





RESEARCH ARTICLE

Cancer Epidemiology

Immunosuppression and cancer risk in kidney transplant recipients: A retrospective cohort study

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Abstract

We assessed whether contemporary immunosuppression agents were associated with cancer among kidney transplant recipients (KTR), and if this association varied by age and sex. We studied a retrospective province-wide cohort of primary KTR (1997–2016). Employing multivariable Cox models, we estimated associations of cumulative doses of prednisone, mycophenolate and tacrolimus administered over the past 10 years, lagged by 2 years, with the incidence of primary malignant neoplasms (PMN). We assessed interactions with age and sex. To assess the impact of exposure recency, we used weighted cumulative exposure (WCE) modeling. Among 1064 KTR, 108 (10.2%) developed PMN over median follow-up of 73 months (interquartile range: 32–120). Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of 0.96 (0.64–1.43), 1.34 (0.96–1.86), and 1.06 (0.88–1.29) were estimated for cumulative daily doses of prednisone (5 mg), mycophenolate (1000 mg), and tacrolimus (2 mg) administered continuously over the past 10 years, respectively. PMN risk associated with cumulative tacrolimus exposure was modified by age (interaction $p = .035$) and was more pronounced in 15-year and 30-year-old KTR (aHRs of 1.57 [1.08–2.28] and 1.31 [1.03–1.66], respectively) in comparison to older KTR. PMN risk increase associated with higher cumulative mycophenolate dose was more pronounced in females (aHR = 1.86 [1.15–3.00]) than in males (aHR = 1.16 [0.74–1.81]; interaction $p = .131$). WCE analyses suggested increased PMN risk the higher the mycophenolate doses taken 5–10 years ago. A trend toward increased PMN risk with long-term mycophenolate exposure, particularly in females, and more pronounced risk with long-term tacrolimus exposure in younger KTR, identify opportunities for tailored immunosuppression to mitigate cancer risk.

KEYWORDS

age, cancer, immunosuppression, kidney transplantation, sex

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What's new?

The general inhibition of the immune system makes kidney transplant recipients more susceptible to infections and cancer. However, data on the associations between contemporary immunosuppression agents and cancer risk remain limited. This analysis of a retrospective cohort of over 1000 kidney transplant recipients with detailed longitudinal prescription data found that the risk of primary malignant neoplasms increased with higher cumulative doses of mycophenolate in female kidney transplant recipients. The risk also increased with long-term tacrolimus exposure among younger kidney transplant recipients. The findings suggest that personalized immunosuppression regimens could help mitigate cancer risk.

1 | INTRODUCTION

Kidney transplantation is the preferred treatment for end-stage kidney disease (ESKD).^{1,2} The success of transplantation is credited to evolving immunosuppression agents (IAs) geared toward the prevention of allograft rejection. However, the general inhibition of the immune system makes kidney transplant recipients (KTR) more susceptible to infections and cancer.

Risk of cancer among KTR is 2-to-4-fold higher than the general population.³ Cancer risk associated with IAs varies by type and the implicated site with lung, colon, liver, lymphoma, melanoma and non-melanoma skin cancer (NMSC) occurring more frequently among transplant recipients.^{4–8} KTR are at a particularly increased risk of cancers associated with oncogenic viruses, such as non-Hodgkin lymphomas (caused by Epstein–Barr virus [EBV]), as well as anogenital and oropharyngeal cancers (caused by human papillomavirus [HPV]).^{9–11} In addition to adherence to IAs,^{3,8,12} risk factors include ESKD cause, transplant era, time on dialysis, and previous malignancies.^{13,14}

Older KTR are at increased risk of cancer^{15–17} and young KTR have a 15–30-fold higher cancer risk than youth in the general population.¹⁸ These findings suggest that exposure to IAs exacerbates this risk. Moreover, female KTR transplanted before the age of 45 were significantly more likely than men to be diagnosed with cancer^{3,18} and hormone-sensitive cancer sites vary by sex. In addition to gender differences in medication adherence and utilization of health care services,¹⁹ sex disparities in pharmacokinetics and pharmacodynamics of IAs, may also be at play.^{20,21}

Unlike azathioprine and cyclosporine that have been classified as human carcinogens by the International Agency for Research on Cancer (IARC),^{22,23} evidence on the carcinogenic effect of contemporary IAs, including mycophenolate (mycophenolate mofetil [MMF] or mycophenolic acid) and tacrolimus, is limited. Observational studies investigating the associations between contemporary IAs and cancer risk among KTR had limited information on cumulative exposure to IAs, and clinical trials offered too short of a follow-up to allow cancer outcome ascertainment.^{5,24} To further clarify the carcinogenic potential of contemporary IAs, we leveraged provincial administrative healthcare database with longitudinal immunosuppression data and applied specialized methods to account for cumulative effects of long-term exposures.²⁵ We further assessed whether cancer-risk associated with cumulative exposure to contemporary IAs was modified by KTRs' age and sex.

2 | MATERIALS AND METHODS

2.1 | Study design, data source, and population

We created a province-wide retrospective cohort of KTR, with up to 20 years follow-up, from Quebec, Canada, by linking two provincial administrative healthcare databases, (i) the *Régie de l'assurance maladie du Québec* (RAMQ), which captures medical services and prescription drug claims, and (ii) the hospital discharge database *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (Med-ECHO) using a unique healthcare number assigned to all individuals in Quebec at birth.

