MALIGNANCY AND SOLID ORGAN TRANSPLANTATION: OUTCOMES OF RECIPIENTS WITH PRE-TRANSPLANT MALIGNANCIES, UPTAKE OF CANCER SCREENING, AND CANCER MORTALITY AFTER SOLID ORGAN TRANSPLANTATION

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Introduction:

Solid organ transplant recipients (SOTRs) are at greater risk of developing some cancers than the general population;[1,2] however, because they are also at increased risk of mortality from non-cancer causes, the effect of transplantation on cancer mortality is unclear.[3-5] In addition, it is uncertain whether deaths caused by recurrent pre-transplant malignancies (PTM) are a major contributor to cancer mortality in SOTRs and whether recipients with PTM have worse outcomes.[6]

The high incidence post-transplant *de novo* malignancy has been attributed to decreased immunosurveillance, activation of oncogenic viruses, and chronic stimulation of the immune system. Similarly, PTM are considered a relative contraindication for transplantation due to the heightened risk of cancer recurrence associated with immunosuppression. It has also been hypothesized that because SOTR are followed up closely, earlier detection and diagnosis could lead to increased incidence malignancy (lead-time bias). However, cancer screening in SOTR is considered controversial owing to reduced life expectancy and competing causes of death. Although routine cancer screening recommendations for the general population are also suggested for SOTRs,[7] the adherence to these recommendations is unknown.

Improving our understanding of the burden of cancer in this population is important. If SOTR are at a high risk of dying of cancer, different screening and treatment strategies may be needed for this population. Moreover, assessment of the overall cancer mortality, including deaths caused by recurrent PTM and those associated with *de novo* malignancies, is important to fully quantify the cancer burden and to develop strategies to reduce cancer death. Additionally, as older patients are now being accepted for transplantation, the number of transplant candidates with PTM continues to grow. A more thorough evaluation of the impact of PTM on the outcomes of transplant recipients is hence timely. We therefore designed a series of population-based cohort studies to explore the outcomes of SOTR with PTM, the uptake of cancer screening in SOTR, and the burden of cancer mortality in this population.

Objectives:

1. To evaluate overall survival and cancer-related outcomes among transplant recipients with pre-existing malignancies, and to determine factors associated with better outcomes.
2. To determine the uptake of breast, cervical, and colorectal cancer screening rates among SOTR and identify factors associated with up-to-date screening.
3. To describe cancer mortality in SOTRs and to assess whether SOTRs are at increased risk of cancer mortality compared with the general population.

Methods:
We conducted a series of population-based cohort studies using transplant and cancer registries linked to administrative data. First, all Ontario residents undergoing solid organ transplant between 1991 and 2010 were identified in the Canadian Organ Replacement Register (CORR) and linked to the Ontario Cancer Registry (OCR) to identify recipients with PTM. Recipients with PTM were matched to recipients without any PTM using a propensity score and overall survival (OS) was compared using Kaplan-Meier graphs and Cox proportional hazard models. For cause-specific mortality, organ/graft failure, and post-transplant cancer incidence, cause-specific hazard models were used and the cumulative incidence of the events was plotted and compared using the Gray's test. Second, all patients receiving a solid organ transplant in Ontario between 1997 and 2010 were identified from CORR and liked to administrative databases to determined the uptake of breast, cervical, and colorectal cancer screening and to identify factors associated with becoming up-to-date with screening using recurrent event analysis. Lastly, SOTR were identified from CORR and linked to OCR and administrative databases, and cancer mortality for SOTRs was compared with that of the general population using standardized mortality ratios (SMRs). Mortality and cause of death were ascertained by record linkage between the CORR, the OCR, and the Office of the Registrar General of Ontario death database.

