



Comparison of All-Cause Mortality Between Canadian Kidney Transplant Recipients and Patients With Cancer: A Population-Based Cohort Study

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Abstract

Background: Understanding rates of mortality in kidney transplant recipients relative to other common diseases can enhance our understanding of the mortality burden in kidney transplant recipients.

Objective: To compare the survival probability in Canadian female and male kidney transplant recipients with patients with common cancers (female: breast, colorectal, lung, or pancreas; male: prostate, colorectal, lung, or pancreas) in a contemporary population.

Design: Population-based cohort study using linked administrative health care databases.

Setting: Ontario, Canada.

Patients: A total of 6888 incident kidney transplant recipients (median age was 50 and 51 years in females and males, respectively) and a total of 532 452 incident patients with cancer (median age range 60 to 72 years across cancer types) from 1997 to 2015.

Measurements: All-cause mortality.

Methods: The survival of study participants was described using the Kaplan-Meier product limit estimator. The rate of survival was compared between kidney transplant recipients and patients with cancer using extended Cox regression with a Heaviside function.

Results: Kidney transplant recipients had a higher survival probability compared with all cancer types. For example, male kidney transplant recipients had a 5-year survival probability of 89.6% (95% confidence interval [CI]: 88.6%-90.5%) compared with 83.3% (95% CI: 83.1%-83.5%) in patients with prostate cancer, and 14.0% (95% CI: 13.7%-14.3%), 56.1% (95% CI: 55.7%-56.5%), and 9.1% (95% CI: 8.5%-9.7%) in patients with lung, colorectal, and pancreas cancer, respectively. After presenting survival probabilities by age at cohort entry and after adjusting for clinical characteristics, similar results were found with a few exceptions. Unlike the unadjusted analysis, in the adjusted analysis males with prostate cancer had a significantly higher survival compared with kidney transplant recipients and females with breast cancer had higher survival compared with kidney transplant recipients at 2+ years of follow-up. In a subpopulation of the cohort who had information available on cancer stage (ie, stages 1-4), we generally found similar results to our primary analysis with kidney transplant recipients having a higher survival probability compared with each cancer stage. However, female kidney transplant recipients had a lower survival probability compared with females with stage 1 breast cancer, whereas male kidney transplant recipients had a lower survival probability compared with males with stage 1 to 3 prostate cancer.

Limitations: External generalizability, residual confounding, and cancer stage could only be provided for a subpopulation.

Conclusion: Mortality in kidney transplant recipients is lower than in patients with several cancer types. These results improve our understanding of the mortality burden in this population and reaffirm kidney transplantation as a good treatment option for end-stage kidney disease but also highlight the continuing need to improve posttransplant survival.

Trial registration: This is not applicable as this is a population-based cohort study and not a clinical trial.

Abrégé

Contexte: La comparaison du taux de mortalité des receveurs d'une greffe rénale par rapport à celui des patients atteints d'autres maladies courantes pourrait améliorer notre compréhension du fardeau que cela représente chez les transplantés rénaux.



Objectifs: Comparer la probabilité de survie des transplantés rénaux canadiens, femmes et hommes, à celle de patients atteints de cancers fréquents (femmes : sein, colorectal, poumons ou pancréas; hommes : prostate, colorectal, poumons ou pancréas) dans une population contemporaine.

Type d'étude: Étude de cohorte représentative d'une population réalisée à partir des données administratives en santé.

Cadre: Ontario, Canada.

Sujets: L'étude porte sur 6 888 transplantés du rein incidents (âge médian : 50 ans [femmes] et 51 ans [hommes]) et un total de 532 452 patients atteints d'un cancer (âge médian : 60 à 72 ans pour tous les types de cancers) répertoriés entre 1997 et 2015.

Mesures: Mortalité toutes causes confondues.

Méthodologie: La survie des patients a été décrite à l'aide de l'estimateur produit-limite de Kaplan-Meier. Une régression étendue de Cox avec une distribution de Heaviside a servi à comparer les taux de survie des transplantés rénaux et des patients atteints d'un cancer.

Résultats: La probabilité de survie des transplantés Renaud s'est avérée plus élevée que celle observée pour tous les types de cancer. À titre d'exemple, la probabilité de survie des hommes transplantés était de 89,6 % (IC à 95 % : 88,6-56,9 %) après 5 ans alors qu'elle s'établissait à 83,3 % (IC 95 % : 83,1-83,5 %) chez les patients atteints d'un cancer de la prostate et à 14,0 % (IC à 95 % : 13,7-14,3 %), 56,1 % (IC 95 % : 55,7-56,5 %) et 9,1 % (IC 95 % : 8,5-9,7 %) chez les patients atteints respectivement d'un cancer du poumon, colorectal et du pancréas. Des résultats similaires, à quelques exceptions près, ont été observés après une présentation des probabilités de survie selon l'âge à l'inclusion dans la cohorte et après correction en fonction des caractéristiques cliniques. Dans l'analyse corrigée, contrairement à l'analyse non corrigée, la probabilité de survie des hommes atteints d'un cancer de la prostate et celle des femmes atteintes d'un cancer du sein étaient significativement plus élevées que celle des receveurs d'une greffe rénale après plus de deux ans de suivi. Une sous-population issue de la cohorte de patients disposant d'informations sur le stade du cancer (stades I à 4) a montré des résultats généralement similaires à ceux de notre analyse primaire; les transplantés rénaux montrant une probabilité de survie plus élevée comparativement à chaque stade de cancer. Cependant, les receveuses d'une greffe rénale présentaient une probabilité de survie plus faible que les femmes atteintes d'un cancer du sein de stade I; un résultat similaire a été observé chez les receveurs d'un rein comparativement aux hommes atteints d'un cancer de la prostate de stade I à 3.

Limites: Généralisabilité externe; facteurs de confusion résiduels; stade du cancer connu pour une sous-population uniquement.

Conclusion: Le taux de mortalité chez les receveurs d'un greffe rénale est inférieur à celui des patients atteints de plusieurs types de cancer. Ces résultats permettent de mieux comprendre le fardeau que représente la mortalité dans cette population et de réaffirmer la transplantation rénale comme option de traitement valide pour l'insuffisance rénale terminale. Ces résultats rappellent également qu'il demeure indispensable d'améliorer les taux de survie post-transplantation.

Enregistrement de l'essai: Sans objet. Il s'agit d'une étude de cohorte basée sur une population et non d'un essai clinique.

Keywords

kidney transplant recipient, all-cause mortality, survival, cancer, cohort study

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Introduction

Over the past decade, the outcomes of kidney transplant recipients have improved, with 1-year graft survival in deceased donor kidney transplant recipients increasing from 92.6% in 2008 to 93.8% in 2018.¹⁻³ However, mortality is still high in kidney transplant recipients with 6.2% dying within the first 3 years of transplant compared with 1.4% in a matched general population.⁴ Despite a substantial risk of mortality in kidney transplant recipients, interventions designed to improve survival have slowed (eg, trials evaluating immunosuppression medications), potentially due to a misconception that current outcomes are acceptable.⁵ Moreover, unlike other diseases, such as cancer, kidney disease often goes unrecognized by the public as a potentially fatal disease.⁵

It provides context to understand rates of mortality in kidney transplant recipients relative to other common diseases, which also informs future health care policy and funding decisions. Cancer is a common disease that is well known by the public and can be used as a comparison group to help understand the burden of mortality in kidney transplant recipients. We previously compared survival in patients receiving maintenance dialysis with patients with common cancers, finding that survival in patients receiving dialysis was lower than in patients with several different cancers.⁶ However, kidney transplant recipients are generally healthier than patients receiving dialysis and have a better prognosis.

