant recipients than in the general population, these cancers may be detected incidentally at an early stage because of the frequent imaging studies and close patient follow-up performed in this population. It is important to note that patients are seen at least every 3 months during the first year after the transplantation; are seen every 6 months from one year onward; and are seen at least once a year from 10 years onward. This process may have an impact on the

magnitude of the SIRs, given that the patients are being closely monitored and diseases are more likely to be detected in early years than later (Pita-Fernandez, 2009). In addition, impact on mortality would be delayed and mortality due to such causes would likely be attenuated (Wisgerhof, 2010).

As reported in the literature, the risk of cancer post-liver transplantation was 3-fold higher than that for the general population of the same age and sex (Wisgerhof, 2010).

With regards to heart transplantations, a few studies have shown high frequencies of solid tumours among these recipients; however, no comparison with the general population was reported (Kellerman, 2009).

5.2.2.1 Stratified SIR

Stratified analyses were conducted in kidney transplants for follow-up interval, transplant date, sex, and age at surgery. The results indicate that SIR for all cancers tends to increase over time, is higher in males than in females, and decreases with age of transplant recipient. These findings are supported by Aberg et al. (2008), and Villeneuve et al. (2007), who employed a similar approach using SIR to establish the same trends in liver transplant recipients.

Similar trends were found in a stratified analysis, where NHL was associated with male sex, young age, and the immediate post-transplant period (Aberg, 2008).

Similarly, older age at transplantation and re-transplantation were risk factors for the development of solid-tumor malignancies in heart transplant patients (Kellerman, 2009).

Since the interval between transplantation and diagnosis of cancer is time dependent, the follow-up period is indicative of whether incidence is modified with length of follow up.

Even though the type of tumour and the age of the patient generally cause variability, the average latency period is reported to be approximately three to five years after transplantation (Pita-Fernandez, 2009).

5.2.3 Objective 3

5.2.3.1 Cox Proportional Hazards Model

The Cox proportional hazards model was used to assess the effect of risk factors, such as sex, age, and length of follow up, on cancer incidence.

As observed in Table 4.4.A - F, there was an increased risk of developing all cancers for all types of transplants, which increased with age, with a risk of 2.6 in patients from age 40 to 60, and of 6.0 in patients over 60. These findings suggest a linear increase based on age; however, a similar trend is also expected in the general Canadian population.

With regards to cancer risk for kidney transplants, females seemed to have a lower risk than males, where HR = 0.8. Sex was a significant factor in liver transplants recipients, but in no other transplants. Similar findings were presented in studies by Arend et al. (1997), Villeneuve et al. (2007), and Jiang et al. (2008), where the HR for females varied from 0.7 to 0.8.

All HRs presented for NHL indicated no statistically significant variations in risk.

5.2.3.2 Logistic Regression Model

Referring to the third objective—the effect of risk factors on the association between transplant and cancer development—logistic regression results show that year of surgery, age at surgery, and sex are all significant predictors of mortality in kidney transplants,

while diabetes, smoking status and race were not significant. Further, odds ratios indicate the reduced risk in mortality in later years (post-1990), a reduced risk in females and an inverse relationship between age and the odds of dying.

In a similar study, multivariate analysis suggested that a young age at the start of renal-replacement therapy, and commencing renal-replacement therapy before 1983, contributed to an increased risk of death. There was a weak interaction between transplantation and the decade in which renal-replacement therapy was started (P=0.07). In addition, a study heart transplant recipients indicated that age at transplantation and sex were significant predictors of mortality (P<0.05). (Norman, 2001).

Few, if any, studies attempted to fit the same predictor variables in a model, which makes results between studies difficult to compare.

5.2.3.3 Cumulative Incidence

Cumulative incidence was used to analyse survival patterns. As depicted in Figure 4.6.A - B, there was a steep increase in the number of deaths among kidney transplant recipients during the first 30 days, which continued up to 3 months, followed by an apparently linear relationship between the number of deaths and time. A similar pattern was observed for heart transplants.

As previously established by Villeneuve et al. (2007), the steep increase in the number of deaths during the first 30 days indicates that the first month post-transplantation is crucial in patient survival.

In both types of transplantations, cancer cumulative incidence shows a steep slope, with a cancer cumulative incidence of approximately 35% for kidney and 48% for heart

transplant recipients after 14 years of follow up. The cumulative incidence of death in kidney patients is approximately 5% in kidney recipients and 12% in heart transplant recipients, also after 14 years of follow up.

As expected, the slope for mortality is less steep than that observed in cancer incidence, indicating that not all cancers lead to mortality. Jiang et al. (2008) observed similar findings in kidney transplant recipients.

5.2.3.4 PAR

PAR was used to quantify the impact of organ transplantation on cancer incidence and mortality. Tables 4.7.A and 4.7.B show the population attributable risk of developing cancer (all cancers and site specific), and of dying due to all causes and cause specific. The extremely low PARs of < 1% in cancer incidence and mortality indicate that there is very low probability of population risk of developing and of dying, which may be attributed to the transplantation itself. It can be said, therefore, that the additional risk of developing cancer or of dying due to the transplantation procedure itself is almost negligible.

The magnitude of the PAR is not surprising, provided the small sample size of this cohort in comparison to the general Canadian population; however, this type of analysis is necessary in a government setting, where PARs may be useful for public health planning and resource allocation.

5.3 Power of the Study

In most epidemiological study designs, samplesize is determined in order to meet a desired accuracy of selected parameters. This project was based on a previously collected sample of more than 40,000 patient records, which is not alterable. Therefore, the sample size determination is not relevant, but the power of the study is a must-know. Since the sample size and detectable relative risks have a non-linear reciprocal relationship—when one is known the other can be determined following a non-linear formula—we can estimate the power of the study based on the size of the studied population. More specifically, this report examines the magnitude of relative risk using the Least Significant Relative Risk (LSRR) based on sample size, and estimated disease rate in the reference group. In the processing of this study, a one-sided test for transplant recipients versus the general population, with $\alpha = 0.05$ and $\beta = 0.20$, was performed. Power calculations are included in Appendix 2.

5.4 Ethical Considerations

5.4.1 Security Measures

The proposed project was approved by the Health Canada Research Ethics Board. The mortality and cancer incidence linkage process was approved by the Policy Review Committee of Statistics Canada. The record linkage process and some data analysis were performed by Statistics Canada and CIHI. The analysis file was prepared by Statistics Canada employees and was stored in an isolated computer workstation. In addition, access was further restricted by account/password protection, by a firewall which segments the workstation to selected users only, and by automatic login restrictions and

directory/file protection. This security constitution has been reviewed and approved by the Statistics Canada's EDP Security Officer for storing confidential data.

5.4.2 Confidentiality

Confidentiality of all subject information was assured, and no direct contact with patients took place. The record linkage process including manual resolution of uncertain links was processed under oath by Statistics Canada and CIHI cost-recovery record linkage teams. All identifying information was removed and the order of the records was scrambled from the analysis file. Presentation of results was in statistical form for aggregates of individuals following Statistics Canada and CIHI guidelines, and no specific individuals were identified.