Results:
In the first cohort, a total of 443 recipients with PTM were matched to 886 recipients without PTM. Recipients with PTM had a worse OS compared to recipients without PTM (median OS: 10.3 versus 13.4 years, p<0.001, **Figure 1a**). When stratifying the patients with PTM by the time between cancer diagnosis and transplantation, only the subgroup with intervals ≥5 years were at increased risk of all-cause mortality (HR: 1.61, 95% CI: 1.32-1.97, **Figure 1b**). Similarly, only recipients with high-risk PTM (those that require minimum cancer remission times of 5 years before listed for transplantation) were at increased risk of all-cause mortality (HR: 2.04, 95% CI: 1.58-2.64, **Figure 1c**). Recipients with PTM were not only at increased risk of cancer-specific mortality (HR: 1.85, 95% CI: 1.21-2.83) but also at increased risk of non-cancer death (HR: 1.29, 95% CI: 1.07-1.52, **Figure 1d**). Similarly, recipients with PTM were at increased risk of organ/graft failure and death with functioning graft (p=0.02 and P=0.01).

In the second study, we identified 4,436 SOTR eligible for colorectal, 2,252 for cervical, and 1,551 for breast cancer screening. Of those, 3,437 (77.5%), 1,572 (69.8%), and 1,417 (91.4%), respectively, were not up-to-date for cancer screening at some point during the observation period. The proportion of screening up-to-date recipients increased over time from transplantation for breast, cervical, and colorectal cancer screening (P<0.001). Similarly, the rates of visits to a primary care physician (PCP) and transplant specialist decreased over time. Factors associated with cancer screening uptake in the recurrent event analysis among recipients who were not up-to-date are presented in **Figure 2**. Recipients with fewer comorbidities had higher rates of becoming screen up-to-date. Assessment by a primary care physician (PCP) in the previous year was associated with being up-to-date with all forms of screening (breast RR: 1.40, 95% CI: 1.12-1.76, cervical RR: 1.29, 95% CI: 1.06-1.57, colorectal RR: 1.30, 95% CI: 1.15-1.48), while a visit to a transplant specialist in the previous year was not. However, visits to a transplant specialist restricted to those happening at a transplant centre were also associated with being up-to-date.

Lastly, a total of 11,061 SOTRs were identified for the third cohort, including 6,516 kidney, 2,606 liver, 929 heart, and 705 lung transplantations. Recipients had a median (interquartile range) age of 49 (37-58) years, and 4,004 (36.2%) were women. Of 3,068 deaths, 603 (20%) were cancer related. Cancer mortality in SOTRs was significantly elevated compared with the Ontario population (SMR, 2.84, 95% CI: 2.61-3.07, **Figure 3a**). The risk remained elevated when patients with PTM (n = 1124) were excluded (SMR: 1.93, 95% CI: 1.75-2.13, **Figure 3b**). The increased risk was observed irrespective of transplanted organ. The SMR for cancer death after solid-organ

transplantation was higher in children (SMR: 84.61, 95% CI: 52.00-128.40) and lower in patients older than 60 years (SMR: 1.88, 95%CI: 1.62-2.18) but remained elevated compared with the general population at all ages.

Discussion:

Our study demonstrated that SOTRs are at increased risk of cancer death compared with the general population. Cancer was the second leading cause of death in all SOTRs, indicating a substantial cancer burden in this population. The excess risk of cancer death persisted after excluding cancer mortality from PTM. However, our cohort of SOTR with PTM confirmed that this subgroup of patients was at increased risk of cancer mortality, although interestingly, *de novo* malignancies were responsible for one third of cancer-related deaths.

The factors underlying the increased burden of cancer mortality in SOTRs are likely complex. The increased risk of cancer death in SOTR was observed regardless of age, sex, transplanted organ, and transplant period, and probably reflects the underlying increased incidence of cancer after transplantation. However, it is possible that other factors might be associated with the observed increase in cancer mortality. The finding that cancer screening for most SOTR does not adhere to standard recommendations brings into question whether the increased incidence observed for cervical and colorectal cancer is secondary to close follow-up. Moreover, as for most malignancies, earlier detection is associated with improved outcomes, these findings suggest that the increased mortality observed for colon cancer is due to differences in tumor biology, stage at diagnosis, and cancer treatment.