RAMQ is a public health insurance plan. Since its inception in 1969, the RAMQ has served 7.7 million Quebec residents. Individuals >65 years, who are on welfare, and who are ineligible for private, group, or employee insurance plans, are covered by RAMQ. The RAMQ database is a repository of patient demographics, healthcare services, and associated costs. Prescriptions issued under the provincial drug insurance plan, including date, form, dose, prescription type (new or renewal), pharmacy substitution, and treatment duration are captured by the RAMQ's Prescription Drug Claims database. RAMQ medical billing codes were reviewed for kidney transplant-related medical act codes using a previously validated high-performance algorithm.²⁶ Med-ECHO is a repository of hospital-based healthcare services in Québec since 1976. Med-ECHO includes cancer diagnoses adhering to the *International Classification of Diseases, 9th Revision* (ICD-9 since 1984) and *10th Revision* (ICD-10 since 2006).

All first-time KTR in the RAMQ database (January 1, 1997 to December 31, 2016) were eligible for inclusion. Individuals transplanted for the first-time outside Quebec, and those undergoing multi-organ or re-transplantation, were excluded. KTR exposed to IAs pre-transplant for a period of ≥ 1 week, experiencing primary graft nonfunction, with prevalent cancer, and with gaps in RAMQ coverage, were also excluded. The manuscript was written in accordance with the STROBE Statement.²⁷

2.2 | Exposure, outcome definition, and covariates

Eligible KTR were typically prescribed maintenance IAs including a calcineurin inhibitor (CNI), an antimetabolite, with or without prednisone.

Computer-recorded variables in the RAMQ database allowed the direct calculation of the daily dose of IAs as pill strength (in milligrams [mg]) times the number of pills divided by the number of days supplied. Days supplied and consecutive prescription dates confirmed the duration of each dispensing and allowed identifying gaps between the end of a prescription and the start of the next one. Prescribed IAs and their doses were converted to standardized medications such that for each Drug Identification Number representing a similar active preparation, the daily equivalent in mg of mycophenolate mofetil, tacrolimus and prednisone doses were assigned. For example, mycophenolic acid 180 mg was converted to mycophenolate mofetil 250 mg and systemic (but not inhaled and topical) corticosteroids were converted to equivalent prednisone doses.

Incident cancer events, defined as the first diagnosis of primary malignant neoplasm (PMN) after the cohort entry, and the corresponding initial diagnosis dates, were identified from the Med-ECHO database. PMNs were ascertained by ICD-9 and ICD-10 codes and categorized based on the involved site. To address concerns of ascertainment bias, cancer events identified by Med-ECHO hospital discharge data were validated against the Quebec cancer registry, the *Fichier des tumeurs du Québec* (FTQ), which relies on surgeries and hospitalizations to identify cancer events.²⁸ Incident cancer events captured in Med-ECHO and FTQ were reported contemporaneously. Med-ECHO captured incident cancer events more comprehensively than FTQ.

Additional covariates, including KTRs' age at transplantation, sex, and transplant year were obtained from the RAMQ database. Importantly, the acquisition of donor-related data with the RAMQ dataset was not authorized. In the absence of a provincial registry, transplant characteristics, typically collected at each center, were unavailable in the administrative database.

2.3 | Statistical analysis

Descriptive statistics were employed to describe the participants' characteristics. Main analyses focused on the associations between IA exposure and PMN incidence and relied on time-to-event methodology. All eligible KTR were followed from 2 years post-transplant (time 0) until either the occurrence of a cancer event, death, loss to follow-up, or registry end date, whichever occurred first. The 2-year lag was implemented to account for the latency between exposures and cancer occurrence.²⁹ We first estimated PMN incidence rates by recipients' age at transplantation and sex. We then fit a multivariable Cox proportional hazards model to estimate the adjusted hazard ratios and 95% confidence intervals (aHRs [95% CIs]) for PMN incidence as a function of 10-year cumulative doses of, respectively, prednisone, mycophenolate, and tacrolimus. Cumulative doses of all three drugs were included in the same model (i.e., mutually adjusted for each other). For each IA, the corresponding 10-year cumulative dose was modeled as a time-varying continuous covariate, updated monthly during follow-up, and calculated as the sum of all doses taken from 12 years before until 2 years before a given month, to account for the

2-year lag. Figure S1 illustrates the calculation of the 10-year cumulative doses. Other time windows (e.g., 5, 8, and 15 years) had been tested in preliminary analyses but, according to the Akaike Information Criterion (AIC), did not improve the fit to data. While our model allows HR calculations for various 10-year long exposure patterns (e.g., at constant high-dose vs. non-use, at decreasing over time dose vs. non-use), for ease of interpretation, for each IA we report the HR for constant standard dose use versus non-use of the same IA over the 10-year period. Models were adjusted for age at transplantation (modeled as a continuous variable), sex, transplant era (years 1997–2001, 2002–2006, or 2007–2016) as well as the time-varying covariates representing the lagged 10-year cumulative doses of the other two IAs. To assess if the associations of the three drugs varied by age and/or sex, we expanded the aforementioned model by adding the three two-way interactions between each main 10-year cumulative exposure and (i) age at transplant in a first model, and (ii) sex in a second model.

The cumulative dose used in primary analyses relied on an implicit assumption that all past exposures are equally important, regardless of how long ago they occurred. Thus, in additional post-hoc sensitivity analyses, we used flexible spline-based weighted cumulative exposure (WCE) modeling in which the time-varying exposure was defined as the *weighted* sum of past doses,^{30,31} for the respective IAs, over the same time window of 12 to 2 years ago. WCE modeling involves estimating a flexible weight function that assigns differential importance weights to past doses, depending on the time since a given dose was taken, relative to the time when the cancer risk is evaluated, which offers insights regarding the etiologic relevance of past exposures.^{30,31} The WCE analyses were carried out separately for each IA, while adjusting for the unweighted cumulative doses of the other two drugs, sex, age, and transplant era. The small number of events did not permit performing subgroup stratified WCE analyses. We used the AIC³² to compare goodness-of-fit of conventional unweighted Cox regression models versus WCE models.