Previous studies in the kidney transplant population have compared mortality in kidney transplant recipients with patients with cancer, but have limitations such as failure to adjust for multiple risk factors and not reporting results by cancer stage.⁵ A review article demonstrated that 5-year patient survival in deceased donor kidney transplant recipients was comparable with patients diagnosed with breast cancer after regional spread.⁵ Similarly, a United States Renal Data System (USRDS) report found mortality in kidney transplant recipients aged ≥ 66 years was comparable with cancer patients, adjusting for age, sex, and race.⁷ For example, male kidney transplant recipients and male patients with cancer aged 66 to 74 years had an incidence rate of 67.5 deaths per 1000 person-years.⁷

We conducted the current study to compare the survival probability in female and male kidney transplant recipients with patients with common cancers (female: breast, colorectal, lung, or pancreas; male: prostate, colorectal, lung, or pancreas) in a contemporary Canadian population. We also examined survival probabilities presented by age at cohort entry and cancer stage, trends in survival probability over time, and the rate of all-cause mortality after adjusting for clinical characteristics.

Methods

Design and Setting

We conducted a population-based cohort study using administrative health care databases from Ontario, Canada, held at

ICES (ices.on.ca). ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. These data sets were linked using unique encoded identifiers and analyzed at ICES Western. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The reporting of this study follows the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement (Supplementary Table S1).⁸

Data Sources

We used the Canadian Organ Replacement Register (CORR) to identify kidney transplant recipients. We previously found CORR can accurately identify kidney transplant recipients with a sensitivity and positive predictive value $> 95\%$.⁹ Patients with cancer (excluding nonmelanoma skin cancer) were identified from the Ontario Cancer Registry which has $>95\%$ of Ontario's cancer pathology reports.¹⁰ The Registered Persons Database provides demographic and vital status information. The Canadian Institute for Health Information Discharge Abstract Database provides information on diagnostic and procedural codes used during a hospitalization, whereas the National Ambulatory Care Reporting System reports on emergency department visits. Information on Ontario physician diagnostic and billing codes was ascertained from the Ontario Health Insurance Plan. Further details on the databases and coding definitions used can be found in Supplementary Table S2.

Cohort

Kidney transplant recipients. We included individuals who received a kidney transplant from January 1, 1997 to December 31, 2015. We excluded recipients who were aged <18 years, had a history of cancer, previously received a solid organ transplant, and recipients who received a simultaneous multi-organ transplant (eg, kidney-pancreas transplant). The date of kidney transplantation was considered the cohort entry (or index) date.

Cancer. We included individuals with a date of cancer diagnosis from January 1, 1997 to December 31, 2015. We selected cancers that were common or were associated with a higher mortality.¹¹ For females, we included the following cancers: breast, lung, colorectal, or pancreas. For males, we included prostate, colorectal, lung, or pancreas cancer. We excluded individuals aged <18 years, individuals with a previous cancer diagnosis, and individuals with chronic kidney disease (including dialysis and kidney transplantation). The cancer diagnosis date was the index date. We have used this cohort in a previously published study.⁶

All-Cause Mortality

Our outcome was all-cause mortality which can be accurately obtained through our administrative databases.¹² We present all results by sex and for the cancer cohort by cancer type. We followed individuals until death or the maximum follow-up date (March 31, 2017).

Statistical Analyses

We presented continuous variables as medians (25th, 75th percentile) and categorical variables as proportions. We used the Kaplan-Meier estimator to determine the probability of survival and the associated log-rank test to examine for statistical differences in survival distributions across groups (kidney transplant recipients and patients with different cancer types). Median survival was determined using the Kaplan-Meier estimator (ie, survival time at which 50% of the cohort remains event-free). We also examined 1-, 5-, and 10-year survival probabilities and survival probabilities stratified by age at cohort entry (18-39, 40-59, 60-69, and ≥ 70 years) and by cancer stage (stages 1, 2, 3, and 4 cancer). Due to limitations in data availability, our analysis by cancer stage was restricted to patients entering the cohort after April 1, 2008. We used a Cox proportional hazards model to examine the relationship between all-cause mortality and the independent variables (kidney transplant recipients [reference] vs each cancer type). The proportional hazards assumption was assessed using the Kolmogorov-type supremum test. When there was evidence of nonproportionality, we used the extended Cox model with a Heaviside function, presenting hazard ratios that were proportional during different time periods.¹³ We adjusted for several covariates determined from a literature review and clinical expertise, including age, cohort entry year, income quintile, residence (urban vs rural), myocardial infarction, heart failure, hypertension, diabetes, coronary artery disease with angina, hemorrhagic stroke, ischemic stroke, chronic liver disease, peripheral vascular disease, and chronic obstructive pulmonary disease. To examine trends in survival over time, we used the Kaplan-Meier estimator to produce 1-, 5-, and 10-year unadjusted survival probabilities by era of cohort entry (1997-2001, 2002-2006, 2007-2011, 2012-2015). We also used the Cox proportional hazards model to examine the association between era of cohort entry (independent variable) and all-cause mortality (dependent variable), adjusting for all the aforementioned covariates except year of cohort entry.

Data were missing for the following variables: income quintile (<1%, imputed missing as quintile 3) and residence (<1%, imputed missing as urban). Emigration from the province was the only reason for lost follow-up and was ignored in this study (less than 0.5% per year).¹⁴ We considered a 2-sided P -value < .05 to represent statistical significance. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Baseline Characteristics

We included 6888 kidney transplant recipients (females, $n = 2550$ [37.0%] and males, $n = 4338$ [63.0%]) and 532 452 patients with cancer (females, $n = 256 938$ [48.3%]; males, $n = 275 514$ [51.7%]) (Supplemental Figure S1). Baseline characteristics for female and male kidney transplant recipients and cancer patients are presented in Tables 1 and 2, respectively. Among kidney transplant recipients, 58.0% ($n = 1479$) of females and 61.2% ($n = 2655$) of males were a recipient of a kidney from a deceased donor. Kidney transplant recipients were younger when compared with patients with cancer. For example, the median age of male kidney transplant recipients was 51 years compared with 68, 69, 68, and 67 years for prostate, lung, colorectal, and pancreas cancer, respectively. Compared with patients with cancer, kidney transplant recipients generally had more comorbidities. For example, 37.6% of female kidney transplant recipients had coronary artery disease with angina compared with 11.0%, 20.8%, 18.0%, and 20.1% of breast, lung, colorectal, and pancreas patients with cancer, respectively. Among patients with information available on cancer stage, 9.4% of females with breast cancer had stage 4 cancer and 45.8%, 16.7%, and 24.9% with lung, colorectal and pancreas cancer. In males, 7.6% of patients with prostate cancer had stage 4 cancer and 49.7%, 17.2%, and 48.3% with lung, colorectal and pancreas cancer.

Over a maximum follow-up of 20.2 years (3 248 814 person-years of total follow-up time), 23.8% of kidney transplant recipients ($n = 1636$) died compared with 51.2% of patients with cancer ($n = 272 782$). Table 3 demonstrates the median follow-up and the number of deaths for kidney transplant recipients and each cancer type.

Survival

Figures 1A and B demonstrate the survival probabilities for all-cause mortality, which were significantly different across groups (kidney transplant recipients and cancer types) (log-rank P -value < .001). Male and female kidney transplant recipients had the longest median survival compared with all cancer types. Male kidney transplant recipients demonstrated a median survival of 18.7 years, whereas patients with prostate, lung, colorectal, and pancreas cancer had a median survival of 15.6, 0.6, 6.9, and 0.4 years, respectively (Table 3). Male and female kidney transplant recipients also had the highest unadjusted 1-, 5-, and 10-year survival probabilities compared with all cancer types (Table 3). Female kidney transplant recipients had an unadjusted 5-year survival probability of 90.8% (95% confidence interval [CI]: 89.5%-91.9%), whereas females with cancer had 5-year survival probabilities of 82.1% (95% CI: 81.9%-82.4%), 19.7% (95% CI: 19.4%-20.1%), 56.8% (95% CI: 56.3%-57.2%), and

Table 1. Baseline Characteristics of Female Kidney Transplant Recipients and Females With Breast, Lung, Colorectal, or Pancreas Cancer.

