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Uptake of Cancer Screening Tests Among Recipients of Solid Organ Transplantation

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Running title: Cancer screening in solid organ transplant recipients

Abbreviations

SOTR: Solid organ transplant recipients.
CORR: Canadian Organ Replacement Register
OHIP: Ontario Health Insurance
OBSP: Ontario Breast Screening Program
RPDB: Registered Persons Database
OCR: Ontario Cancer Registry
ICES: Institute for Clinical Evaluative Sciences
IPDB: ICES Physician Database
FOBT: Fecal Occult Blood Test
CCS: Charlson comorbidity score

Abstract

Population-based cancer screening recommendations are also suggested for solid organ transplant recipients (SOTR); however, recommendation adherence is unknown. In a population-based cohort of SOTR in Ontario between 1997 and 2010, we determined the uptake of breast, cervical, and colorectal cancer screening tests and identified factors associated with up-to-date screening using recurrent event analysis. 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 tests during the observation period. However, these rates are likely an overestimate due to the inability to differentiate between tests done for screening or for diagnosis. SOTR with fewer comorbidities had higher rates of becoming screen up-to-date. Assessment by a primary care physician (PCP) was associated with becoming up-to-date with cancer 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). Similar results were observed for continuity of care by transplant specialist at a transplant center. In conclusion, cancer screening for most SOTR does not adhere to standard recommendations. Involvement of PCPs in post-transplant care and continuity of care at a transplant centre may improve the uptake of screening.

Introduction

An important complication associated with solid organ transplantation is the development of malignancy (1-3). Solid organ transplant recipients (SOTR) are at increased risk of developing and dying from malignancies compared to the general population. Cancer is a leading cause of death in this population (4-6), and as the management of cardiovascular and infectious diseases improves, the relative burden of cancer mortality in transplant recipients is expected to increase (7). Several factors have been associated with poor outcomes in SOTR with cancer: malignancies in SOTR tend to be biologically more aggressive (8, 9), and patients may receive less aggressive cancer treatment due to increased toxicity and coexisting comorbidities (10).

Although no randomized controlled screening trials have been performed in SOTR (11), decision modeling studies in the kidney transplant population have shown screening for colon and cervical cancer to be cost-effective and for breast cancer similar costs with reduced benefit (12-15). Given the available evidence, current recommendations for breast, colorectal and

cervical cancer screening generally parallel the guidelines available for the general population (16-20). Adherence to these recommendations among transplant recipients is currently unknown. We therefore designed this study to evaluate the post-transplant screening rates for colorectal, breast, and cervical cancer among SOTR in Ontario, Canada, and identify factors associated with screening.

Methods

The Research Ethics Board of St. Michael's Hospital, Toronto, Canada approved the protocol for this study (11-235).

Data Sources

Our SOTR cohort was assembled using the Canadian Organ Replacement Register (CORR) housed at the Canadian Institute for Health Information. CORR is a national registry that contains information on virtually all Canadian patients who have undergone solid organ transplantation since 1981 (21). Uptake of cancer screening services was captured using the Ontario Health Insurance Plan (OHIP) database. The OHIP database captures all physician, laboratory, and radiology services provided to Ontario residents since July 1991. Uptake of mammography was augmented with data from the Ontario Breast Screening Program (OBSP) database, including all services related to the provincial breast screening program. Health insurance eligibility and mortality information were obtained from the Registered Persons Database (RPDB). RPDB is a roster of all individuals eligible for OHIP including permanent residents and refugees, which contains vital status information and location of residence. Cancer diagnosis was determined through linkage to the Ontario Cancer Registry (OCR). This registry contains information on all incident cancers since 1964 in Ontario and has been estimated to be over 95% complete (22). Lastly, the ICES Physician Database (IPDB), was used to obtain information about physician demographics, specialty training and practice location in Ontario. All data sources were deterministically linked using encrypted unique direct patient identifiers that allow for longitudinal tracking of patients across all data sources. Direct personal identifiers were removed and a unique identifier was applied using an algorithm. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES), Toronto, Canada.

Study Subjects and Screening Cohorts

All Ontario residents 18 years old and older transplanted for kidney, liver, lung or heart from January 1, 1997 through December 31, 2010 were included (n=7,994). Patients were excluded if they died (n=340) or developed a malignancy (n=173) within a year after transplantation, or had a history of malignancy pre-transplantation (n=793). Additionally, recipients who were not eligible for health insurance for more than three months were excluded (n=296). Women who underwent hysterectomy prior to transplantation were also excluded from the cervical screening cohort. The breast screening cohort included women age 50 to 74, the cervical screening cohort included women age 21 to 69, and the colorectal cancer screening cohort included all recipients age 50 to 74.

Outcome

First, we evaluated the rate of cervical, breast, and colorectal cancer screening among all eligible SOTR. Using the OHIP database, we identified SOTR who underwent a colonoscopy, flexible sigmoidoscopy, fecal occult blood test (FOBT), Pap test, and mammography between January 1, 2000 and December 31, 2013 using billing codes (Appendix 1). Cancer screening test were identified starting in January 1, 2000 due to availability of test-specific procedure codes in OHIP and establishment of screening programs in Ontario. However, the OHIP billing codes do not distinguish between screening and diagnosis tests. To minimize the inclusion of diagnostic and surveillance test, patients with prior history of malignancy were excluded, as previously indicated. The main outcome was the rate of SOTR being up-to-date with cancer screening consistent with Ontario guidelines for cancer screening. Cancer screening-specific time frames started when transplant recipients became age-eligible for screening or on the date of the cancer screening-specific event (if any). Female recipients were considered up-to-date with breast and cervical cancer screening if they received a mammography within 2 years and a Pap test within 3 years, respectively. Transplant recipients were considered up-to-date with colorectal cancer screening if they received a FOBT within 2 years, a flexible sigmoidoscopy within 5 years, or colonoscopy within 10 years. For SOTR who were not adherent with screening at some point during follow up, we looked for factors associated with the rate of becoming up to date with screening, by the type of screening.