Further sensitivity analyses assessed if and how the results would change if the lag period were shortened from 2 to 1 year as well as when considering the subsets of high-fatality, hormone-sensitive,³³ and infection-related cancers.^{9–11,34} Finally, given the prominence of NMSC in our cohort, we re-estimated associations of 10-year cumulative (unweighted) doses of prednisone, mycophenolate, and tacrolimus with NMSC by fitting multivariable Cox regression models similar to those used in primary analyses for all cancers.

Data management and statistical analyses were conducted using SAS software 9.4 (SAS Institute, Inc.) and R (version 4.2.1),³⁵ including the R package WCE for the WCE analysis.³⁶

3 | RESULTS

We identified 3770 primary KTR who were transplanted between January 1, 1997 and December 31, 2016, without prevalent cancer by the date of transplantation or pre-transplant exposure to IAs (Figure 1). Of the 3770 primary KTR, 527 were followed for less than

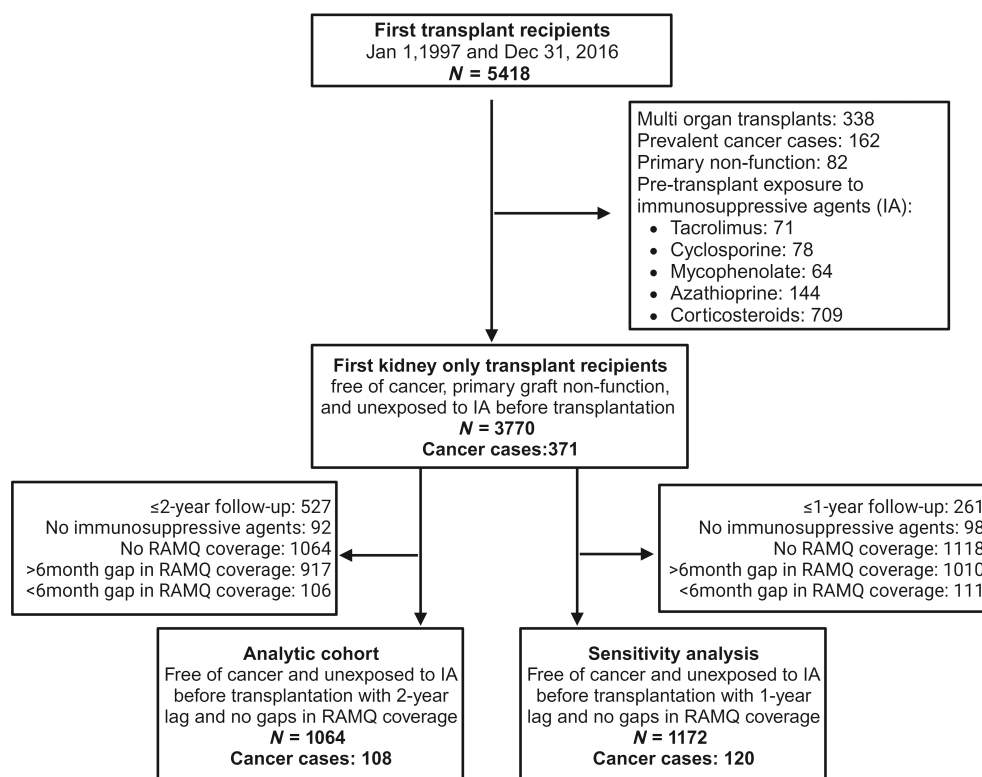


FIGURE 1 Study flow diagram. Visualization created with [BioRender.com](https://www.biorender.com).

TABLE 1 Baseline^a characteristics of first-time kidney transplant recipients in the province of Quebec 1997–2016 and analytic cohort.

Characteristic	Primary kidney only transplant cohort (N = 3770) N (%)	Analytic cohort (2-year lag) (N = 1064) N (%)	Sensitivity analysis cohort (1-year lag) (N = 1172) N (%)
Sex			
Male	2397 (63.6%)	682 (64.1%)	755 (64.4%)
Female	1373 (36.4%)	382 (35.9%)	417 (35.6%)
Age at transplantation (years)			
Median (IQR)	50.0 (39.0, 59.0)	55.0 (43.0, 64.0)	56.0 (43.8, 65.0)
0–17	186 (4.93%)	34 (3.20%)	32 (2.73%)
18–34	513 (13.6%)	114 (10.7%)	118 (10.1%)
35–49	1150 (30.5%)	238 (22.4%)	259 (22.1%)
50–64	1459 (38.7%)	419 (39.4%)	462 (39.4%)
65+	462 (12.3%)	259 (24.3%)	301 (25.7%)
Calendar year of transplantation			
1997–2001	990 (26.3%)	279 (26.2%)	288 (24.6%)
2002–2006	917 (24.3%)	251 (23.6%)	252 (21.5%)
2007–2011	947 (25.1%)	337 (31.7%)	335 (28.6%)
2012–2016	916 (24.3%)	197 (18.5%)	297 (25.3%)

Abbreviation: IQR, interquartile range.

^aBaseline is defined as the date of kidney transplantation, after January 1st, 1997.

2 years after their transplants and 2179 had gaps in RAMQ coverage, resulting in an analytic cohort of 1064 KTR (Figure 1). The baseline characteristics of primary KTR from Quebec and the analytic cohort are presented in Table 1.