	Kidney transplant recipient (n = 2550)	Breast cancer (n = 138 512)	Lung cancer (n = 54 746)	Colorectal cancer (n = 53 108)	Pancreas cancer (n = 10 572)
Demographics					
Age, years	50 (39, 60)	60 (50, 71)	69 (61, 77)	71 (60, 80)	72 (63, 80)
Age categories, years					
18-39	677 (26.5)	7671 (5.5)	496 (0.9)	1232 (2.3)	152 (1.4)
40-59	1225 (48.0)	59 793 (43.2)	11 707 (21.4)	11 651 (21.9)	1877 (17.8)
60-69	516 (20.2)	32 875 (23.7)	15 775 (28.8)	11 395 (21.5)	2362 (22.3)
≥70	132 (5.2)	38 173 (27.6)	26 768 (48.9)	28 830 (54.3)	6181 (58.5)
Income quintile ^a					
1 (low)	596 (23.4)	24 118 (17.4)	13 293 (24.3)	10 781 (20.3)	2230 (21.1)
2	519 (20.4)	27 040 (19.5)	11 959 (21.8)	11 170 (21.0)	2283 (21.6)
3 (mid)	518 (20.3)	27 801 (20.1)	11 002 (20.1)	10 639 (20.0)	2113 (20.0)
4	467 (18.3)	28 797 (20.8)	9711 (17.7)	10 172 (19.2)	2035 (19.2)
5 (high)	450 (17.6)	30 756 (22.2)	8781 (16.0)	10 346 (19.5)	1911 (18.1)
Urban residence ^b	2294 (90.0)	120 650 (87.1)	46 030 (84.1)	44 898 (84.5)	9086 (85.9)
Era of index date					
1997–2001	542 (21.3)	32 635 (23.6)	12 750 (23.3)	13 279 (25.0)	2483 (23.5)
2002–2006	585 (22.9)	34 991 (25.3)	13 992 (25.6)	13 992 (26.3)	2674 (25.3)
2007–2011	743 (29.1)	38 171 (27.6)	15 330 (28.0)	14 643 (27.6)	3021 (28.6)
2012–2015	680 (26.7)	32 715 (23.6)	12 674 (23.2)	11 194 (21.1)	2394 (22.6)
Comorbidities^c					
Coronary artery disease with angina	959 (37.6)	15 173 (11.0)	11 406 (20.8)	9552 (18.0)	2124 (20.1)
Myocardial infarction	44 (1.7)	797 (0.6)	991 (1.8)	752 (1.4)	163 (1.5)
Heart failure	345 (13.5)	4229 (3.1)	4400 (8.0)	3622 (6.8)	763 (7.2)
Hypertension ^d	1816 (71.2)	52 854 (38.2)	26 619 (48.6)	26 180 (49.3)	5678 (53.7)
Diabetes ^d	780 (30.6)	18 301 (13.2)	8987 (16.4)	9683 (18.2)	3074 (29.1)
Hemorrhagic stroke	6 (0.2)	124 (0.1)	96 (0.2)	63 (0.1)	16 (0.2)
Ischemic stroke	12 (0.5)	523 (0.4)	581 (1.1)	484 (0.9)	118 (1.1)
Chronic liver disease	256 (10.0)	2656 (1.9)	1505 (2.7)	1326 (2.5)	1089 (10.3)
Peripheral vascular disease	278 (10.9)	370 (0.3)	884 (1.6)	333 (0.6)	92 (0.9)
Chronic obstructive pulmonary disease	29 (1.1)	1324 (1.0)	4692 (8.6)	1195 (2.3)	268 (2.5)
Cancer stage^e					
1		24 534 (39.8)	4450 (18.3)	4690 (21.2)	216 (4.6%)
2		20 824 (33.8)	1528 (6.3)	5001 (22.6)	507 (10.9%)
3		7724 (12.5)	4343 (17.8)	5454 (24.7)	379 (8.1%)
4		2775 (4.5)	11 157 (45.8)	3700 (16.7)	1162 (24.9%)
Missing		5808 (9.4)	2861 (11.8)	3284 (14.8)	2401 (51.5%)

Note. Data are presented as n (%) or median (25th, 75th percentile).

^aIncome presented as quintiles of average neighborhood income.

^bUrban defined as living in an area with a population > 10 000.

^cComorbidities captured in the 5 years prior to index date.

^dHypertension and diabetes defined as 2 Ontario Health Insurance Plan codes or 1 hospitalization with a diagnosis of hypertension or diabetes, in the 5 years prior to index date.

^eCancer stage information is restricted to individuals who received a cancer diagnosis on or after April 1, 2008. Stage information is not as complete in our administrative databases prior to this date.

9.4% (95% CI: 8.9%-10.0%) in breast, lung, colorectal, and pancreas cancer, respectively.

When we examined survival probabilities by age at cohort entry, results were generally comparable with the primary analysis (Table 4). However, in female kidney transplant

recipients aged 40 to 59 years, 1- and 10-year survival was comparable with patients with breast cancer (eg, 1-year survival: 98.0% in kidney transplant recipients vs 98.1% in breast cancer patients). Female kidney transplant recipients aged 60 to 69 years had a lower survival compared with

Table 2. Baseline Characteristics of Male Kidney Transplant Recipients and Males With Prostate, Lung, Colorectal, or Pancreas Cancer.

	Kidney transplant recipient (n = 4338)	Prostate cancer (n = 139 664)	Lung cancer (n = 63 411)	Colorectal cancer (n = 62 036)	Pancreas cancer (n = 10 403)
Demographics					
Age, years	51 (40, 61)	68 (61-74)	69 (62-76)	68 (59-76)	67 (59-76)
Age categories, years					
18-39	1010 (23.3)	35 (0.0)	418 (0.7)	1311 (2.1)	164 (1.6)
40-59	2119 (48.8)	27 888 (20.0)	12 184 (19.2)	15 002 (24.2)	2658 (25.6)
60-69	956 (22.0)	53 584 (38.4)	19 797 (31.2)	17 875 (28.8)	3050 (29.3)
>70	253 (5.8)	58 157 (41.6)	31 012 (48.9)	27 848 (44.9)	4531 (43.6)
Income quintile ^a					
1 (low)	946 (21.8)	21 678 (15.5)	15 169 (23.9)	11 350 (18.3)	1942 (18.7)
2	898 (20.7)	26 554 (19.0)	14 245 (22.5)	12 842 (20.7)	2158 (20.7)
3 (mid)	878 (20.2)	28 119 (20.1)	12 611 (19.9)	12 690 (20.4)	2172 (20.9)
4	859 (19.8)	29 501 (21.1)	11 447 (18.0)	12 642 (20.4)	2015 (19.4)
5 (high)	757 (17.5)	33 812 (24.2)	9939 (15.7)	12 512 (20.2)	2116 (20.3)
Urban residence ^b					
	3829 (88.3)	117 861 (84.4)	52 669 (83.1)	51 724 (83.4)	8766 (84.3)
Era of index date					
1997-2001	877 (20.4)	33 185 (23.8)	17 439 (27.5)	15 166 (24.4)	2444 (23.5)
2002-2006	1002 (23.1)	38 919 (27.9)	16 815 (26.5)	16 420 (26.5)	2501 (24.0)
2007-2011	1320 (30.4)	41 602 (29.8)	16 529 (26.1)	17 397 (28.0)	2922 (28.1)
2012-2015	1129 (26.0)	25 958 (18.6)	12 628 (19.9)	13 053 (21.0)	2536 (24.4)
Comorbidities					
Coronary artery disease with angina	2022 (46.6)	30 484 (21.8)	17 779 (28.0)	14 410 (23.2)	2513 (24.2)
Myocardial infarction	124 (2.9)	2053 (1.5)	1556 (2.5)	1262 (2.0)	211 (2.0)
Heart failure	661 (15.2)	6056 (4.3)	6191 (9.8)	4047 (6.5)	4047 (6.5)
Hypertension ^d	3134 (72.2)	69 145 (49.5)	28 403 (44.8)	28 323 (45.7)	4821 (46.3)
Diabetes ^d	1634 (37.7)	25 769 (18.5)	13 372 (21.1)	14 083 (22.7)	3622 (34.8)
Hemorrhagic stroke	19 (0.4)	198 (0.1)	123 (0.2)	96 (0.2)	11 (0.1)
Ischemic stroke	40 (0.9)	880 (0.6)	803 (1.3)	616 (1.0)	108 (1.0)
Chronic liver disease	423 (9.8)	2667 (1.9)	2282 (3.6)	1992 (3.2)	1422 (13.7)
Peripheral vascular disease	473 (10.9)	926 (0.7)	1602 (2.5)	652 (1.1)	125 (1.2)
Chronic obstructive pulmonary disease	50 (1.2)	2288 (1.6)	5452 (8.6)	1544 (2.5)	282 (2.7)
Cancer stage^e					
1		9675 (17.1)	3363 (13.4)	5596 (21.4)	161 (3.4%)
2		28 598 (50.5)	1652 (6.6)	5635 (21.6)	510 (10.9%)
3		6445 (11.4)	4616 (18.5)	6360 (24.3)	360 (7.7%)
4		4280 (7.6)	12 441 (49.7)	4485 (17.2)	1396 (29.7%)
Missing		7647 (13.4)	2952 (11.8)	4054 (15.5)	2264 (48.3%)