5.5 Potential Strengths and Limitations

Using CORR data is advantageous in that it is cost efficient and a large data volume is available. Some limitations of the registry are related to the details of the information recorded for each patient; and although coverage by CORR is complete in that all 86 Canadian transplant replacement centers, the data are submitted voluntarily, and the database has never been validated (Schaubel, 2002). However, such factors pose no major threat to the validity of our findings because it is doubtful that the reporting of mortality was incomplete.

Through the cooperation of the provincial cancer registries, cancer registration in Canada is more than 95% complete. Since reporting of deaths is mandatory (Villeneuve, 2007), very few events occurring in Canada would have gone unrecorded. In addition, Canadian

deaths are 100% registered through the Canadian Vital Statistical Committee, in collaboration with provincial and territorial representatives.

With regards to logistics, the ability to link the CORR cohort to these databases was excellent, given the detailed personal identifying information available. The CORR, CMDB, CCR linkage was performed under a contractual agreement with Statistics Canada, whereby this linkage has been reviewed by Statistics Canada's Ethic Review Committee and a MOU between Health Canada and Statistics Canada. The deliverable included the two linkage files used in this study (i.e., CORR/CMDB and CORR/CCR) along with a data quality report for the record linkage procedure, which is housed within Statistics Canada.

In addition, because of the medical needs of these patients in Canada, it is expected that few of the individuals would have emigrated. It is unlikely, therefore, that the observed number of incident cases discussed in this study was excessively under-reported as a result of residential mobility, and no biases can be attributed to such patients (Jiang, 2008).

Overall, the availability of accurate data on the type of renal-replacement therapy, and the long duration of follow up with minimal loss to follow up, enabled us to provide valid and reasonably precise estimates of long-term survival and to identify modifiable and unmodifiable risk factors for death.

There are, however, several limitations to this study. First, linkage data was only available until 1998, which allows the possibility of variations in the magnitude of the findings presented in this study; however, the trends observed are not expected to have

changed over the course of the past 12 years. Further, the study has a minimized follow up with respect to residential mobility outside Canada.

In addition, low cell counts will not allow adequate power to produce conclusive evidence for less common cancer sites. Furthermore, we have little data on immunosuppressive drugs and little information on type and duration of treatment. In particular, with the evolution of clinical practice, the use of immunosuppressive agents has changed over time, from five pharmaceutical agents in 1990 to 12 in 2001. This in turn is likely to have a significant impact on transplantation outcomes. The CORR database is deficient in that it does not contain any specific related to treatment regimens. As well, very few lifestyle risk factors, which may act as confounders, were included in this study.

Also, despite the large size of this cohort, when stratifying by transplant type, sex, age, time of transplant or follow-up period, particularly for less common types of transplant (e.g., single lung, bilateral lung, heart-lung), some cell numbers were very small, ultimately leading to insignificant results.

Finally, there is a known selection bias among transplant recipients: younger, more severely ill candidates are preferred over older patients who are not as severely ill. Generally, organs are provided to those who need them the most; however, in the event that two individuals have similar profiles, the transplant goes to the individual who applied first. Moreover, some subjectivity may be inevitable in the choosing of recipients based on their potential contribution to society and/or familial decisions (i.e., transplants given to family members only).

An additional bias occurred in this study by not removing cancer patients registered in the CORR/CCR linkage when calculating rates for the general Canadian population.

Sensitivity analyses are commonly used to address potential biases due to unmeasured confounders, classification errors, and selection bias. No such analyses were performed in this study since we were unable to determine from literature a set of confounders to be measures for this particular cohort. In addition, outcome misclassification is unlikely to have occurred since the outcomes of interest comprises of mortality and histologically confirmed cancer. Further, the exposure variables in this study were age, sex, age at transplant, year of surgery and time of follow-up. Again, the chance of misclassification is low. Lastly, as previously acknowledged in this section, selection bias is inevitable.

Since the methods used to assess different risk factors vary, it is difficult to make comparisons between studies. While consistency in SIRs and SMRs 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, since estimation of the SIR is based on the age and sex distribution of the cohort under study, which may vary from region to region (Villeneuve, 2007).

6. CONCLUSIONS

6.1 Summary of Findings

The first objective of this study was to examine post-transplant mortality in organ replaced patients in comparison to the general population. As discussed, mortality is higher in organ transplant recipients and was highest due to genitourinary diseases, followed by endocrine, nutritional and metabolic diseases, and lastly infectious diseases. Neoplasms appeared to have the lowest SMRs and PMRs in comparison to other casues of death, indicating that mortality due to cancer is only slightly higher than that observed in the general Canadian population. Low SIRs further indicated that the incidence of cancers in the transplant population is only moderately higher than that observed in the general Canadian population. The third objective was to determine the impact of risk factors on the association between organ transplant and cancer development. Age, sex, follow-up interval, and year of surgery were all significant risk factors for cancer incidence, while age, sex and year of surgery were significant predictors of mortality. Finally, low PARs for mortality and cancer incidence further confirmed that there is a very low percentage of risk attributable to the transplantation procedure itself.

6.2 Conclusions

Improved patient survival after organ transplantation over the years reflects advances in surgical techniques, anaesthesia, critical care, and infection control, as well as the development of targeted, potent immunosuppressants. With better chances of patient survival, more transplants are being performed annually; however, due to a shift toward a larger proportion of older recipients undergoing transplantations, morbidity and

ultimately mortality are encountered more frequently. In this study, increased morbidities and mortality of organ recipients in comparison to the general Canadian population highlight the need for better management of medical complications in order to improve long-term outcomes.

6.3 Recommendations

This study calls for a more detailed analysis using additional databases (i.e., Discharge Abstract Database, Ontario Drug and Benefit Program), using more recent data. Such findings could aid quantifying the risk of developing cancer and/or of dying, as well as assessing the impact of potential confounders and co-morbidities.

In addition, this study highlights the importance of patient surveillance post-transplantation, as well as the need for further research on immunosuppression strategies associated with a lower morbidity and mortality risk. Strategies to reduce mortality and cancer incidence in organ transplant recipients include implementing screening strategies that are acceptable to the general population and implementing new strategies for those cancers that are increased dramatically in the transplant population. (Kiberd, 2009). The same screening programme could also be implemented to detect other diseases that have a high risk of leading to mortality, such as those of the genitourinary system, as well as endocrine, nutritional and metabolic diseases.

Future research should be directed at ways of using a combination of drugs to reduce the medication burden, reduce the insurance burden, and to improve patient compliance. Novel use of medical teams consisting of nurses, nutritionists, as well as the physician, to educate the patient and evaluate progress should be explored. Lastly, it is clear that

patients need to become more empowered to assume responsibility for their own care and risks; for example, practices such as monitoring and recording blood pressure and blood glucose levels at home should be encouraged.

In addition, further public-health research and policy development on targeted risk assessments could help elucidate the population-based picture of the adverse health effects of organ replacement in Canada.

8. GLOSSARY

Bilateral lung transplant: the replacement of both lungs in a patient, also known as a double lung transplant.

Bronchiolitis obiterans syndrome (BOS): is the clinical definition of chronic organ dysfunction following lung transplantation and refers to a progressive obstructive ventilatory disorder.

Cardiovascular disease (CVD): refers to conditions or diseases of the heart and blood vessels in general, including CAD, angina, congestive heart failure, and high blood pressure, and stroke.