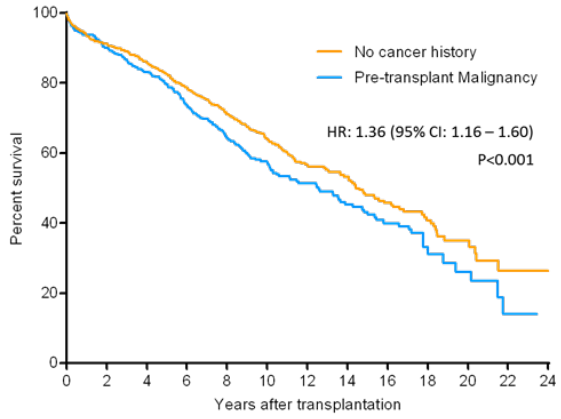
Our cohort study also demonstrated that SOTR with PTM are at increased risk of all-cause mortality. However, this was not driven by the increased risk of cancer-specific mortality alone. The increased risk of non-cancer mortality could also be associated with increased risk of organ/graft failure. Longer time with end-stage organ disease or dialysis prior to transplantation, and differences in donor characteristics or immunosuppressant management could contribute the increased incidence of de novo malignancy and non-cancer deaths.

Lastly, it is possible that because of the complexity of SOTR, routine health maintenance may be overlooked. Our findings suggest that involvement of PCPs in the care of SOTR and continuity of care at the transplant centre may improve the uptake of screening.

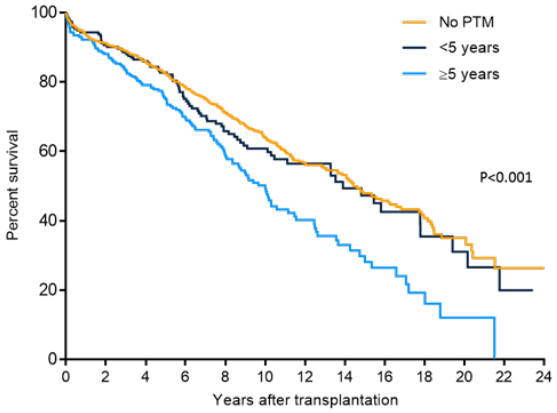
While the information provided by these studies does not provide a road map for how to prevent or treat cancer in SOTR, it suggests that preventative strategies and surveillance are probably required to minimize cancer related deaths. Our study results support existing recommendations of targeted cancer screening in SOTR. This is an important message at a time when many guidelines recommend against cancer screening for certain malignancies in the general population, an effect that may inappropriately spill over to the SOTR population.

Figure 1. Outcomes of Recipients with Pre-transplant Malignancies

A Overall survival by history of pre-transplant malignancy

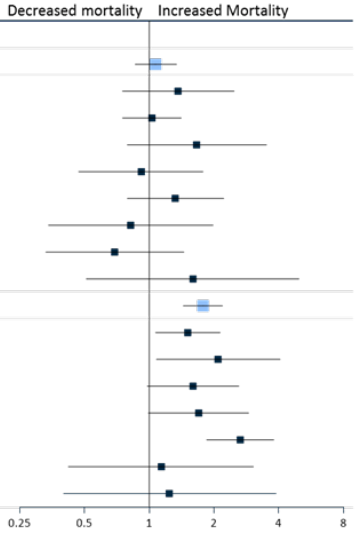


B Overall survival by time between cancer diagnosis and transplant



C Risk of all-cause mortality by pre-transplant malignancy site

Cancer-site	No. of SOTR	No. of deaths	Hazard Ratio (95% CI)	
No pre-transplant cancer	882	341 (38.6)	Ref	
Low-risk malignancies	329	144 (43.8)	1.06	0.86 – 1.31
Bladder	20	11 (55.0)	1.29	0.76 – 2.20
Kidney	109	43 (39.5)	1.03	0.76 – 1.41
Oral cavity and pharynx	12	7 (58.3)	1.47	0.60 – 3.58
Other	22	9 (40.9)	1.02	0.54 – 1.93
Prostate	34	15 (44.1)	1.33	0.70 – 1.82
Testis	15	5 (33.3)	0.89	0.37 – 2.12
Thyroid	25	7 (28.0)	0.71	0.37 – 1.36
Unknown	7	≤ 5	1.66	0.67 – 4.08
High-risk malignancies	113	71 (62.8)	1.81	1.47 – 2.23
Hematologic	69	33 (47.8)	1.68	1.15 – 2.46
Lung	14	9 (64.3)	1.81	0.84 – 3.91
Breast	35	17 (48.6)	1.55	1.01 – 2.20
Melanoma	18	14 (77.8)	1.76	1.12 – 2.77
Gastrointestinal	47	33 (70.2)	2.54	1.85 – 3.45
Uterus	8	≤ 5	1.20	0.51 – 2.80
Ovary	7	≤ 5	1.22	0.45 – 3.33