Note. Data are presented as n (%) or median (25th, 75th percentile).

^aIncome presented as quintiles of average neighborhood income.

^bUrban defined as living in an area with a population >10 000. ^cComorbidities captured in the 5 years prior to index date.

^dHypertension and diabetes defined as 2 Ontario Health Insurance Plan codes or 1 hospitalization with a diagnosis of hypertension or diabetes, in the 5 years prior to index date.

^eCancer stage information is restricted to individuals who received a cancer diagnosis on or after April 1, 2008. Stage information is not as complete in our administrative databases prior to this date.

patients with breast cancer (eg, 10-year survival: 56.8% in kidney transplant recipients vs 75.8% in breast cancer patients) and 10-year survival was the same as patients with colorectal cancer (56.8% vs 56.8%). Male kidney transplant recipients generally had higher survival compared with patients with cancer across all age groups studied. However,

male kidney transplant recipients aged 40 to 59 years had a lower 1-, 5-, and 10-year survival compared with patients with prostate cancer (eg, 10-year survival in kidney transplant recipients was 76.8% vs 89.5% in prostate cancer patients); similar findings were found in males aged 60 to 69 years.

Table 3. All-Cause Mortality for Female and Male Kidney Transplant Recipients and Females and Males With Cancer.

Female					
Patient populations	Kidney transplant recipient (n = 2550)	Breast cancer (n = 138 512)	Lung cancer (n = 54 746)	Colorectal cancer (n = 53 108)	Pancreas cancer (n = 10 572)
Number of events ^a (%)	540 (21.2)	40 815 (29.5)	46 141 (84.3)	28 853 (54.3)	9706 (91.8)
Total person-years follow-up	21 313	1 116 081	126 775	306 755	14 079
Median follow-up, years ^a (25th, 75th percentile)	7.5 (4.1, 12.2)	7.1 (3.5, 12.0)	0.8 (0.2, 2.6)	4.2 (1.4, 9.2)	0.4 (0.1, 1.1)
Median survival, years ^a	>19.5	19.4	0.8	7.5	0.4
1-year survival probabilities ^b % (95% CI)	97.2 (96.5-97.8)	95.8 (95.7-95.9)	45.0 (44.6-45.5)	79.6 (79.3-80.0)	26.8 (26.0-27.6)
5-year survival probabilities ^b % (95% CI)	90.8 (89.5-91.9)	82.1 (81.9-82.4)	19.7 (19.4-20.1)	56.8 (56.3-57.2)	9.4 (8.9-10.0)
10-year survival probabilities ^b % (95% CI)	77.9 (75.9-79.8)	69.8 (69.5-70.1)	13.0 (12.6-13.3)	44.1 (43.7-44.6)	6.7 (6.1-7.2)
Male					
Patient populations	Kidney transplant recipient (n = 4388)	Prostate cancer (n = 139 664)	Lung cancer (n = 63 411)	Colorectal cancer (n = 62 036)	Pancreas cancer (n = 10 403)
Number of events ^a (%)	1096 (25.3)	46 700 (33.4)	56 769 (89.5)	34 249 (55.2)	9549 (91.8)
Total person-years follow-up	35 747	1 143 842	118 080	352 600	13 540
Median follow-up, years ^a (25th, 75th percentile)	7.4 (4.1, 11.6)	7.7 (4.1, 11.8)	0.6 (0.2, 1.8)	4.1 (1.5, 8.8)	0.4 (0.1, 1.1)
Median survival, years ^a	18.7	15.6	0.6	6.9	0.4
1-year survival probabilities ^b % (95% CI)	97.4 (96.9-97.8)	95.9 (95.8-96.0)	37.4 (37-37.8)	81.4 (81.1-81.7)	27.5 (26.6-28.3)
5-year survival probabilities ^b % (95% CI)	89.6 (88.6-90.5)	83.3 (83.1-83.5)	14.0 (13.7-14.3)	56.1 (55.7-56.5)	9.1 (8.5-9.7)
10-year survival probabilities ^b % (95% CI)	73.5 (71.9-75.1)	68.3 (68.0-68.6)	8.6 (8.4-8.9)	42.4 (41.9-42.8)	6.3 (5.8-6.9)

Note. CI = confidence interval.

^aMaximum follow-up of 20.2 years.

^bSurvival probabilities are unadjusted.

When we examined survival probability presenting each cancer type by cancer stage (stages 1-4), the results were generally comparable with the primary analysis, with kidney transplant recipients having a higher survival probability compared with each cancer stage (Supplementary Figure S2-Figure S9). However, female kidney transplant recipients had a lower survival probability compared with patients with stage 1 breast cancer (Supplementary Figure S2) and male kidney transplant recipients had a lower survival probability compared with patients with stages 1, 2, and 3 prostate cancer (Supplementary Figure S6).

Figure 2 presents adjusted hazard ratios (aHRs) for all-cause mortality for males and females with cancer compared with male and female kidney transplant recipients (reference) with results presented stratified by follow-up time. In both males and females, patients with lung and pancreas cancer had a significantly higher hazard of mortality compared with kidney transplant recipients across follow-up times. However, there was no significant difference in the hazard of mortality between patients with pancreas cancer and kidney transplant

recipients at 6+ years. The hazard ratios declined over time when comparing patients with lung and pancreas cancer with kidney transplant recipients, with the highest hazard of mortality observed in the first year of follow-up. For example, male patients with lung cancer had a significantly higher hazard of all-cause mortality compared with kidney transplant recipients at 0 to <1 year of follow-up (aHR: 26.03, 95% CI: 21.6-31.36); however, at 4 to <6 years of follow-up, the aHR decreased to 3.34 (95% CI: 2.82-3.95). When comparing females with colorectal cancer with kidney transplant recipients, females with colorectal cancer had a significantly higher hazard of all-cause mortality until 4 to <5 years of follow-up; at 5+ years of follow-up, patients with colorectal cancer had a significantly lower hazard of mortality (aHR: 0.77, 95% CI: 0.69-0.86). Dissimilar to the unadjusted analysis, male patients with prostate cancer had a significantly lower hazard of mortality compared with kidney transplant recipients across follow-up times. In females, patients with breast cancer had a significantly lower hazard of all-cause mortality at 2+ years of follow-up (aHR: 0.85, 95% CI: 0.77-0.93).