CCR: Canadian Cancer Registry

CCRDB: Canadian Cancer Registry Data Base

CIHI: Canadian Institute of Health Information

CMDB: Canadian Mortality Data Base

CORR: Canadian Organ Replacement Registry

Cumulative incidence is defined as the probability that a particular event, such as occurrence of a particular disease (e.g., cancer), has occurred before a given time. It is equivalent to the incidence, calculated using a period of time during which all of the individuals in the population are considered to be at risk for the outcome (e.g, cancer or death).

ESRD Registry: End Stage Renal Disease Registry

GRLS: Generalized Record Linkage System

ICD: International Classification of Diseases

Metabolic Syndrome (MS) is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes.

New onset diabetes mellitus: A condition characterized by hyperglycemia resulting from the body's inability to use blood glucose for energy. In type 1 diabetes, the pancreas no longer makes insulin and therefore blood glucose cannot enter the cells to be used for energy. In type 2 diabetes, either the pancreas does not make enough insulin or the body is unable to use insulin correctly.

NCIRS: National Cancer Incidence Reporting System

Population-attributable risk (PAR) is the reduction in incidence of a disease (e.g., cancer) that would be observed if the population were entirely unexposed (e.g., no transplant), compared with its current exposure pattern (e.g., transplant population).

Proportional mortality rate (PMR) is the observed proportion of a specific disease in a particular transplantation group with the corresponding proportion of this disease in the Canadian population obtained from Statistics Canada.

Protein-calorie malnutrition (PCM) refers to a form of malnutrition where there is inadequate protein intake.

Rate per million population (RPMP) refers to the incidence of a new case within a population with a defined disease that requires organ replacement; in this case, incidence is presented as rate per million population (RPMP) so that there is an understanding of the relative proportion of people in the population who are newly diagnosed.

Standardized incidence ratio (SIR) is the ratio of the observed-to-expected number of incident cancers due to a selected cause

Standardized mortality ratios (SMR) represents the ratio of the observed-to-expected number of deaths and morbidities due to a selected cause.

Urinary tract infection (UTI) refers to an infection of one or more structures in the urinary system.

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APPENDIX 1: Power calculations using Walter's Method of least significant relative risk (LSRR), with $\alpha = 0.05$, $\beta = 0.20$, and a one-sided test transplant recipients versus the general Canadian population from January 1, 1981 to December 31, 1998

Type of Cancer	H_o Incidence Rate	LSRR
All cancers	403/100,000	(2.03, 0.37)
Colon cancer	53/100,000	(5.62, 0.08
Lung	64/100,000	(4.98, 0.09)
Non-Hodgkin's Lymphoma	15/100,000	(7.51, 0.03)
Prostate cancer	113/100,000	(1.38, 0.68)
Breast cancer	100/100,000	(1.38, 0.68)

APPENDIX 2: ICD-9 Codes for Variables Used

Cause of death	ICD-9	LCDC*
All causes	001-999	1
Infections and parasitic	001-139	2
Neoplasms	140-239	3
Endocrine/nutritional/metabolic	240-279	4
Circulatory	390-459	8
Respiratory	460-519	9
Digestive	520-579	10
Genitourinary	580-629	11

*LCDC is the disease code as it appears in Orius, the internal software used to generate the expected rates of death or disease incidence

Cancer Site	ICD-9	LCDC
All Cancers	140-208	19
Kidney	189	245
Non-Hodgkin's Lymphoma	155	94
Liver	200, 202	236
Colorectal	153, 154	259
Lung	162	104

APPENDIX 3: Search Strategy

The following strategy was applied for each transplant in combination with each individual cause of death or cancer type:

"Kidney Transplantation/statistics and numerical data"[Mesh] AND ("Infection"[Mesh] OR "Infection/statistics and numerical data"[Mesh])

Limit: English language and yr="2000 -Current")

APPENDIX 4: Preliminary list of variables included in CORR analysis

Variable	Inclusion Status	Type of analysis
Cardiovascular disease	Excluded	N/A
Cerebrovascular accident	Excluded	N/A
Date of transplant	Included	Start of follow-up
Date of cancer incidence		End of follow-up in cancer incidence analysis
Diabetes status	Excluded	Logistic regression
Disease other organ	Excluded	N/A
Donor age	Excluded	N/A
Donor cause of death	Excluded	N/A
Donor province of death	Excluded	N/A
Donor gender	Excluded	N/A
Donor Hep. C	Excluded	N/A
Donor HIV	Excluded	N/A
Donor racial origin	Excluded	N/A
Height/weight/code	Excluded	N/A
Kidney failure	Excluded	N/A
Lung diseases	Excluded	N/A
Malignant site (cancer)	Included	Cancer incidence analysis
Medical status (i.e., at home, hospitalized)	Excluded	N/A
Onset age	Excluded	N/A
Organ cause of failure	Excluded	N/A
Organ failure date	Excluded	N/A
Organ type	Included	Stratified analyses
Patient cause of death	Included	Mortality analysis
Patient birthdate	Included	Used to calculate age
Patinet blood type	Excluded	N/A
Patient deathdate	Included	Enf of follow-up
Patient diagnosis date	Included	N/A
Patient gender	Included	Stratified analyses, logistic regression
Patient height	Excluded	N/A
Patient racial origin	Included	Demographics, logistic regression
Patient residing city	Excluded	N/A
Patient residing province/territory	Included	Demographics
Patient weight	Excluded	N/A
Smoking status	Included	Logistic regression

APPENDIX 5: Characteristics of patients who received various types of transplants, Canadian Organ Replacement Registry, 1981 to 1998. Only patients who survived 30 days post surgery were included in this study

A) Kidney transplant

Characteristic	Number of Patients	Percentage
Age at surgery		
0 <10	290	2.6
10<20	695	6.3
20<30	1686	15.3
30<40	2544	23.1
40<50	2558	23.2
50<60	2071	18.8
60<70	1046	9.5
≥70	138	1.2
Sex		
Male	6968	63.2
Female	4060	36.8
Year of surgery		
1981-1983	904	8.2
1984-1986	1716	15.6
1987-1989	2092	19.0
1990-1992	2117	19.2
1993-1995	2329	21.1
1996-1998	1870	17.0

B) Liver transplant

Characteristic	Number of Patients	Percentage
Age at surgery		
0 <10	266	13.1
10<20	113	5.6
20<30	137	6.7
30<40	248	12.2
40<50	494	24.3
50<60	473	23.2
60<70	287	14.1
≥70	16	0.8
Sex		
Male	1068	52.5
Female	966	47.5
Year of surgery		
1981-1983	3	0.2
1984-1986	85	4.2
1987-1989	266	13.1
1990-1992	467	23.0
1993-1995	663	32.6
1996-1998	550	27.0

C) Heart transplant

Characteristic	Number of Patients	Percentage
Age at surgery		
0 <10	62	3.6
10<20	83	4.9
20<30	108	6.4
30<40	151	8.9
40<50	419	24.6
50<60	689	40.4
60<70	189	11.1
≥70	1	0.1
Sex		
Male	1416	83.2
Female	286	16.8
Year of surgery		
1981-1983	16	0.9
1984-1986	161	9.5
1987-1989	412	24.2
1990-1992	366	21.5
1993-1995	438	25.7
1996-1998	309	18.2