3.1 | Incidence of PMN

Median follow-up of KTR in the analytic cohort was 73 months (interquartile range [IQR]: 32–120), for follow-up starting 2 years post-transplant. A total of 108 patients (10.2%) were diagnosed with PMN over follow-up (incidence rate (IR) = 1519 per 100,000 person-years (pyrs); 95% CI: 1246–1834). Cancer IR was higher in KTR >55 years ($n = 68$, IR = 2275 per 100,000 pyrs; 95% CI: 1766–2884) than in KTR ≤55 years ($n = 40$, IR = 971 per 100,000 pyrs; 95% CI: 694–1322). In situ neoplasms accounted for 19.4% of all primary cancer cases ($n = 21$). Cancers of the skin, mainly NMSC ($n = 63$), were the most frequent with an IR of 886 per 100,000 pyrs (95% CI: 681–1134). Table S1 describes the distribution of cancer events by ICD-codes in the cohort noting cancer sites (whenever available) and subsets of high-fatality, hormone-sensitive, and infection-related cancers.

3.2 | Cumulative IA exposure and PMN risk

The initial regimen included mycophenolate and tacrolimus in 89% and 78.2% of KTR, among whom mycophenolate and tacrolimus were

TABLE 2 Hazard ratios^a for 10-year cumulative exposure to immunosuppressive agents and risk of primary malignant neoplasms and non-melanoma skin cancers among kidney transplant recipients in the analytic cohort (N = 1064).

Exposure	All cancers (n = 108)		Non-melanoma skin cancers (n = 63)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Mycophenolate	1.33 (0.98,1.79)	1.34 (0.96, 1.86)	1.26 (0.86,1.86)	1.33 (0.90, 1.98)
Prednisone	1.07 (0.72,1.58)	0.96 (0.64, 1.43)	1.08 (0.66,1.75)	1.06 (0.65, 1.74)
Tacrolimus	1.03 (0.84,1.25)	1.06 (0.88, 1.29)	0.89 (0.66,1.21)	0.97 (0.73, 1.28)
Sex		1.11 (0.75, 1.63)		1.34 (0.81, 2.22)
Age at transplant (10-year increments)		1.56 (1.32, 1.85) ^a		2.16 (1.65, 2.82) ^a
Transplant era				
1997–2001		Ref		Ref
2002–2006		1.13 (0.69, 1.85)		1.32 (0.69, 2.53)
2007–2016		1.48 (0.86, 2.54)		1.79 (0.85, 3.78)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aHazard ratios were calculated for a drug user exposed at a median dose continuously over the 10-year time window versus a non-user of this drug (median daily doses in milligrams: mycophenolate, 1000; prednisone, 5; tacrolimus, 2).

^ap < .001.

maintained over follow up in 78.7% and 78.9%, stopped in 10.4% and 8.39%, or switched to another agent in 10.8% and 12.7%, respectively. Prednisone was prescribed at baseline for 85.1% of KTR and was maintained in 81.6%. Of the 14.9% of KTR prescribed a steroid sparing regimen at baseline, 39.6% did not receive any form of systemic corticosteroids over follow up.

The associations between cumulative 10-year lagged IA exposures and the risk of PMN are presented in Table 2. For each IA, Table 2 reports the adjusted hazard ratio (aHR) associated with continuous use of a given drug, at a constant standard dose in the past 2 to 12 years, relative to a patient who did not use the same IA during this 10-year window (note that this patient in the reference group could be using another IA). After adjustment for age, sex, transplant era, and the unweighted cumulative doses of the other two maintenance IA agents during the same time window, unweighted multivariable Cox models yielded aHRs (95% CIs) for PMN incidence of 0.96 (0.64–1.43), 1.34 (0.96–1.86), and 1.06 (0.88–1.29) associated with 10-year continuous use of prednisone (5 mg daily), mycophenolate (1000 mg daily) and tacrolimus (2 mg daily), respectively. Whereas these results suggest a possible slight risk increase for long-term use of mycophenolate, uncertainty remains regarding the effect size for the various IAs studied. HRs for the cumulative effects of other plausible exposure patterns of time-varying mycophenolate doses are also presented in Figure S2.

3.3 | Assessing effect modification by age and/or sex

When assessing how the risk of PMN by cumulative exposure to each of the IAs was modified by recipients' age (modeled as a continuous variable) and sex, only the interaction between tacrolimus

exposure and age at transplantation ($p = .035$, Figure 2) met the conventional threshold for statistical significance. Adjusted hazard ratios (95% CIs) for PMN associated with tacrolimus exposure were more pronounced in younger recipients (aHR = 1.57 [1.08–2.28] and aHR = 1.31 [1.03–1.66] for 15- and 30-year-old KTR, respectively) in comparison to older transplant recipients. Furthermore, there was greater certainty about the risk associated with long-term use of mycophenolate among females (aHR = 1.86 [1.15–3.00]) in comparison to males (aHR = 1.16 [0.74–1.81] KTR, interaction $p = .131$).

3.4 | Sensitivity analyses

Similar trends were observed in WCE analyses for mycophenolate (1000 mg daily), prednisone (5 mg daily), and tacrolimus (2 mg daily) over a 10-year period with aHRs (95% CIs) of 1.32 (0.94–1.79), 0.95 (0.59–1.38), and 1.01 (0.76–1.20), respectively, versus a non-user of the same IA. However, AICs of WCE models were slightly higher than AIC of the corresponding unweighted model (within 4 points, data not shown), indicating that WCE models did not improve the fit to the data, possibly due to small numbers of incident cancers. Accordingly, we considered our WCE analyses as exploratory or hypothesis-generating analyses. Still, we screened the WCE estimates to get preliminary insights regarding whether and how cancer risks may potentially vary depending on the timing of the past exposures to each of the three IAs of interest. Figure 3 presents weight functions for each IA estimated in the analytical cohort. For mycophenolate, there appears to be a considerable latency between exposure and possibly increased cancer risks, with the highest impact of doses taken 5–10 years ago, as reflected by relatively high positive weights over this time interval (Figure 3A). Figure S3 illustrates the relative importance of past