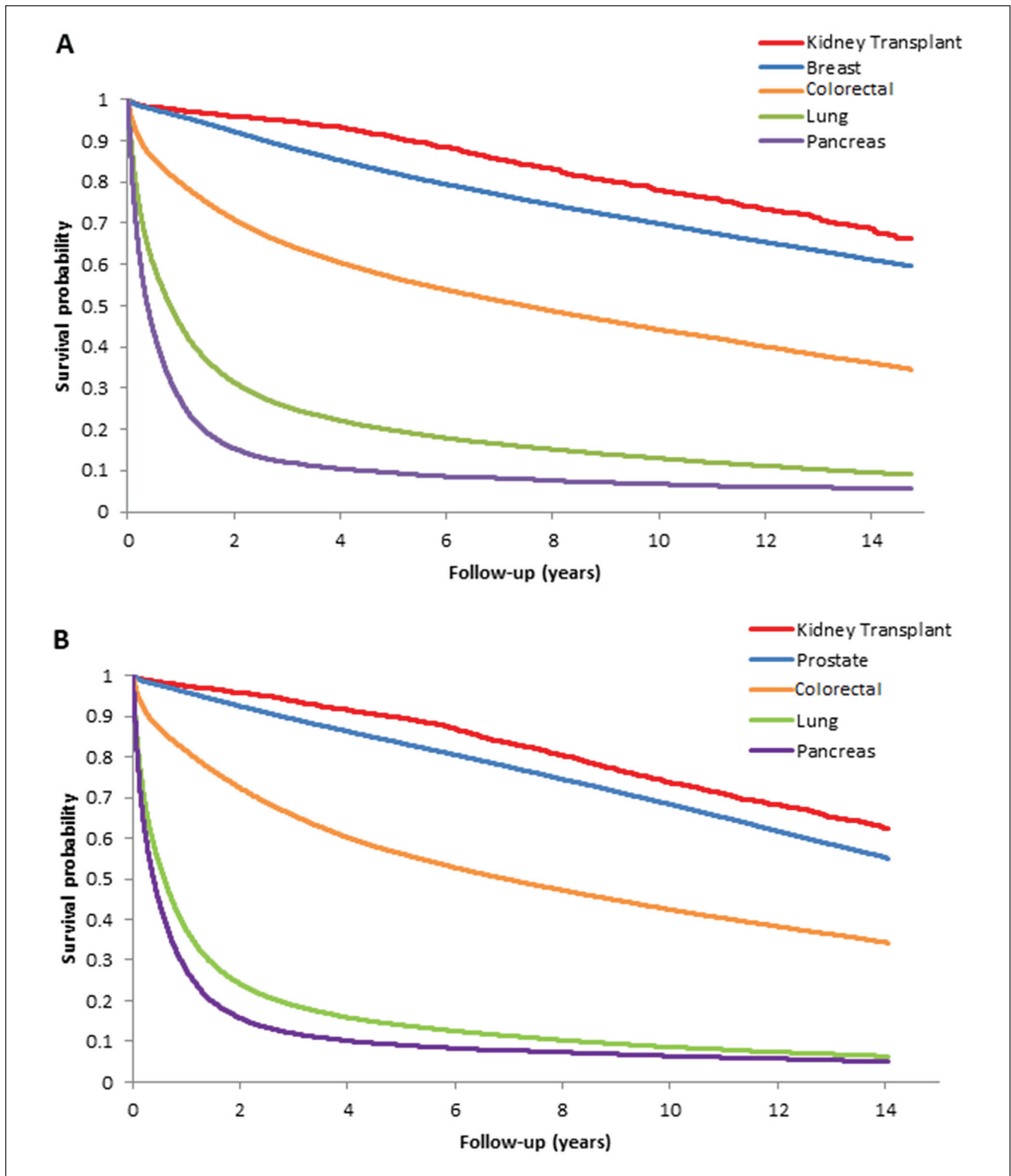


Figure 1. Survival probabilities for all-cause mortality in (A) female kidney transplant recipients and patients with cancer (log-rank $P < .001$) and (B) male kidney transplant recipients and patients with cancer (log-rank $P < .001$).

Table 4. Unadjusted 1-, 5-, and 10-Year Survival Probabilities for All-Cause Mortality for Female and Male Kidney Transplant Recipients and Females and Males With Cancer by Age at Cohort Entry.

	1-year survival % (95% CI)	5-year survival % (95% CI)	10-year survival % (95% CI)
Female			
Age			
18-39			
Breast cancer	97.9 (97.6-98.2)	83.7 (82.9-84.6)	75.0 (73.9-76.0)
Pancreas cancer	71.7 (63.8-78.2)	53.5 (45.1-61.2)	46.1 (36.8-54.9)
Lung cancer	66.9 (62.6-70.9)	42.8 (38.4-47.2)	38.9 (34.3-43.3)
Colorectal cancer	91.6 (89.9-93.0)	71.7 (69.0-74.3)	67.8 (64.8-70.6)
Kidney transplant	98.7 (97.5-99.3)	94.6 (92.5-96.1)	89.1 (86.0-91.5)
40-59			
Breast cancer	98.1 (98.0-98.2)	88.7 (88.5-89.0)	81.6 (81.2-81.9)
Pancreas cancer	42.5 (40.3-44.7)	17.2 (15.5-19.0)	14.1 (12.4-16.0)
Lung cancer	54.0 (53.1-54.9)	26.4 (25.6-27.2)	20.6 (19.8-21.4)
Colorectal cancer	90.2 (89.7-90.7)	70.5 (69.6-71.3)	64.1 (63.2-65.1)
Kidney transplant	98.0 (97.1-98.7)	93.1 (91.4-94.4)	81.1 (78.2-83.7)
60-69			
Breast cancer	97.2 (97.0-97.4)	86.8 (86.4-87.2)	75.8 (75.2-76.3)
Pancreas cancer	34.3 (32.3-36.2)	11.0 (9.7-12.4)	7.6 (6.4-8.9)
Lung cancer	50.2 (49.4-50.9)	23.2 (22.6-23.9)	15.5 (14.9-16.2)
Colorectal cancer	86.4 (85.8-87.0)	65.9 (65.0-66.8)	56.8 (55.8-57.8)
Kidney transplant	94.2 (91.8-95.9)	82.3 (78.4-85.5)	56.8 (50.9-62.4)
≥70			
Breast cancer	90.7 (90.4-91.0)	67.5 (67.0-68.0)	45.3 (44.7-45.9)
Pancreas cancer	18.0 (17.1-19.0)	5.3 (4.8-5.9)	3.1 (2.6-3.6)
Lung cancer	37.7 (37.2-38.3)	14.2 (13.8-14.7)	7.3 (6.9-7.7)
Colorectal cancer	72.2 (71.7-72.7)	47.1 (46.5-47.7)	30.7 (30.0-31.3)
Kidney transplant	91.7 (85.5-95.3)	78.2 (69.2-84.8)	46.3 (31.7-59.7)
Male			
Age			
18-39			
Prostate cancer	^a	^a	^a
Pancreas cancer	59.1 (51.2-66.2)	40.8 (33.1-48.4)	35.8 (27.5-44.1)
Lung cancer	59.8 (54.9-64.3)	39.5 (34.8-44.2)	36.6 (31.8-41.4)
Colorectal cancer	89.9 (88.2-91.4)	71.3 (68.6-73.7)	65.7 (62.7-68.5)
Kidney transplant	99.2 (98.4-99.6)	96.8 (95.4-97.7)	91.9 (89.6-93.6)
40-59			
Prostate cancer	99.0 (98.9-99.2)	94.8 (94.5-95.0)	89.5 (89.1-90.0)
Pancreas cancer	37.1 (35.3-39.0)	14.0 (12.7-15.4)	10.4 (9.2-11.8)
Lung cancer	42.8 (41.9-43.6)	18.7 (18.0-19.4)	14.2 (13.5-14.9)
Colorectal cancer	88.5 (88.0-89.0)	66.6 (65.8-67.4)	58.4 (57.5-59.2)
Kidney transplant	97.6 (96.8-98.2)	91.3 (90.0-92.5)	76.8 (74.5-79.0)
60-69			
Prostate cancer	98.4 (98.3-98.5)	91.4 (91.1-91.6)	80.9 (80.5-81.3)
Pancreas cancer	30.1 (28.4-31.7)	8.8 (7.8-9.9)	5.8 (4.8-6.9)
Lung cancer	41.0 (40.3-41.7)	16.2 (15.7-16.8)	10.0 (9.6-10.5)
Colorectal cancer	85.6 (85.1-86.1)	63.0 (62.3-63.7)	50.9 (50.0-51.7)
Kidney transplant	95.6 (94.1-96.7)	80.9 (78.0-83.4)	51.1 (46.8-55.3)
≥70			
Prostate cancer	92.1 (91.8-92.3)	70.5 (70.2-70.9)	47.3 (46.8-47.7)
Pancreas cancer	18.9 (17.8-20.0)	5.0 (4.4-5.7)	3.1 (2.5-3.7)
Lung cancer	32.7 (32.2-33.2)	10.3 (10.0-10.7)	5.0 (4.7-5.3)
Colorectal cancer	74.6 (74.1-75.1)	45.5 (44.8-46.1)	27.7 (27.1-28.3)
Kidney transplant	93.7 (89.9-96.1)	74.2 (67.6-79.6)	30.8 (22.4-39.7)