D) Lung transplant

Characteristic	Number of Patients	Percentage
Age at surgery		
0 <10	3	1.4
10<20	4	1.8
20<30	9	40.1
30<40	18	8.2
40<50	71	32.3
50<60	84	38.2
60<70	31	14.1
≥70		
Sex		
Male	105	47.7
Female	115	52.3
Year of surgery		
1981-1983	1	0.4
1984-1986	4	1.8
1987-1989	28	12.7
1990-1992	55	25.0
1993-1995	63	28.6
1996-1998	69	31.4

E) Heart and lung transplant

Characteristic	Number of Patients	Percentage
Age at surgery		
0 <10	2	2.4
10<20	7	8.3
20<30	17	20.2
30<40	26	31.0
40<50	23	27.4
50<60	9	10.7
60<70	-	-
≥70	-	-
Sex		
Male	30	35.7
Female	54	64.3
Year of surgery		
1981-1983	1	1.2
1984-1986	7	8.3
1987-1989	26	31.0
1990-1992	24	28.6
1993-1995	13	15.5
1996-1998	13	15.5

F) Bilateral lung transplant

Characteristic	Number of Patients	Percentage
Age at surgery		
0 <10	1	0.4
10<20	16	5.6
20<30	70	24.6
30<40	54	19.0
40<50	59	20.8
50<60	70	24.6
60<70	14	4.9
Sex		
Male	154	54.2
Female	130	45.8
Year of surgery		
1981-1983	1	0.4
1984-1986	18	6.3
1987-1989	76	26.8
1990-1992	106	37.3
1993-1995	83	29.2

APPENDIX 6: Proportionate mortality ratios (PMRs) for the most common causes of death, as observed between January 1, 1981 and December 31, 1998 for selected transplants in Canada

A) Bilateral lung transplant

Cause of death	Follow-up intervals																			
	0 – 3 months				3 months – 2 years				2 – 5 years				5 – 10 years				>10 years			
	O	E	PMR	95% CI	O	E	PMR	95% CI	O		PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI
All causes	65	65	-	-	51	51.0	-	-	37	37	-	-	14	14	-	-	-	-	-	-
Infections and parasitic	1	2.6	-	-	2	2.2	-	-	1	1.0	-	-	1	0.4	-	-	-	-	-	-
Neoplasms	1	17.6	-	-	4	13.5	-	-	6	14.9	-	-	2	5.1	-	-	-	-	-	-
Endocrine/nutritional/metabolic	23	-	-	-	19		-	-	10	-	-	-	5	-	-	-	-	-	-	-
Circulatory	11	9.5	-	-	3	6.8	-	-	3	7.1	-	-	2	3.0	-	-	-	-	-	-
Respiratory	23	1.7	-	-	21	1.4	-	-	13	1.2	-	-	3	0.5	-	-	-	-	-	-
Digestive	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-	-	-	-
Genitourinary	1	-	-	-	-	0.3	-	-	1	0.3	-	-	-	0.1	-	-	-	-	-	-

B) Lung transplant

Cause of death	Follow-up intervals																			
	0 – 3 months				3 months – 2 years				2 – 5 years				5 – 10 years				>10 years			
	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI
All causes	44	44	-	-	51	51	-	-	25	25	-	-	14	14	-	-	-	-	-	-
Infections and parasitic	5	1.8	-	-	8	1.2	-	-	-	0.5	-	-	-	0.2	-	-	-	-	-	-
Neoplasms	1	16.1	-	-	7	20.5	-	-	3	9.6	-	-	2	6.3	-	-	-	-	-	-
Endocrine/nutritional/metabolic	3	-	-	-	4	1.2	-	-	1	1.0	-	-	-	0.4	-	-	-	-	-	-
Circulatory	7	9.0	-	-	5	11.0	-	-	1	5.9	-	-	1	3.7	-	-	-	-	-	-
Respiratory	21	1.4	-	-	23	1.9	-	-	16	1.0	-	-	8	0.7	-	-	-	-	-	-
Digestive	1	-	-	-	2	1.4	-	-	-	1.4	-	-	1	0.6	-	-	-	-	-	-
Genitourinary	-	0.3	-	-	-	0.4	-	-	2	0.2	-	-	1	0.1	-	-	-	-	-	-

C) Heart-lung transplant

Cause of death	Follow-up intervals																			
	0 – 3 months				3 months – 2 years				2 – 5 years				5 – 10 years				>10 years			
	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI	O	E	PMR	95% CI
All causes	35	35	-	-	17	17	-	-	16	16	-	-	8	8	-	-	1	0	-	-
Infections and parasitic	-	1.3	-	-	1	0.6	-	-	-	0.4	-	-	-	0.2	-	-	-	-	-	-
Neoplasms	1	11.2	-	-	1	3.9	-	-	-	5.3	-	-	-	3.3	-	-	-	-	-	-
Endocrine/nutritional/metabolic	1	-	-	-	2	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-
Circulatory	13	5.0	-	-	8	2.1	-	-	5	1.9	-	-	5	0.9	-	-	-	-	-	-
Respiratory	5	0.9	-	-	2	0.4	-	-	5	0.4	-	-	1	0.1	-	-	1	-	-	-
Digestive	1	-	-	-	1	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-
Genitourinary	-	0.2	-	-	-	0.1	-	-	-	0.1	-	-	-	0.05	-	-	-	-	-	-

APPENDIX 7: Standardized incidence ratios (SIRs) for selected cancer sites among those who received a transplant, by follow-up interval, transplant date, and age at transplant, as observed between January 1, 1981 and December 31, 1998 for selected transplants in Canada.