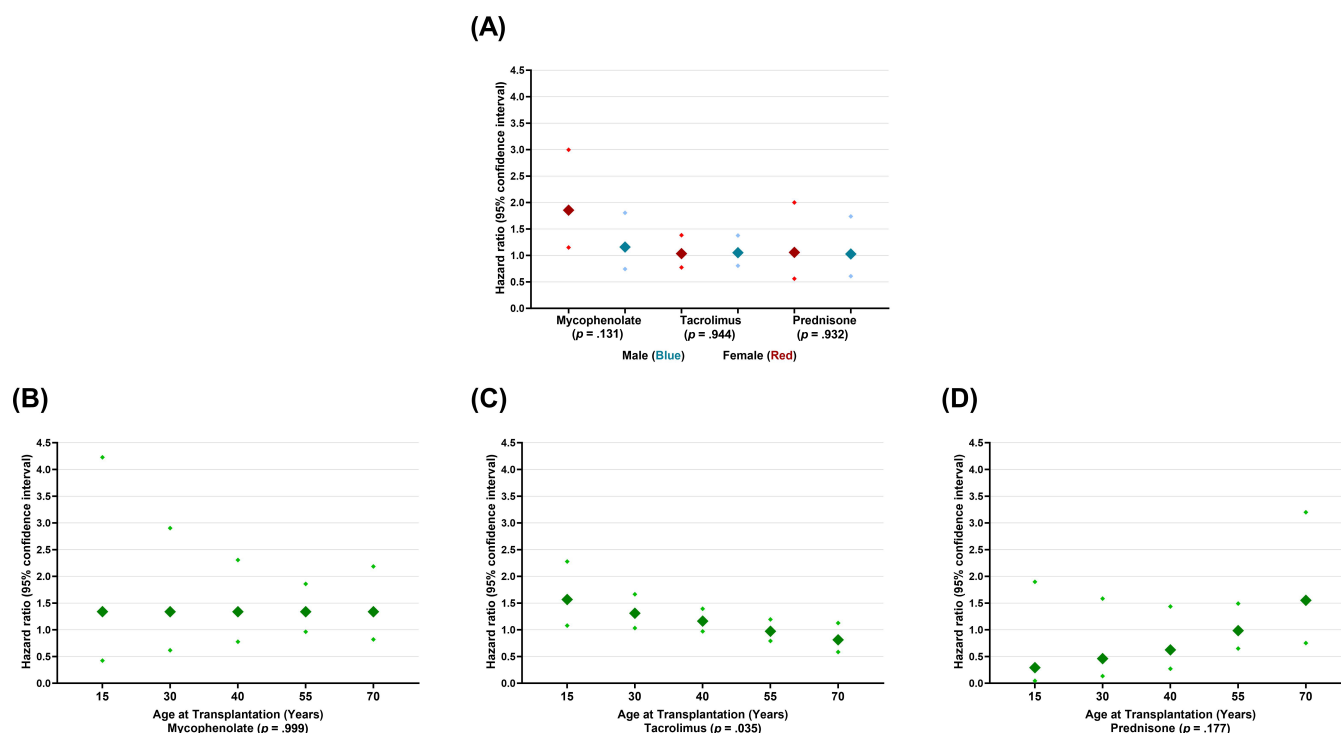


FIGURE 2 Hazard ratios for the 10-year cumulative exposure to immunosuppressive agents and risk of primary malignant neoplasm by kidney transplant recipients' sex (1st row [A]) and continuous age (2nd row), in the analytic cohort ($N = 1064$). Interaction terms with sex were statistically non-significant (mycophenolate $p = .131$; tacrolimus $p = .932$; prednisone $p = .944$), as well as for most interaction terms with age except for tacrolimus (mycophenolate $p = .999$; tacrolimus $p = .035$; prednisone $p = .177$). Hazard ratios were calculated for a user of a median dose continuously administered over the 10-year time window versus a non-user of this drug during the same 10-year period (median daily doses in milligrams: mycophenolate, 1000 [B]; tacrolimus, 2 [C]; prednisone, 5 [D]). Visualization was done using GraphPad Prism version 10.1.2. [Color figure can be viewed at wileyonlinelibrary.com]

mycophenolate exposures in the calculation of the 10-year weighted cumulative doses. For prednisone and tacrolimus, no clear trends could be identified due to wide CIs around the estimated weights, which oscillated between positive and negative values over distinct parts of the time window (Figure 3B,C), consistent with the aHRs being close to null for both drugs.

Sensitivity analyses with exposure lagged by 1 year included 1172 eligible KTR, with 120 (10.2%) diagnosed with cancers (Figure 1). We employed unweighted multivariable Cox models to estimate aHRs associated with continuous use of a given drug, at a constant dose in the past 1–11 years, relative to a patient who did not use the same IA during this 10-year window. After adjusting for age, sex, transplant era, and cumulative doses of the other two maintenance IA agents during the same time window, we estimated aHRs (95% CIs) of 1.08 (0.72, 1.60), 1.23 (0.91, 1.66), and 1.08 (0.91, 1.28) for continuous 10-year use of prednisone (5 mg daily), mycophenolate (1000 mg daily) and tacrolimus (2 mg daily), respectively. Whereas the results suggest a possible slight PMN risk increase for long-term use of mycophenolate, uncertainty remains regarding the effect size across IAs studied. Like the primary analyses, there was greater certainty about the PMN risk associated with long-term use of mycophenolate among female (aHR = 1.69 [1.07–2.66]) in comparison to male (aHR = 1.04 [0.69–1.57]) KTR (interaction $p = .102$). Also, we found an interaction between tacrolimus exposure

and age at transplantation ($p = .041$). However, even if aHRs gradually decreased with older age at transplant, uncertainty remains regarding the effect size across the studied age groups (data not shown).