Note. CI = confidence interval.

^aThere were too few deaths to estimate survival probability.

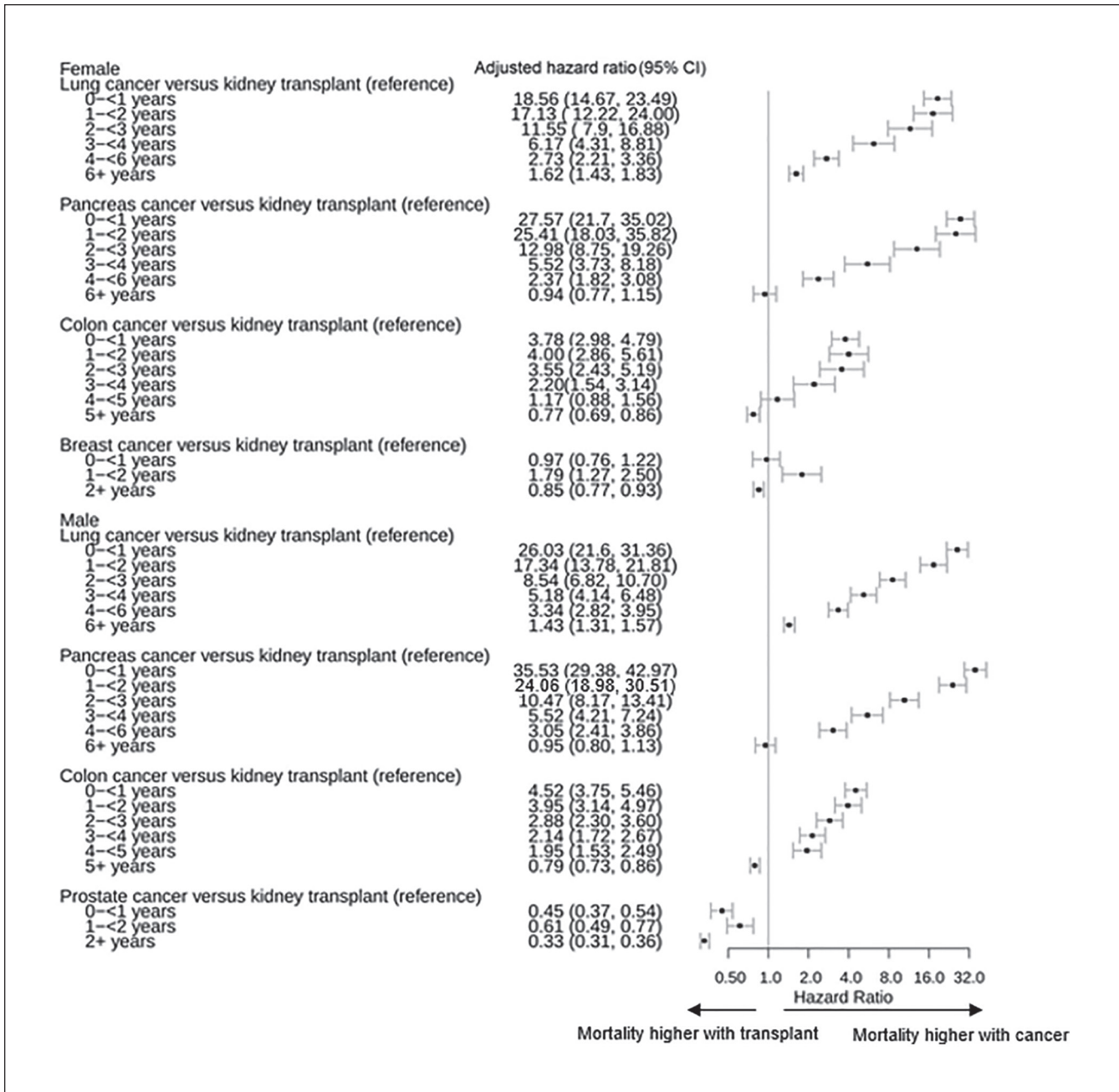


Figure 2. Adjusted hazard ratios for all-cause mortality for male and female kidney transplant recipients compared to males and females with cancer.

Note. Results presented stratified by follow-up time due to nonproportionality within cancer types. Maximum follow-up was 20.2 years. We adjusted for the following variables: age (years), neighborhood income quintile, residence (rural vs urban), coronary artery disease with angina, myocardial infarction, heart failure, hypertension, diabetes, hemorrhagic stroke, ischemic stroke, chronic liver disease, peripheral vascular disease, and chronic obstructive pulmonary disease. CI = confidence interval.

Trends in Survival

Figures 3 and 4 provide the 1-, 5-, and 10-year unadjusted survival probabilities in female and male kidney transplant recipients and each cancer type stratified by the era of cohort entry (1997-2001, 2002-2006, 2007-2011, and 2012-2015). In the unadjusted Cox proportional hazards model,

significant improvements in survival were observed across eras for all cancer types ($P < .001$); however, no significant improvement was observed in kidney transplant recipients (female, $P = .58$; male, $P = .15$). After adjusting for clinical characteristics, similar results were found in all cancer types ($P < .001$). In kidney transplant recipients, adjusting for