A) Heart transplant

	All Cancers				Kidney				NHL				Colorectal				Lung			
Characteristic	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**
Follow-up interval																				
30 d < 1 y	34	6.6	5.2	(3.6, 7.2)	2	0.3	6.7	(0.7, 24.1)	25	0.3	83.3	(53.9, 123.0)	0	0.9	-	-	2	1.3	1.5	(0.2, 5.6)
1 < 5 y	56	25.7	2.2	(1.6, 2.8)	1	1.0	1.0	(0.01, 5.6)	14	1.2	11.7	(6.4, 19.6)	3	3.4	0.2	(0.2,2.6)	8	4.9	1.6	(0.7, 3.2)
5 < 10 y	56	20.4	2.7	(2.1, 3.6)	3	0.7	4.3	(0.9, 12.5)	15	0.9	16.7	(9.3, 27.4)	2	2.6	0.1	(0.09, 2.8)	10	3.8	2.6	(1.2, 4.8)
≥10y	13	5.4	2.4	(1.3, 4.1)	0	0.2	-	-	5	0.2	25.0	(8.1, 58.3)	0	0.7	-	-	2	1.0	2.0	(0.2, 7.2)
Transplant date																				
1981 - 1986	20	9.0	2.2	(1.4, 3.4)	1	0.3	3.3	(0.04, 18.5)	6	0.4	15.0	(5.5, 32.6)	1	1.2	0.01	(0.01, 4.6)	2	1.75	1.1	(0.1, 4.1)
1987 - 1989	52	20.4	2.5	(1.9, 3.3)	2	0.8	2.5	(0.3, 9.0)	17	0.9	18.9	(11.0, 30.2)	1	2.7	0.004	(0.004, 2.1)	10	4.0	2.5	(1.2, 4.6)
1990 - 1992	46	12.9	3.6	(2.6, 4.8)	3	0.5	6.0	(1.2, 17.5)	16	0.6	26.7	(15.2, 43.3)	1	1.7	0.01	(0.01,3.3)	7	2.4	2.9	(1.2, 6.0)
1993 - 1995	27	11.5	2.3	(1.5, 3.4)	0	0.4	-	-	13	0.5	26.0	(13.8, 44.5)	0	1.5	-	-	1	2.1	0.5	(0.006, 2.6)
1996 - 1998	14	4.3	3.2	(1.8, 5.5)	0	0.2	-	-	7	0.2	35.0	(14.0, 72.1)	2	0.5	0.4	(0.4, 14.4)	2	0.7	2.8	(0.3, 10.3
Sex																				
Male	136	51.2	2.6	(2.2, 3.1)	5	2.0	2.5	(0.8, 5.8)	51	2.3	22.2	(16.5, 29.1)	4	6.9	0.2	(0.2, 1.5)	17	10.1	1.7	(1.0, 2.7)
Female	23	6.9	3.3	(2.1, 5.0)	1	0.2	5.0	(0.06, 27.8)	8	0.2	40.0	(17.2, 78.8)	1	0.7	0.02	(0.02, 7.9	5	0.8	6.2	(2.0, 14.6)
Age at surgery																				
<35	20	1.00	20.0	(12.2, 30.9)	0	0.02	-	-	15	0.09	166.7	(93.2, 274.9)	0	0.05	-	-	0	0.04	-	-
35≥y<50	38	10.6	3.6	(2.5, 4.9)	1	0.5	2.0	(0.03, 11.1)	18	0.7	25.7	(5.2, 40.6)	1	1.3	0.01	(0.01, 4.3)	4	1.7	2.4	(0.6, 6.0)
50=<y<60	82	32.4	2.5	(2.0, 3.1)	3	1.2	2.5	(0.5, 7.3)	23	1.4	16.4	(10.4, 24.6)	4	4.3	0.2	(0.2, 2.4)	16	6.4	2.5	(1.4, 4.1)
≥60	19	14.1	1.3	(0.8, 2.1)	2	0.4	5.0	(0.6, 18.1)	3	0.5	6.0	(1.2, 17.5)	0	1.8	-	-	2	2.0	1.0	(0.1, 3.6)
Total	159	58.1	2.7	(2.3, 3.2)	6	2.2	2.7	(1.0, 5.9)	59	2.6	22.7	(17.3, 29.3)	5	7.6	0.2	(0.2, 1.5)	22	11.0	2.0	(1.2, 3.0)

B) Liver transplant

	All Cancers				Kidney				NHL				Colorectal				Lung			
Characteristic	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**
Follow-up interval																				
30 d < 1 y	32	7.2	4.4	(3.0, 6.3)	0	0.2	-	-	19	0.3	63.3	(38.1, 98.9)	3	0.8	3.8	(0.8, 11.0)	0	1.1	-	-
1 < 5 y	49	23.9	2.1	(1.5, 2.7)	2	0.7	2.8	(0.3, 10.3)	15	1.0	15.0	(8.4, 24.7)	4	2.8	1.4	(0.4, 3.7)	7	3.8	1.8	(0.7,3.8)
5 < 10 y	30	11.9	2.5	(1.7, 3.6)	2	0.3	6.7	(0.7, 24.1)	5	0.5	10.0	(3.2, 23.3)	7	1.4	5.0	(2.0, 10.3)	3	1.8	1.7	(0.3,4.9)
≥10y	2	1.6	1.2	(0.1, 4.5)	0	0.04	-	-	1	0.07	14.2	(0.2, 79.4)	0	0.2	-	-	0	0.2	-	-
Transplant date																				
1981 – 1989	26	11.3	2.3	(1.5, 3.4)	4	0.3	13.3	(3.6, 34.1)	5	0.5	10.0	(3.2, 23.3)	2	1.3	1.5	(0.2, 5.6)	4	1.7	2.4	(0.6,6.0)
1990 – 1992	38	12.9	2.9	(2.1, 4.0)	0	0.4	-	-	21	0.6	35.0	(21.7, 53.5)	6	1.5	4.0	(1.5, 8.7)	1	2.0	0.5	(0.01,2.8)
1993 - 1995	34	13.9	2.4	(1.7, 3.4)	0	0.4	-	-	9	0.6	15.0	(6.8, 28.5)	6	1.7	3.5	(1.3, 7.7)	3	2.2	1.4	(0.3,4.0)
1996 - 1998	15	6.5	2.3	(1.3, 3.8)	0	0.2	-	-	5	0.3	16.7	(5.3, 38.9)	0	0.8	-	-	2	1.0	2.0	(0.2,7.2)
Sex																				
Male	60	21.5	2.8	(2.1, 3.6)	4	0.8	5.0	(1.3, 12.8)	20	1.0	20.0	(12.2, 30.9)	7	2.8	2.5	(1.0, 5.2)	6	4.0	1.5	(0.5,3.3)
Female	53	23.2	2.3	(1.7, 3.0)	0	0.5	-	-	20	0.9	22.2	(13.6, 34.3)	7	2.4	2.9	(1.2, 6.0)	4	3.0	1.3	(0.4,3.4)
Age at surgery																				
<35	25	1.6	15.6	(10.1, 23.1)	2	0.04	50.0	(5.6, 180.5)	15	0.1	150	(83.9, 247.4)	1	0.06	16.7	(0.2, 92.7)	0	0.05	-	-
35≥y<50	36	9.3	3.9	(2.7, 5.4)	1	0.3	3.3	(0.04, 18.5)	15	0.5	30.0	(16.8, 49.5)	3	0.9	3.3	(0.7, 9.7)	4	1.1	3.6	(1.0,9.3)
50=<y<60	24	16.9	1.4	(0.9, 2.1)	1	0.5	2.0	(0.02, 11.1)	5	0.7	7.1	(2.3, 16.7)	7	2.0	3.5	(1.4, 7.2)	3	2.8	1.1	(0.2,3.1)
≥60	28	17.0	1.6	(1.1, 2.4)	0	0.5	-	-	5	0.6	8.3	(2.7, 19.4)	3	2.2	1.4	(0.3, 4.0)	3	3.1	1.0	(0.2,2.8)
Total	133	44.7	3.0	(2.5, 3.5)	4	1.4	2.8	(0.8, 7.3)	40	1.9	21.1	(15.0, 28.7)	14	5.2	2.7	(1.5, 4.5)	10	7.0	1.4	(0.7,2.6)