D Cumulative incidence of cancer deaths and non-cancer deaths by history of pre-transplant malignancy

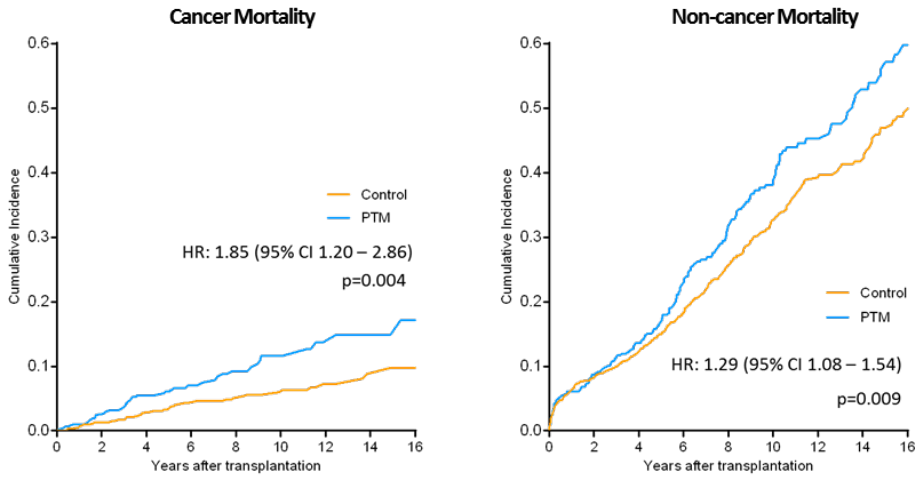
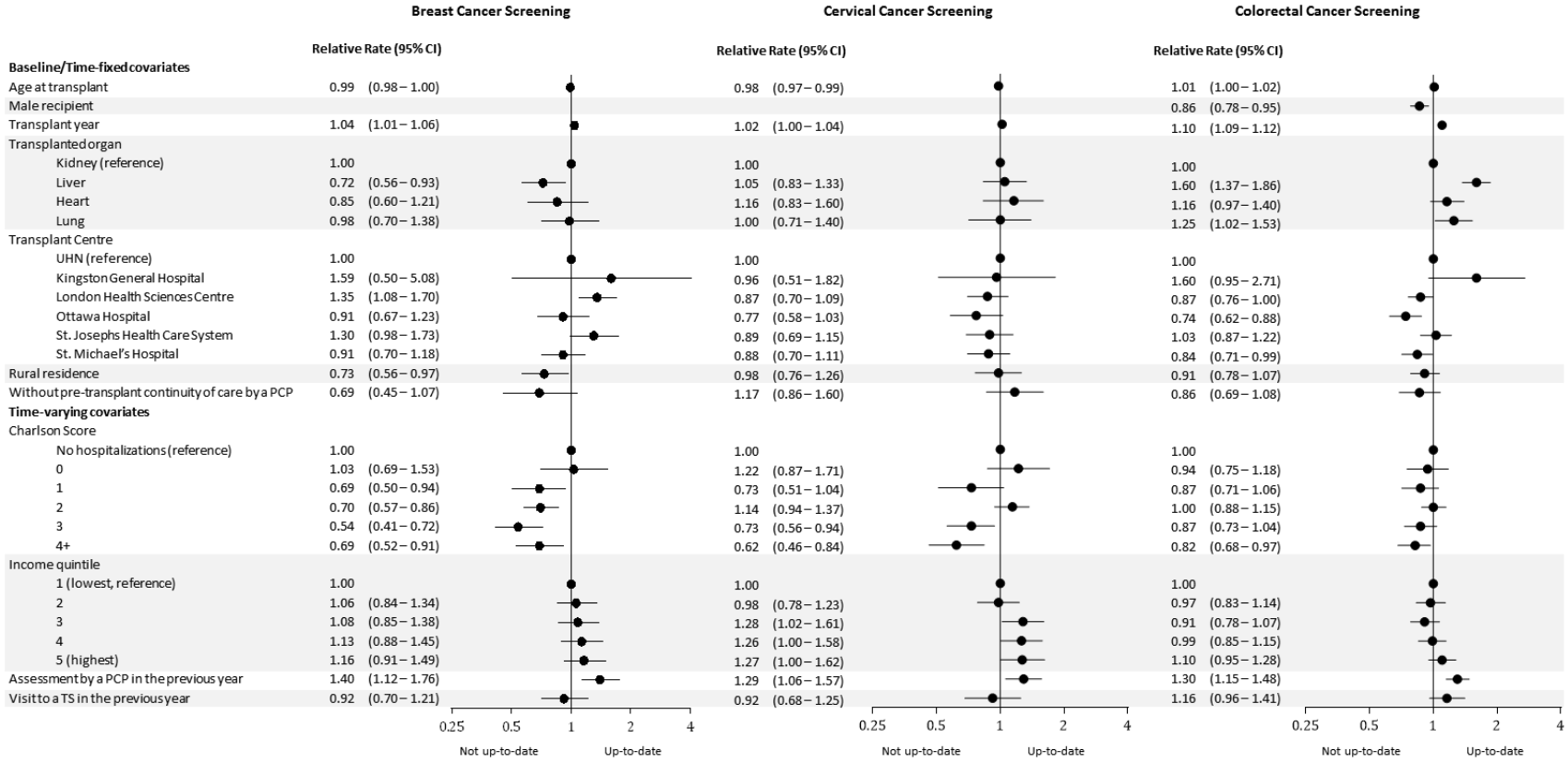