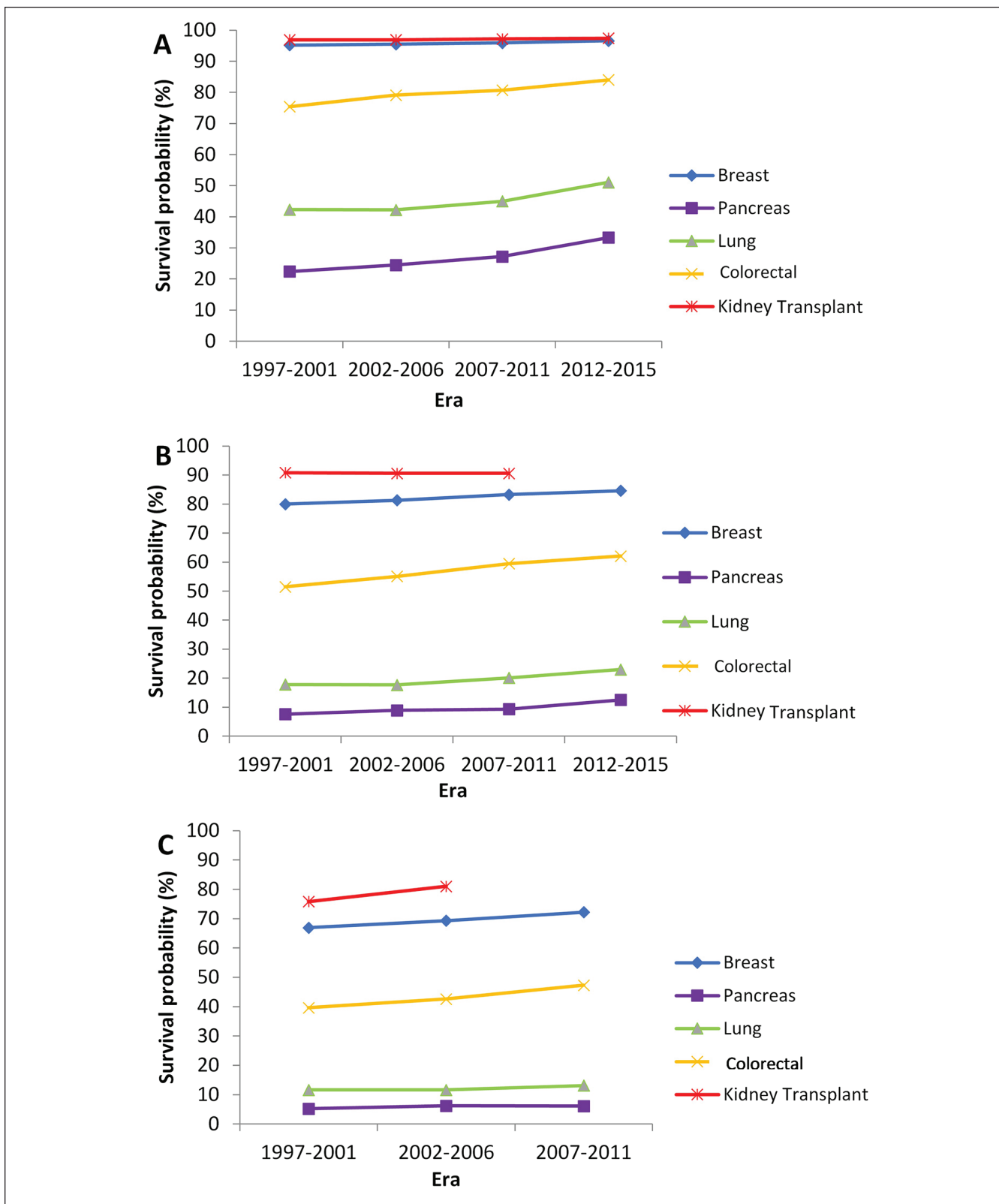


Figure 3. Unadjusted survival probabilities for all-cause mortality by era of cohort entry for female kidney transplant recipients and females with breast, lung, colorectal, or pancreas cancer: (A) 1-year survival probabilities. (B) 5-year survival probabilities; too few deaths to estimate survival probability for kidney transplant recipients in the 2012-2015 era. (C) 10-year survival probabilities; too few deaths to estimate survival probability for kidney transplant recipients in the 2007-2011 era.

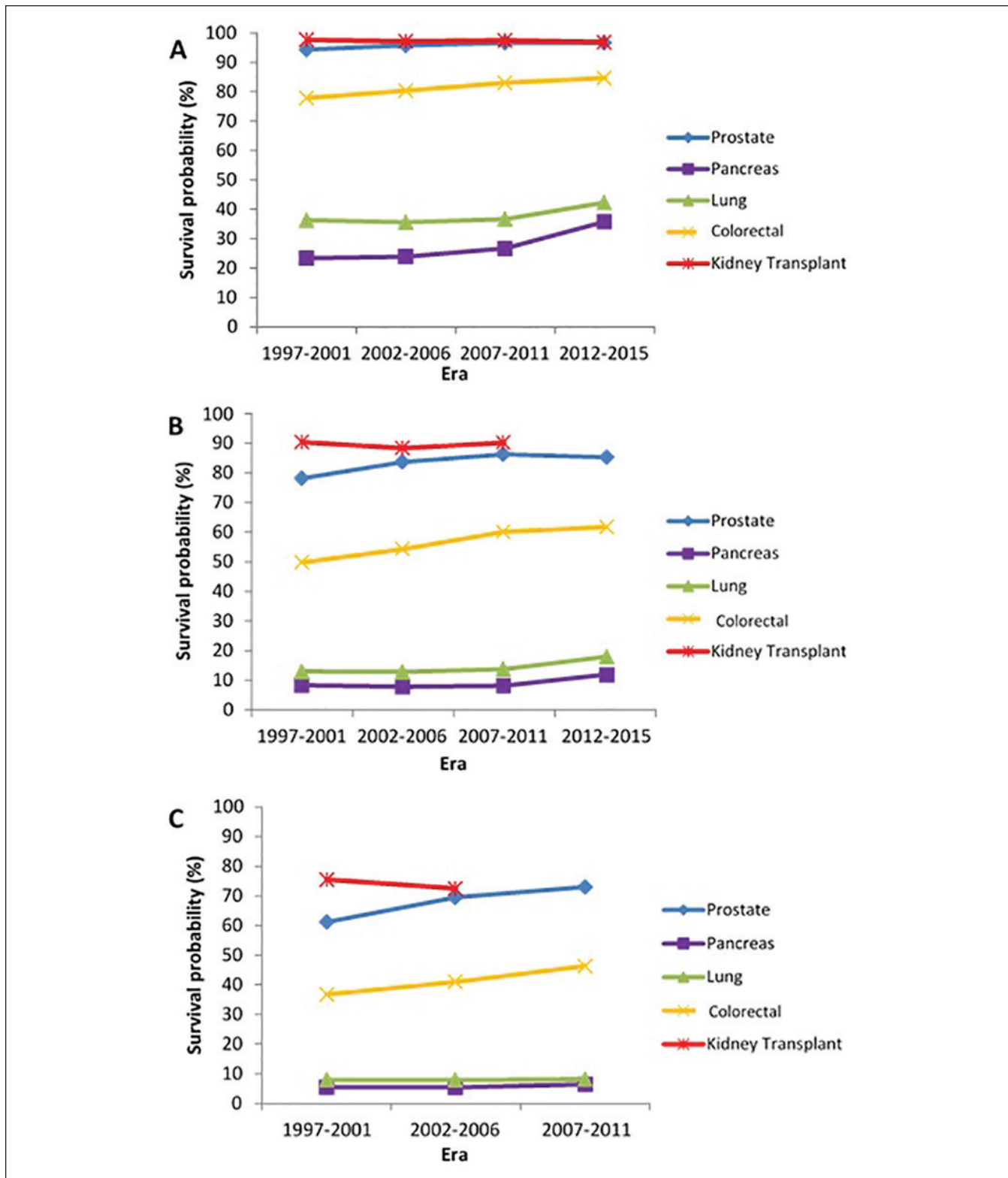


Figure 4. Unadjusted survival probabilities for all-cause mortality by era of cohort entry for male kidney transplant recipients and males with prostate, lung, colorectal, or pancreas cancer: (A) 1-year survival probabilities. (B) 5-year survival probabilities; too few deaths to estimate survival probability for kidney transplant recipients in the 2012-2015 era. (C) 10-year survival probabilities; too few deaths to estimate survival probability for kidney transplant recipients in the 2007-2011 era.

Table 5. Adjusted Hazard Ratios For All-Cause Mortality for Female and Male Kidney Transplant Recipients Presented by Era of Cohort Entry.

Era	Female (n = 2550)	Male (n = 4388)
1997-2001	1.00 (reference)	1.00 (reference)
2002-2006	0.77 (0.62, 0.96)	0.92 (0.79, 1.08)
2007-2011	0.76 (0.59, 0.98)	0.75 (0.62, 0.90)
2012-2015	0.63 (0.42, 0.93)	0.76 (0.58, 0.99)

Note. Data are presented as adjusted hazard ratios (95% confidence intervals). Adjusted for the following variables: age (years), neighborhood income quintile, residence (rural vs urban), coronary artery disease with angina, myocardial infarction, heart failure, hypertension, diabetes, hemorrhagic stroke, ischemic stroke, chronic liver disease, peripheral vascular disease, and chronic obstructive pulmonary disease.

clinical characteristics resulted in an overall significant improvement in survival across eras of cohort entry (female, $P = .03$; male, $P = .01$). However, male kidney transplant recipients who received a transplant from 2002 to 2006 did not have a significantly lower rate of death compared with the reference era (1997-2001; Table 5).