C) Bilateral lung transplant

	All Cancers				Kidney				NHL				Colorectal				Lung			
Characteristic	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**
Follow-up interval																				
30 d < 1 y	6	0.7	8.6	(3.1, 18.6)	-	0.02	-	-	5	0.03	166.7	(53.7, 388.9)	0	0.08	-	-	0	0.1	-	-
1 < 5 y	10	2.1	4.8	(2.3, 8.8)	-	0.07	-	-	1	0.1	10.0	(0.1, 55.6)	1	0.2	5.0	(0.1, 27.8)	2	0.3	6.7	(0.7, 24.1)
5 < 10 y	4	0.7	5.7	(1.5, 14.6)	-	0.02	-	-	2	0.03	66.7	(7.5, 240.7)	0	0.08	-	-	0	0.1	-	-
≥10y	0	0.08	-	-	-	0.002	-	-	0	0.003	-	-	0	0.007	-	-	0	0.009	-	-
Transplant date																				
1981 - 1989	2	0.5	4.0	(0.4, 14.4)	-	0.01	-	-	1	0.02	50.0	(0.6, 278.2)	0	0.04	-	-	0	0.1	-	-
1990 - 1992	9	1.2	7.5	(3.4, 14.2)	-	0.04	-	-	3	0.06	50.0	(10.0, 146.1)	1	0.1	10.0	(0.1, 55.6)	0	0.2	-	-
1993 - 1995	4	1.4	2.8	(0.8, 7.3)	-	0.04	-	-	3	0.06	50.0	(10.0, 146.1)	0	0.1	-	-	0	0.2	-	-
1996 - 1998	5	0.6	8.3	(2.7, 19.4)	-	0.02	-	-	1	0.03	33.3	(0.4, 185.5)	0	0.08	-	-	2	0.1	20.0	(2.2, 72.2)
Sex																				
Male	14	2.1	6.7	(3.6, 11.2)	-	0.08	-	-	4	0.1	40.0	(10.8, 102.4)	0	0.3	-	-	2	0.4	-	-
Female	6	1.6	3.8	(1.4, 8.2)	-	0.03	-	-	4	0.06	66.7	(18.0, 170.7)	1	0.1	10.0	(0.1, 61.8)	0	0.2	5.0	(0.6, 18.1)
Age at surgery																				
<35	1	0.3	3.3	(0.04, 18.5)	-	0.0005	-	-	1	0.02	50.0	(0.6, 278.2)	0	0.01	-	-	0	0.009	-	-
35≥y<50	6	1.0	6.0	(2.2, 13.1)	-	0.03	-	-	3	0.05	60.0	(12.1, 175.3)	1	0.09	11.1		0	0.1	-	-
50=<y<60	11	1.7	6.5	(3.2, 11.6)	-	0.06	-	-	3	0.07	42.8	(8.6, 125.2)	0	0.2	-	-	2	0.3	-	-
≥60	2	0.7	2.8	(0.3, 10.3)	-	0.02	-	-	1	0.02	50.0	(0.6, 278.2)	0	0.09	-	-	0	0.1	-	-
Total	20	3.6	5.6	(3.4, 8.6)	-	0.1	-	-	8	0.2	40.0	(17.2, 78.8)	1	0.4	2.5	(0.03, 13.9)	2	0.5	4.0	(0.4, 14.4)

D) Lung transplant

	All Cancers				Kidney				NHL				Colorectal				Lung			
Characteristic	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**
Follow-up interval																				
30 d < 1 y	8	0.8	10.0	(4.3, 19.7)	-	0.03	-	-	4	0.04	100.0	(26.9, 256.0)	1	0.09	11.1	(0.1, 61.8)	3	0.1	30.0	(6.0, 87.6)
1 < 5 y	5	2.2	2.3	(0.7, 5.3)	-	0.07	-	-	1	0.1	10.0	(0.1, 55.5)	0	0.2	-	-	4	0.3	13.3	(3.6, 34.1)
5 < 10 y	3	1.2	2.5	(0.5, 7.3)	-	0.03	-	-	1	0.04	25.0	(0.3, 139.1)	0	0.03	-	-	1	0.2	5.0	(0.06, 27.8)
≥10y	0	0.2	-	-	-	0.006	-	-	0	0.008	-	-	0	0.03	-	-	0	0.04	-	-
Transplant date																				
1981 - 1989	4	1.2	3.3	(0.9, 8.5)	-	0.04	-	-	2	0.05	40.0	(4.5, 144.4)	1	0.1	10.0	(0.1, 55.6)	0	0.2	-	-
1990 - 1992	3	1.3	2.3	(0.5, 6.7)	-	0.04	-	-	3	0.05	60.0	(12.1, 175.3)	0	0.1	-	-	0	0.2	-	-
1993 - 1995	6	1.3	4.6	(1.7, 10.0)	-	0.04	-	-	0	0.06	-	-	0	0.1	-	-	6	0.2	30.0	(11.0, 65.3)
1996 - 1998	3	0.7	4.3	(0.9, 12.5)	-	0.02	-	-	1	0.03	33.3	(0.4, 185.5)	0	0.08	-	-	2	0.1	20.0	(2.2, 72.2)
Sex																				
Male	11	2.0	5.5	(2.7, 9.8)	-	0.08	-	-	3	0.1	30.00	(6.0, 87.6)	1	0.3	3.3	(0.04, 18.5)	6	0.4	15.0	(5.4, 32.6)
Female	5	2.4	2.1	(0.7, 4.9)	-	0.05	-	-	3	0.09	33.3	(6.7, 97.4)	0	0.2	-	-	2	0.3	6.67	(0.7, 24.1)
Age at surgery																				
<35	3	0.03	100.0	(20.1, 292.2)	-	0.0005	-	-	2	0.002	1000.0	(112.3, 3610.5)	0	0.001	-	-	1	0.0009	11111.1	(145.2, 61820.6)
35≥y<50	3	1.2	2.5	(0.5, 7.3)	-	0.04	-	-	3	0.055	54.6	(11.0, 159.4)	0	0.1	-	-	0	0.1	-	-
50=<y<60	7	2.2	3.2	(1.3, 6.6)	-	0.07	-	-	1	0.09	11.1	(0.1, 61.8)	0	0.3	-	-	5	0.4	12.5	(4.0, 29.2)
≥60	3	1.0	3.0	(0.6, 8.8)	-	0.03	-	-	0	0.04	-	-	1	0.1	10.0	(0.1, 55.6)	2	0.2	10.0	(1.1, 36.1)
Total	16	4.5	3.6	2.0, 5.8)	-	-	-	-	6	0.19	31.6	(11.5, 68.7)	1	0.5	2.0	(0.03, 11.1)	8	0.7	11.4	(4.9, 22.5)