Figure 2. Uptake of Cancer Screening in Solid Organ Transplant Recipients



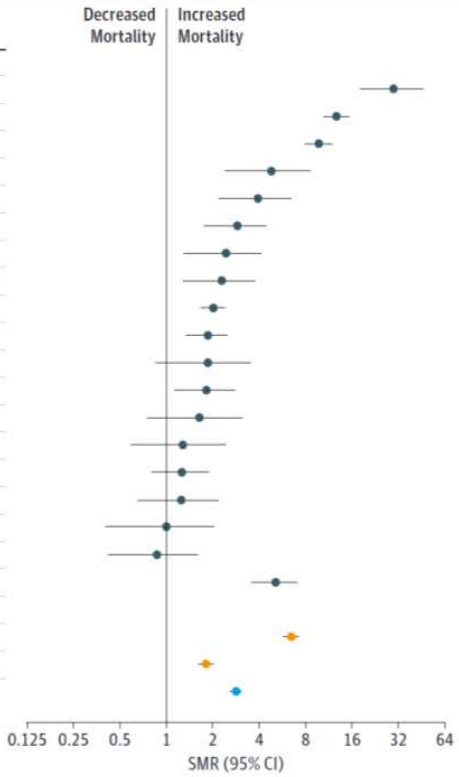
Multivariable recurrent event analysis for recipients not up-to-date with cancer screening.

Abbreviations: CI: Confidence Interval | UHN: University Health Network | PCP: Primary Care Physician | TS: Transplant Specialist