Discussion

We found that kidney transplant recipients had a significantly higher survival probability compared with all cancer types examined, including lung, colorectal, pancreas, breast (females), and prostate cancer (males). Similar results were found in relative survival probability after adjusting for clinical characteristics. However, females with breast cancer had a significantly lower hazard of mortality compared with kidney transplant recipients at 2+ years of follow-up, whereas males with prostate cancer had a significantly lower rate of mortality across follow-up times. After adjusting for clinical characteristics, survival significantly improved in kidney transplant recipients across eras of cohort entry. These findings put the burden of mortality in Canadian kidney transplant recipients into context and suggest survival in kidney transplant recipients is better than previously appreciated.

Kidney transplant recipients had a significantly higher unadjusted survival probability compared with patients with cancer despite having more comorbidities (eg, cardiovascular disease). These results are in contrast with a similar study we conducted which found that Canadian patients on maintenance dialysis had a significantly worse unadjusted and adjusted survival probability compared with patients with prostate, colorectal, and breast cancer.⁶ There are several potential explanations for this. First, kidney transplant recipients represent a highly select group of patients with kidney disease who are required to undergo multiple tests (eg, cardiac stress test, cancer screening) and are encouraged to improve their lifestyle (eg, quit smoking, lose weight) to ensure they are healthy enough to receive a

kidney transplant.¹⁵ In addition, posttransplant, these individuals are followed closely by nephrologists (average of 14 visits in the first-year posttransplant)¹⁶ and guidelines recommend screening for health conditions such as diabetes, hypertension, and cancer (eg, annual skin and lip examination recommended).¹⁷ Second, kidney transplantation is the best treatment option for kidney failure, resulting in improved survival (many patients gain over 10 years of life) compared with remaining on dialysis.^{18,19} Third, despite minimal advances in new interventions designed to directly improve survival in kidney transplant recipients,⁵ there have still been improvements in immunosuppressive therapy and posttransplant care over the last several years.^{7,17,20} These results highlight the importance of kidney transplantation as a lifesaving treatment option for patients with kidney failure and the need for strategies to improve access to kidney transplantation.

Unlike the unadjusted analysis, after adjusting for clinical characteristics, we found that males with prostate cancer had a significantly lower rate of mortality compared with kidney transplant recipients. This is likely being driven by differences in age between the groups, with patients with prostate cancer having better survival after we accounted for age. Similarly, females with breast cancer had a significantly lower rate of mortality compared with kidney transplant recipients at 2+ years of follow-up. This is not surprising as breast and prostate cancer generally have a better prognosis compared with other cancers like pancreas and lung. Although after adjustment kidney transplant recipients had a significantly lower rate of mortality compared with patients with lung and pancreas cancer, over time this relationship was attenuated. After 6+ years, there was no significant difference in the hazard of mortality between kidney transplant recipients and males and females with pancreas cancer. This is likely due to mortality in patients with lung and pancreas cancer being highest in the first few years of diagnosis.

Previous studies have compared survival in kidney transplant recipients with patients with cancer. A review article from the United States found that 5-year patient survival in deceased donor kidney transplant recipients was comparable with patients diagnosed with breast cancer and adenocarcinoma of the colon after regional spread.⁵ Similarly, a USRDS report found that mortality was similar among kidney transplant recipients and patients with cancer.⁷ We found that kidney transplant recipients had better survival compared with several cancer types. However, unlike our study, these comparisons had limited adjustment for relevant risk factors, did not examine a variety of cancer types, did not report results by cancer stage, and included kidney transplant recipients from the United States (difference in mortality has been observed between Canadian and US kidney transplant recipients).²¹ When we presented unadjusted survival probabilities by cancer stage, we generally found similar results to our primary analysis with kidney transplant recipients having

a higher survival probability compared with each cancer stage (ie, stages 1-4). The exceptions included female kidney transplant recipients having a lower survival probability compared with females with stage 1 breast cancer and male kidney transplant recipients having a lower survival probability compared with males with stages 1 to 3 prostate cancer. The higher survival probability in patients with stage 1 breast cancer and stages 1 to 3 prostate cancer compared with kidney transplant recipients likely reflects early detection due to breast and prostate cancer screening and improvements in treatments.^{22,23}

Although kidney transplant recipients generally had higher survival compared with patients with several common cancers, we still should not be satisfied with current survival rates, as recipient survival remains significantly lower than the general population.⁴ Therefore, there is still a need to advocate for clinical trials in this underrepresented population,²⁴ particularly those testing novel immunosuppressive medications.⁵ Furthermore, efforts need to be made to decrease the significant proportion of kidney transplant recipients who die with a functioning graft, with the leading causes of death being from cardiovascular, infectious, and malignant causes.²⁵⁻²⁷

Comparable with previous research, we found survival in both kidney transplant recipients and patients with cancer significantly improved across eras, with cancer patients experiencing more improvement than kidney transplant recipients.^{7,11,28} However, in the unadjusted analysis we only found a significant improvement over time in survival in patients with cancer, but no significant improvement was observed in kidney transplant recipients; of note, both populations had increases in age and comorbidities over time.^{4,29-31} A USRDS report found that after adjusting for sex and race, mortality decreased in both kidney transplant recipients and patients with cancer aged ≥ 65 years from 1996 to 2012 (12% decrease in kidney transplant recipients and 34% in patients with cancer).²⁵ There are several potential explanations for the greater degree of improvement in the cancer population compared with the kidney transplant population. First, there may be a misconception that current outcomes in kidney transplant recipients are acceptable and, as a result, interventions to improve survival have slowed.⁵ Second, unlike cancer, kidney disease is often not recognized by the public as a potentially fatal disease,⁵ which could impact research funding, policy decisions, and the number of researchers interested in the field of transplantation. Third, kidney transplant recipients are frequently excluded from clinical trials^{24,32} and there are fewer trials conducted in nephrology compared with oncology, with nephrology having the fewest number of trials of all medical specialties.^{32,33} Last, there was a higher absolute mortality rate for the cancer types examined relative to kidney transplant recipients, allowing for more quantifiable improvements in survival from interventions in the cancer population.

Limitations of this study are noted. First, this study was restricted to a single province in Canada and the external generalizability of these results may be limited. Second, due to data availability, we were only able to look at cancer stage in patients entering the cohort after April 1, 2008. Third, although we adjusted for multiple confounders in our analysis, we cannot eliminate the possibility of residual confounding as our databases were not able to capture several variables that could impact mortality (eg, body mass index, smoking status).

In conclusion, kidney transplant recipients have superior short- and long-term survival compared with patients with several common cancers. After adjusting for clinical characteristics, survival significantly improved over time in both kidney transplant recipients and patients with cancer. These results further our understanding of the mortality burden in the kidney transplant population. Furthermore, the results highlight that kidney transplantation is an excellent treatment option for end-stage kidney disease, but more work needs to be done to improve short- and long-term survival in this patient population.

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Ethics Approval and Consent to Participate

ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45 and approved by ICES' Privacy and Compliance Office.

Consent for Publication

All authors consent to the publication of this study.

Availability of Data and Materials

The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: G.A.K. has received investigator-initiated research grants from the Canadian Institutes of Health Research (CIHR). A.X.G. received an investigator-initiated grant from Astellas which featured as partnership funds in CIHR funded research. The other authors declare no conflicts of interest. The results presented in this article have not been published previously in whole or part.

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Supplemental Material

Supplemental material for this article is available online.

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