E) Heart-lung transplant

	All Cancers				Kidney				NHL				Colorectal				Lung			
Characteristic	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**
Follow-up interval																				
30 d < 1 y	6	0.1	60.0	(21.9, 130.6)	-	0.003	-	-	6	0.005	1200.00	(438.2, 2612.0)	-	0.010	-	-	-	-	-	-
1 < 5 y	0	0.3	-	-	-	0.008	-	-	0	0.01	-	-	-	0.02	-	-	-	-	-	-
5 < 10 y	1	0.2	5.0	(0.06, 27.8)	-	0.006	-	-	0	0.01	-	-	-	0.02	-	-	-	-	-	-
≥10y	0	0.05	-	-	-	0.001	-	-	0	0.002	-	-	-	0.004	-	-	-	-	-	-
Transplant date																				
1981 - 1986	0	0.07	-	-	-	0.001	-	-	0	0.002	-	-	-	0.003	-	-	-	0.004	-	-
1987 - 1989	2	0.3	6.7	(0.7, 24.1)	-	0.009	-	-	2	0.01	200.0	(22.5, 722.1)	-	0.03	-	-	-	0.03	-	-
1990 - 1992	2	0.2	10.0	(1.1, 36.1)	-	0.005	-	-	1	0.009	111.1	(1.4, 618.2)	-	0.15	-	-	-	0.02	-	-
1993 - 1995	0	0.008	-	-	-	0.002	-	-	0	0.004	-	-	-	0.006	-	-	-	0.008	-	-
1996 - 1998	3	0.05	60.0	(12.1, 175.3)	-	0.001	-	-	3	0.002	1500.0	(301.5, 4382.7)	-	0.005	-	-	-	0.006	-	-
Sex																				
Male	4	0.2	20.0	(5.4, 51.2)	-	0.0085	-	-	4	0.01	400.0	(107.6, 1024.1)	-	0.02	-	-	-	0.03	-	-
Female	3	0.6	5.0	(1.0, 14.6)	-	0.01	-	-	2	0.02	100.0	(11.2, 361.1)	-	0.03	-	-	-	0.04	-	-
Age at surgery																				
<35	2	0.2	10.0	(1.1, 36.1)	-	0.003	-	-	2	0.075	26.7	(3.0, 96.3)	-	0.008	-	-	-	0.008	-	-
35≥y<50	3	0.4	7.5	(1.5, 21.9)	-	0.01	-	-	2	0.02	100.0	(11.2, 361.1)	-	0.03	-	-	-	0.04	-	-
50=<y<60	2	0.1	20.0	(2.2, 72.2)	-	0.005	-	-	2	0.006	333.3	(37.4, 1203.5)	-	0.02	-	-	-	0.02	-	-
≥60	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-		-		
Total	7	0.7	10.0	(4.0, 20.6)	-	0.002	-	-	6	0.03	200.0	(73.0, 435.3)	-	0.06	-	-	-	0.07	-	-

*Individuals were followed up from 30 days after the date of their renal transplant until the earliest date associated with diagnosis of an incident cancer, death or December 31, 1998.

APPENDIX 8: Logistic regression and odds ratios in Transplant Recipients in Canada between January 1, 1981 and December 31, 1998

A) Heart transplant

Analysis of Maximum Likelihood Estimates

Parameter	Standard Estimate	Wald Error	Chi-Square	Pr > ChiSq
Intercept	-0.5849	0.1723	11.5170	0.0007
Year of Surgery	0.6389	0.1723	13.7449	0.0002

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
Year of Surgery (1 vs 2)	3.589	1.826	7.053

B) Liver transplant

Analysis of Maximum Likelihood Estimates

Parameter	Standard Estimate	Wald Error	Chi-Square	Pr > ChiSq
Intercept	-0.7377	0.1809	16.6319	<.0001
Year of Surgery	0.4633	0.1809	6.5593	0.0104

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
Year of Surgery (1 vs 2)	2.526	1.243	5.133

C) Bilateral lung transplant

Analysis of Maximum Likelihood Estimates

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	-0.0645	0.3594	0.0322	0.8575

NOTE: All effects have been removed from the model.

D) Lung transplant

Analysis of Maximum Likelihood Estimates

Parameter		Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	0.2007	0.4495	0.1993	0.6553

NOTE: All effects have been removed from the model.

E) Heart-lung transplant

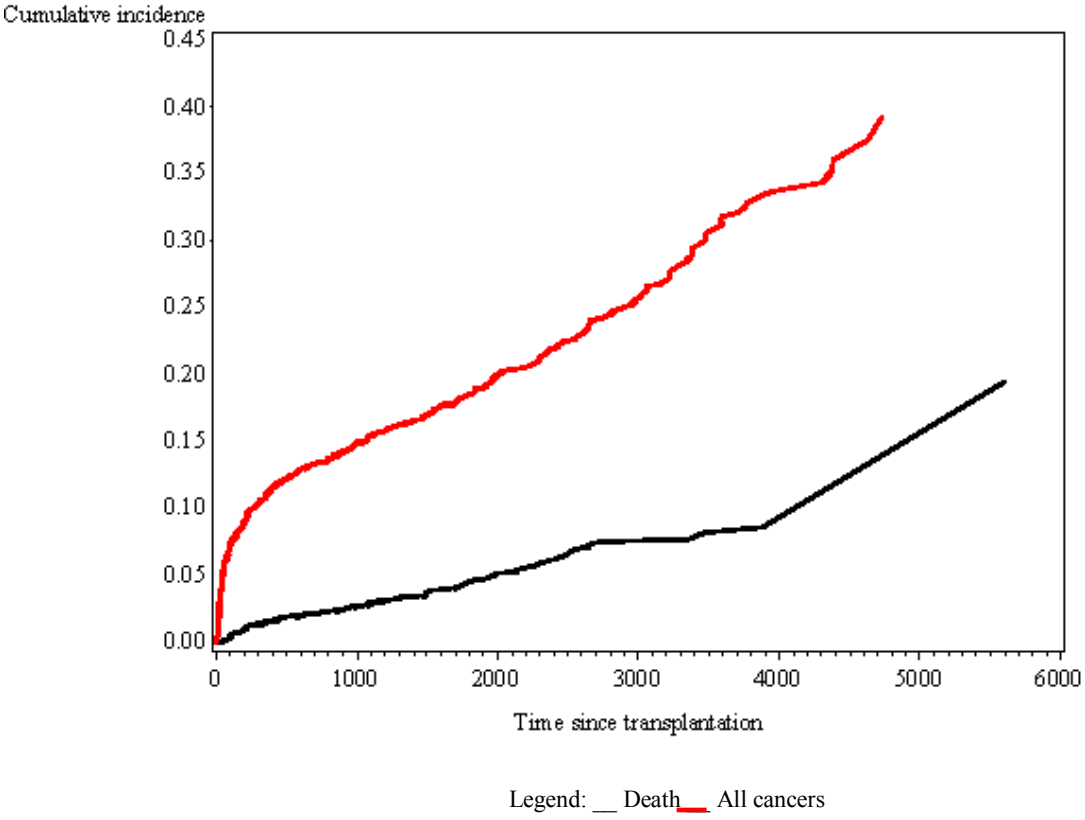
Analysis of Maximum Likelihood Estimates