Given a small number of events representing cancer subtypes, we employed Cox models to estimate the unadjusted HRs for the association between continuous 10-year lagged by 2 year use of prednisone (5 mg daily), mycophenolate (1000 mg daily) and tacrolimus (2 mg daily) with high-fatality cancers of 1.25 (0.55–2.87), 1.85 (1.14–3.01), and 1.05 (0.64–1.72); unadjusted HRs for hormone-sensitive cancers of 1.46 (0.65–3.29), 1.86 (0.97–3.56), and 1.24 (0.80–1.91), and unadjusted HR for infection-related cancers of 0.89 (0.14–5.68), 1.51 (0.50–4.55), and 1.35 (0.92–1.99), respectively.

Finally, Table 2 and Figure 4 describe, respectively, the estimated aHRs for the associations of 10-year cumulative IA lagged by 2 years with the hazard of NMSC, and how they are modified by KTRs' age and sex. Like the primary analyses of PMN, there was a trend toward increased NMSC risk the higher the long-term cumulative mycophenolate doses, and more so among females (interaction $p = .364$). We also observed a trend toward a stronger impact of cumulative prednisone exposure for older KTR (interaction $p = .063$) with aHR 2.20 (0.89–4.94) for 70-year-old KTR, but there was uncertainty in the estimated effect size, possibly due to low statistical power resulting from a small number of NMSC events.

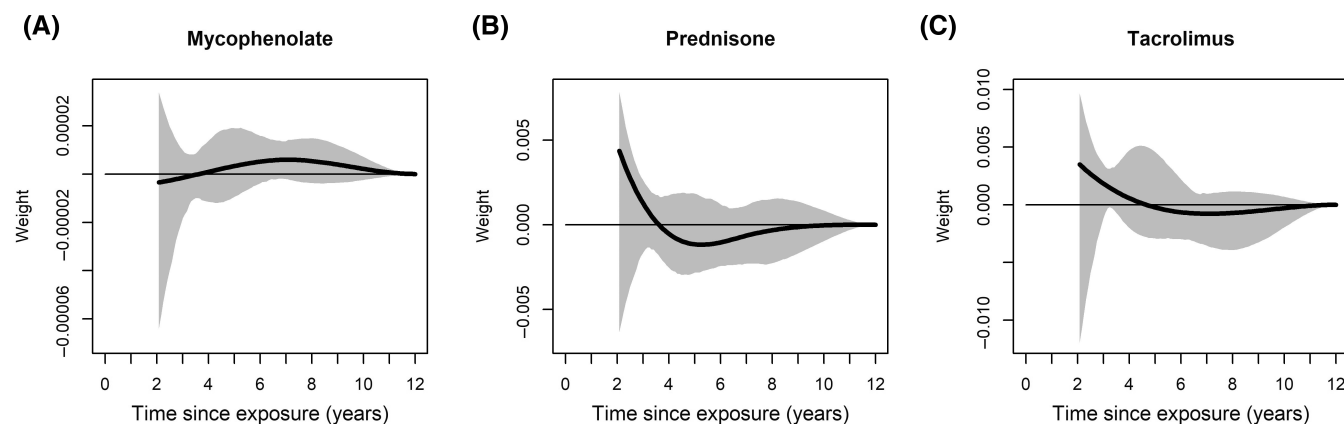


FIGURE 3 Association between cumulative exposure to contemporary immunosuppression agents and primary malignant neoplasm in the analytic cohort of kidney transplant recipients ($N = 1064$). Estimated weight functions (bold black lines) from weighted cumulative exposure (WCE) models for (A) mycophenolate, (B) prednisone, and (C) tacrolimus, with 95% bootstrap confidence intervals (gray areas). Positive weights indicate risk increase while negative weights represent risk reduction.