Figure 3. Cancer Mortality Among Solid Organ Transplant Recipients

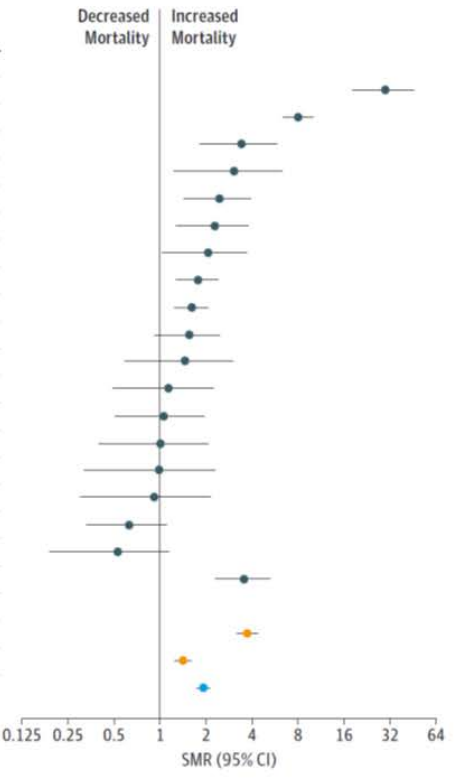
A All Post-transplant Cancer Deaths

	Observed Deaths, No. (%)	SMR (95% CI)
Cancer Site		
Nonmelanoma skin	20 (3.3)	29.85 (18.23-46.10)
Liver/biliary	107 (17.7)	12.72 (10.43-15.37)
Non-Hodgkin lymphoma	96 (15.9)	9.76 (7.91-11.93)
Bone and soft tissues	11 (1.8)	4.80 (2.40-8.59)
Melanoma	15 (2.5)	3.93 (2.20-6.48)
Leukemia	20 (3.3)	2.89 (1.76-4.46)
Oral cavity and pharynx	13 (2.2)	2.44 (1.30-4.16)
Stomach	15 (2.5)	2.29 (1.28-3.78)
Lung	126 (20.9)	2.02 (1.68-2.40)
Colorectal	43 (7.1)	1.86 (1.34-2.50)
Bladder	9 (1.5)	1.86 (0.85-3.54)
Pancreas	21 (3.5)	1.82 (1.13-2.78)
Kidney	9 (1.5)	1.64 (0.75-3.11)
Esophagus	9 (1.5)	1.28 (0.59-2.43)
Other	24 (4.0)	1.26 (0.81-1.87)
Prostate	12 (2.0)	1.25 (0.65-2.19)
Gynecologic	7 (1.2)	1.00 (0.40-2.05)
Breast	10 (1.7)	0.87 (0.42-1.60)
Unknown primary site	36 (6.0)	5.12 (3.58-7.08)
Etiology		
Infectious[a]	301 (49.9)	6.47 (5.76-7.25)
Noninfectious	302 (51.1)	1.81 (1.61-2.02)
Any	603 (100)	2.84 (2.61-3.07)



B Post-transplant *de novo* Cancer Deaths

	Observed Deaths, No. (%)	SMR (95% CI)
Cancer Site		
Nonmelanoma skin	20 (4.9)	29.85 (18.23-46.10)
Non-Hodgkin lymphoma	79 (19.2)	8.05 (6.38-10.04)
Melanoma	13 (3.2)	3.42 (1.82-5.85)
Bone and soft tissues	7 (1.7)	3.06 (1.23-6.30)
Leukemia	17 (4.1)	2.46 (1.43-3.93)
Stomach	15 (3.6)	2.29 (1.28-3.78)
Oral cavity and pharynx	11 (2.7)	2.07 (1.03-3.70)
Colorectal	41 (10.0)	1.78 (1.28-2.42)
Lung	98 (23.8)	1.58 (1.28-1.92)
Pancreas	18 (4.4)	1.56 (0.92-2.47)
Bladder	7 (1.7)	1.46 (0.59-3.00)
Esophagus	8 (1.9)	1.14 (0.49-2.24)
Prostate	10 (2.4)	1.06 (0.51-1.96)
Gynecologic	7 (1.7)	1.01 (0.40-2.07)
Liver/biliary	12 (2.9)	1.52 (0.78-2.65)
Kidney	5 (1.2)	0.92 (0.30-2.15)
Other	12 (2.9)	0.63 (0.33-1.11)
Breast	6 (1.5)	0.53 (0.19-1.15)
Unknown primary site	25 (7.02)	3.56 (2.30-5.26)
Etiology		
Infectious[a]	174 (42.3)	3.74 (3.21-4.34)
Noninfectious	237 (57.7)	1.42 (1.24-1.61)
Any	411 (100)	1.93 (1.75-2.13)



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