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1.6094	1.0954	2.1586	0.1418

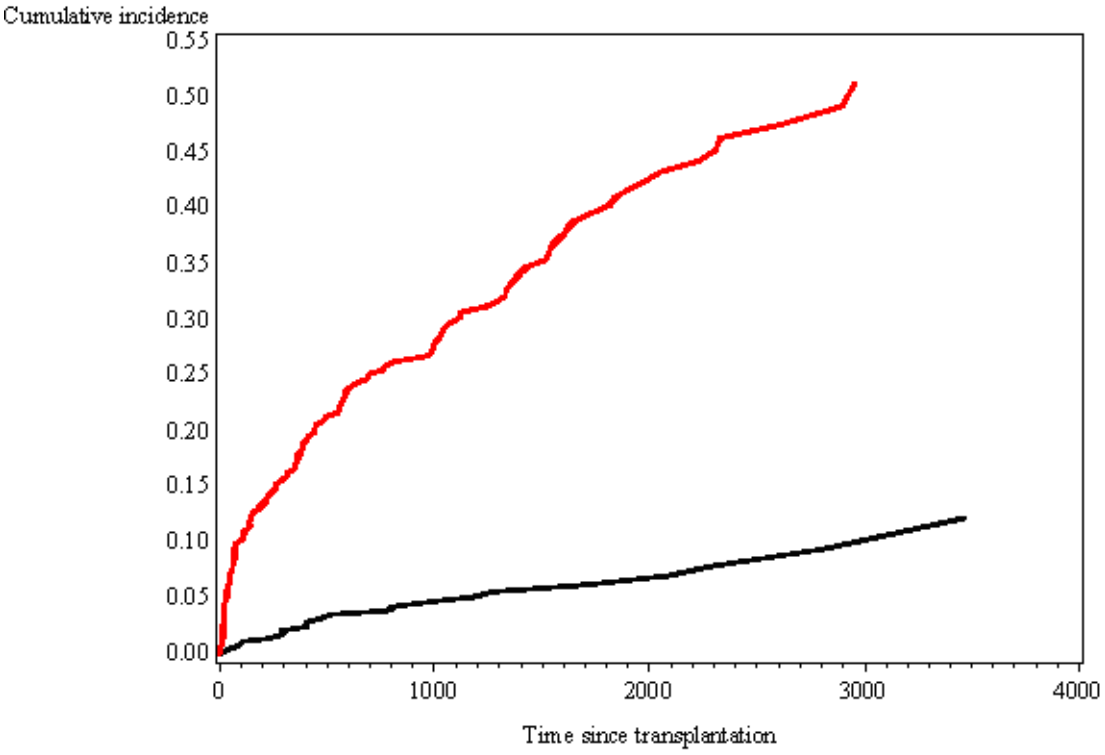
WARNING: The validity of the model fit is questionable.

APPENDIX 9: Cumulative incidence of cancer and death among transplant recipients in Canada between January 1, 1981 and December 31, 1998, by time since transplantation

A) Liver transplant

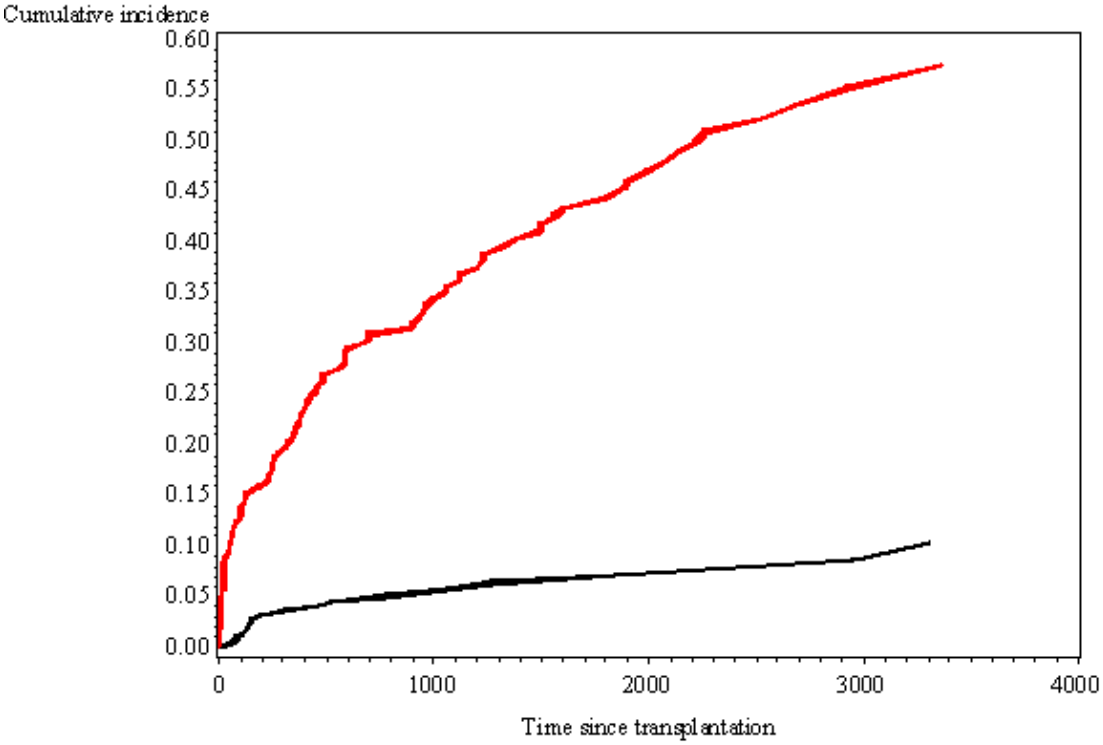


B) Bilateral lung transplant



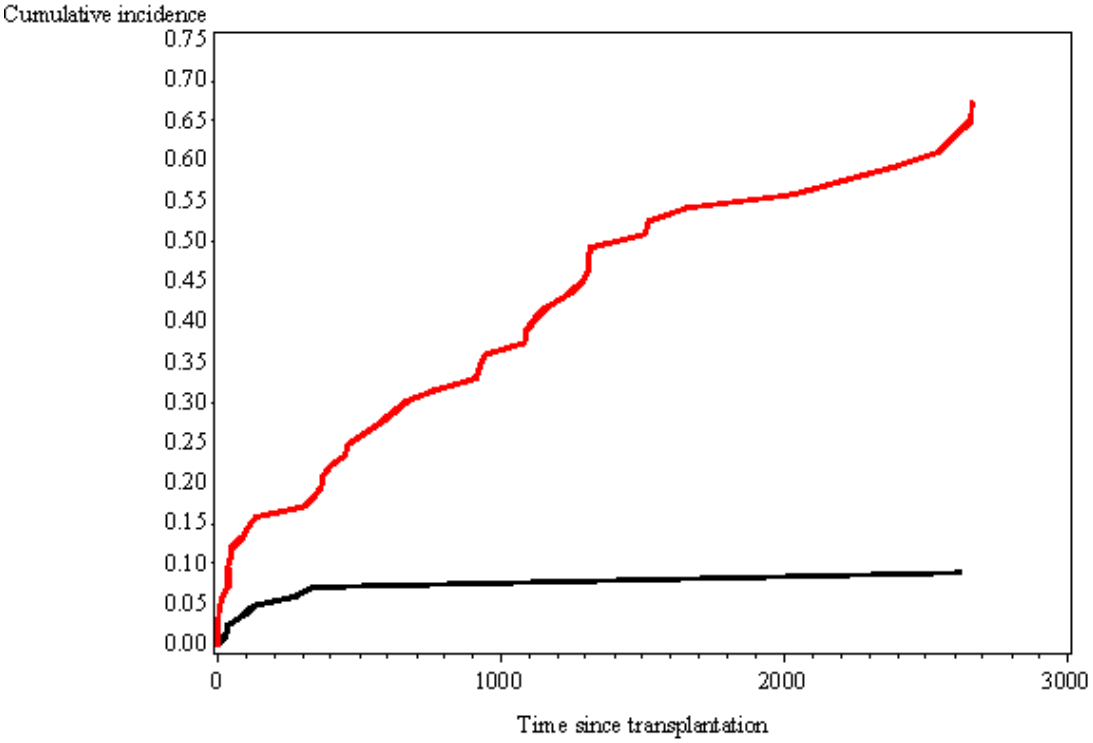
Legend: __ Death __ All cancers

C) Lung transplant



Legend: __ Death __All cancers

D) Heart-lung transplant



Legend: __ Death__ All cancers