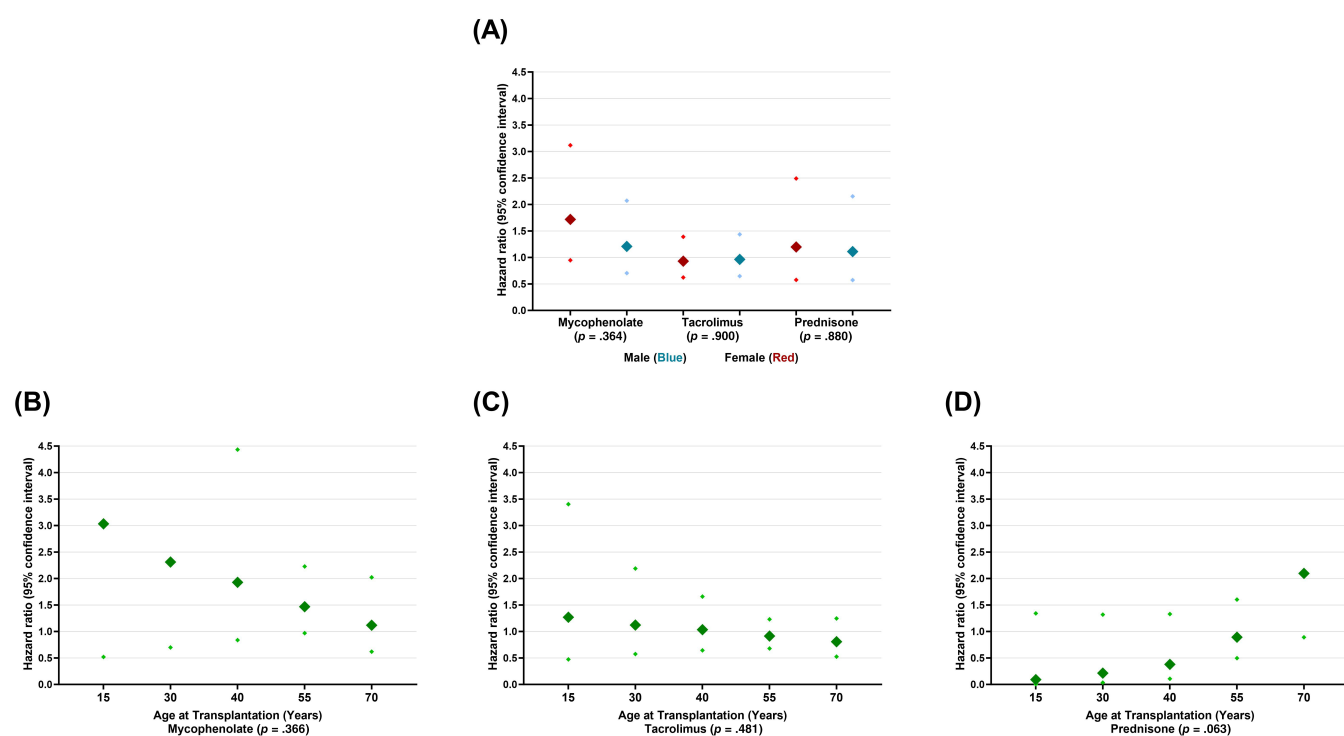


FIGURE 4 Hazard ratios for the 10-year cumulative exposure to immunosuppressive agents and risk of non-melanoma skin cancer by kidney transplant recipients' sex (1st row (A)) and continuous age (2nd row), in the analytic cohort ($N = 1064$). Interaction terms with sex were statistically non-significant (mycophenolate $p = .364$; tacrolimus $p = .900$; prednisone $p = .880$), as well as for interaction terms with age except for prednisone (mycophenolate $p = .366$; tacrolimus $p = .481$; prednisone $p = .063$). Hazard ratios were calculated for a user with a median dose continuously over the 10-year time window versus a non-user of this drug (median daily doses in milligrams: mycophenolate, 1000 [B]; tacrolimus, 2 [C]; prednisone, 5[D]). For legibility and consistency of aHR and 95% CI scale across the figures, note that the upper confidence interval bounds were out of the y-axis range for 15- and 30-year-old KTR in the mycophenolate figure (upper bound of 95% CI = 17.70 and 7.64, respectively) and for 70-year-old KTR in the prednisone figure (upper bound of 95% CI = 4.94) and, thus, are not represented in the figure. Visualization was done using GraphPad Prism version 10.1.2. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ijc.34875)]

4 | DISCUSSION

We studied a retrospective cohort of KTR from the province of Quebec, Canada with detailed longitudinal prescription data to estimate

the associations of cumulative exposure to contemporary IAs with cancer risk and assessed if this risk was modified by KTR's age at transplantation and sex. In our analytic cohort, with a median follow-up of 73 months, we observed a trend toward increased risk of

PMN with long-term mycophenolate exposure, with higher risk in females, and a potentially smaller risk with long-term prednisone and tacrolimus exposure. Risks for PMN were more pronounced the higher the cumulative exposure to tacrolimus and the younger the KTR.

Despite major improvements in transplant care, cancer remains a major cause of morbidity and mortality.^{19,37} The cumulative PMN incidence we observed in Quebec KTR prescribed mycophenolate and tacrolimus-based regimens, with some also prescribed corticosteroids, was comparable to prior publications,^{10,38} which reported cumulative incidence of 4%–5%, 10% and up to 25% after 5, 10 and 20 years, respectively.³ Another Canadian study that used administrative healthcare databases including Ontarian KTR, transplanted in 1981–1998, and prescribed primarily azathioprine and corticosteroids, reported a cumulative cancer incidence of 12% over 17-year-long follow-up.³⁹ In contrast, however, the Ontario cohort excluded NMSC events, suggesting potentially lower incidence of non-cutaneous PMN with contemporary IAs in the Quebec cohort.

We estimated a trend toward increased risks of PMN and NMSC with higher cumulative mycophenolate doses, with more pronounced risk of PMN in females. There is some controversy in the literature regarding sex disparities in cancer risk among KTR, with some publications reporting a higher risk of cancer (including NMSC) for males,^{12,40} while others for females, especially if transplanted at a younger age.^{3,18} Estimated glomerular filtration rate, which varies by sex, affects mycophenolate elimination.^{41,42} Whether lowering cumulative exposure to mycophenolate will prevent cancer (without increasing rejection) in female KTR and how gender disparities in adherence and participation in cancer screening may affect cumulative IA exposure and time to cancer diagnosis, warrant further study.

As cancer risk is about 2-fold higher in 65-year-old KTR than in the general population and 3-fold higher among KTR aged ≥ 55 years than those < 35 years at transplantation¹⁸ there has been an increased interest in IA minimization in older KTR.^{16,24,43} While there is paucity of trial data, Lentine et al.¹⁷ examined the impact of induction and early maintenance immunosuppression regimens (first 6-months) in a national cohort of U.S. KTR. This study, which additionally adjusted for donor characteristics, suggested that lower-intensity regimens (e.g., steroid-sparing) may be preferable in older KTR.

NMSC was the most common cancer in our cohort. KTR experience lifetime risks of squamous cell carcinoma and basal cell carcinoma, respectively, 65–200 times and 10–16 times higher than in the general population.⁴⁴ We estimated a trend toward a higher risk of NMSC with increased cumulative prednisone dose among older KTR. While, as a group, corticosteroids are classified by the IARC as group 3 (inadequate evidence for carcinogenicity in humans),^{45,46} time- and dose-dependent cumulative exposure to systemic corticosteroids may predispose older and more frail patients to infection.⁴⁷ Oncogenic infections such as EBV, HPV and human herpesvirus-8, have been shown to increase the risk of post-transplant lymphoproliferative disease, NMSC and Kaposi's sarcoma, respectively.^{4,48} Yet, the number of infection-related cancers in our cohort was too small to probe for this association. Large long-term prospective cohort studies are needed to verify effects of steroid avoidance and withdrawal toward

infection-related cancer prevention and whether this risk is modified by KTRs' age.

Our analyses suggest an increased risk of PMN the higher the cumulative tacrolimus dose in younger KTR. In a systematic review of 92 randomized controlled trials evaluating IAs' impact on NMSC prevention in solid organ transplant recipients, Chung et al.⁴⁸ concluded that the evidence on efficacy and safety of specific treatments was of low or very low certainty, with substantial methodological limitations, small number of events, and considerable heterogeneity across studies. Moderate certainty evidence, however, indicated that mammalian target of rapamycin inhibitors (mTORi) reduced the risk of skin cancer compared to CNIs by 38% over a median treatment duration of 22 months. While our analyses did not estimate an increased risk of NMSC as a function of tacrolimus exposure, it has been proposed that nonrapid tacrolimus metabolizers had higher cutaneous cancer risk.⁴⁹ Also, while estimated PMN and NMSC risks in our cohort did not differ by KTRs' sex, it is known that absorption, distribution, metabolism, and elimination of drugs vary by sex, leading to sex-specific efficacy and toxicity.²¹ For example, sex-dependent compositional difference and activity of the P450 superfamily of enzymes influences CNI distribution and metabolism, respectively.^{20,50} Future studies should assess whether tacrolimus pharmacokinetic parameters, rather than the prescribed dose, associate with cancer.

Strengths of this study include the availability of population-level KTR data. Many trials assessing IAs were criticized for insufficient follow-up to assess long-term outcomes.^{24,51,52} Also, previous studies found that prostate, melanoma, NMSC, and bladder cancers were underreported in cancer registries,²⁸ possibly leading to underestimation of burden of cancer among KTR. In contrast, our access to the Med-ECHO database and PMN diagnoses allowed us to estimate PMN incidence, including NMSC events, more comprehensively. Additionally, longitudinal prescription data allowed us to improve upon exposure measurement in comparison to prior studies that relied upon pharmacy claims limited to the first 6-months post-transplant.¹⁷

Despite these advantages, we note some limitations. Patient-level data on induction and supplemental IAs for rejection, typically administered during hospitalization, were not available from RAMQ. Additionally, administrative databases do not capture established cancer risk factors like comorbidities or patient body mass index,⁵³ which may contribute to toxicity related to drugs for which therapeutic drug monitoring is not readily available (e.g., mycophenolate and corticosteroids). Additionally, we did not have access to information on behaviors (e.g., smoking and nonadherence^{3,8,12}) or environmental exposures. These, in turn, may result in residual confounding, even if certain risk factors are unlikely to be associated with cumulative IA exposures. Gaps in RAMQ coverage resulted in exclusion of a sizable portion of eligible participants. Yet, similar participant characteristics and distribution of primary cancer events, suggest that our findings may be applicable to the wider population of Quebec KTR. Finally, despite the long follow-up, the number of cancer events observed was too small to firmly establish effects of the relatively weak associations and did not allow us to accurately analyze risks for specific cancer

sites or rely on WCE analyses to identify etiologically most relevant time windows of past exposures.

In conclusion, while the overall immunosuppressed state is associated with an increased risk for cancer, independent associations of long-term exposure to contemporary IAs with cancer among KTR are not well established. Our results suggest that some associations may be specific to sex- and/or age-defined subgroups of KTR. These findings are consistent with simulation studies that have shown that systematic associations may be present in selected subgroups, even in the presence of a non-significant overall effect in the entire population,⁵⁴ emphasizing the need to assess for interactions and conduct subgroup analyses by KTRs' age and sex. If replicated in a larger, adequately powered independent studies, our subgroup analyses results may help identify opportunities for dynamic modification in IAs and tailoring regimens to individual KTR's needs. Given the long follow-up required to observe PMNs, it would be challenging to confirm our observations in clinical trials. Thus, large observational studies linking administrative databases with laboratory data are needed to verify whether lower cumulative intensity regimens, therapeutic drug monitoring, and surveillance for oncogenic viruses, may help mitigate risk of PMN and NMSC in susceptible KTR.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. *Conceptualization*: RSP, CL, LA, ELF, BN. *Data curation*: RSP, CL, MK, XZ, ADV, BN. *Formal analysis*: MK, XZ, MEB, MA. *Funding acquisition*: RSP, CL, MEB, LA, ELF, MA, BN. *Investigation*: RSP, CL, MEB, MK, XZ, ADV, LA, ELF, MA, BN. *Methodology*: MEB, MA. *Project administration*: RSP, CL, BN. *Software*: MEB, MA. *Supervision*: RSP. *Writing—original draft*: RSP, CL, BN. *Writing—review & editing*: RSP, CL, MEB, MK, XZ, ADV, LA, ELF, MA, BN.

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CONFLICT OF INTEREST STATEMENT

RSP received Fellowship Support to the Foundation of McGill University Health Centre from Paladin Labs Inc. These funds were not used to support the work presented in this manuscript. LA served on

consulting and advisory committees for Pfizer and Roche. Other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Institut de la statistique du Québec (<https://statistique.quebec.ca/fr>) and the Commission d'accès à l'information du Québec, following approval of an application. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The McGill University and McGill University Health Centre Ethics Review Boards, in Montreal, Canada, approved this study (2018-4536). The *Commission d'Accès à l'Information du Québec* approved the use of administrative data (reference number: 1018134-S).


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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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