Covariates

Transplant recipients' characteristics included age, sex, neighborhood income quintile, and rural residence. Median annual income by neighborhood was determined by using the 2001

or 2006 census data (closest to the index procedure date), which was linked to postal forward sortation areas and categorized into community-specific quintiles within census regions. We used city, postal code, and dissemination area of patient residence to assign rural residence (defined as population < 10,000). The Charlson comorbidity score (CCS) was computed for each patient and categorized as no hospitalization, 0, 1, 2, 3, or ≥4. (23) Comorbid conditions were evaluated based on ICD-9 codes for those with hospital discharges within 2 years of the index date.(24) There are six adult transplant centers in the province and each was included as a covariate in the models.

We identified outpatient visits by SOTR with a primary care provider (PCP) or transplant specialist in the year before their transplant and each year following transplant. Information on PCP and specialty training was obtained from the ICES Physician Database. Outpatient visits to PCPs were determined by general assessment OHIP fee codes claimed by general practitioners/family physicians (Appendix 1). Patients were considered to have continuity of care provided by a PCP if they had more than 3 visits to the same PCP within the prior 2-year period. Visits to a transplant specialist were identified using billing codes claimed by a cardiologist for heart transplant recipients, a respirologist for lung transplant recipients, a gastroenterologist or internist for liver transplant recipients, and a nephrologist for kidney transplant recipients (Appendix 1). As the specialty code for nephrologists was not introduced to OHIP until 2009, we identified nephrologists using a pre-defined algorithm of billing codes for a nephrologist consult and dialysis (Appendix 1)(25). Visits to a transplant specialist were further categorized as happening at the original transplant centre using the institution codes associated with the OHIP billing codes.

Statistical Analysis

The χ^2 Cochran-Armitage linear trend test was used to assess for time trends in the rates of cancer screening, visits to a PCP, and visits to a transplant specialist.(26) Transplant recipients could be eligible to receive cancer screening multiple times during the observation window. Therefore, we modeled the association between covariates and the rate of becoming up-to-date with cancer screening using an Andersen-Gill(27) recurrent event regression model under a counting process framework.(28) Interval start time was defined for each SOTR on the day when the patient was not up-to-date with screening (meaning they were due for screening) and interval end time was defined when the screening test occurred, or when the patient was censored.

Patients were followed from the date of transplantation until the development of a post-transplant *de novo* malignancy, end of screening eligibility, graft/organ failure, loss of health insurance eligibility, death, or March 31, 2013. For cervical cancer screening, patients were censored at the time of first colposcopy. This provided a minimum of 27 months of follow-up for all cohort members. The concept of discontinuous risk intervals were used to account for the fact that a patient is only "at risk" of becoming up-to-date once they are not-up-date. A patient who is always up-to-date will, by definition, never contribute any "at risk" intervals to this analysis. We used the Breslow approach to account for ties. To address correlation among screening events from the same patient, robust standard errors of the model parameter estimates were calculated using a sandwich approach[4].

The covariates included in the model were selected *a priori*. Neighborhood income quintiles, CCS [no hospitalizations, 0, 1, 2, 3, 4 or more], and visits to PCP and transplant specialists [treated as a dichotomous variable] were incorporated into the recurrent event model as time-varying covariates. That is, for each patient, at any given time t, these covariates reflected the exposure in the prior year. The statistical and clinical literature offer several examples on the implementation of such time-varying covariates in a recurrent event model.(28-34) The multivariable model also adjusted for baseline/time-fixed characteristics at transplantation (age [treated as a continuous variable], sex, transplant year, transplanted organ [kidney, liver, heart, and lung], transplant center [center 1-6], rural vs urban residence, and pre-transplant continuity of care (within one year prior to transplantation) provided by a PCP [treated as a dichotomous variable]). A sensitivity analysis was performed by increasing the screening windows by 6 months for all screening modalities. An additional recurrent event model was created incorporating visits to a transplant specialist at their transplant center [as time-varying dichotomous variable] instead of visits to any transplant specialist to explore the effect of follow-up at their transplant center on becoming up-to-date with screening. All tests were 2-sided with a P value of less than 0.05 considered statistically significant. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

We identified 6,392 SOTR who met our inclusion criteria (Figure 1): 4,436 eligible for colorectal cancer screening, 2,252 eligible for cervical cancer screening, and 1,551 eligible for breast cancer screening. Of those, 3,436 (77.5%), 1,572 (69.8%), and 1,417 (91.4%) were not

continuously adherent to recommended colorectal, cervical, and breast cancer screening, respectively and were included in the multivariable analysis examining factors associated with becoming screen up-to-date. Notably, a sizable proportion of eligible SOTR had no screening during their observation period: 1,595 (35.9%), 769 (34.1%), and 477 (30.7%) had no screening for colorectal, cervical, and breast cancer screening, respectively.

The proportion of screening up-to-date recipients increased over time from transplantation for breast ($p<0.001$), cervical ($p<0.001$), and colorectal ($P<0.001$) screening (Figure 2). Among the SOTR eligible for breast cancer screening, only 36% had a screening mammography during the first year after transplantation. By year 15 after transplantation, 51% of SOTR were up-to-date with breast cancer screening. Similarly, the proportion of SOTR up-to-date with colorectal screening ranged from 35% during the first year after transplantation to 53% at 15 years after transplantation. The proportion of SOTR up-to-date with cervical cancer screening varied, with 51% and 61% of SOTR up-to-date with screening at post-transplant year 1 and 15, respectively. The characteristics of the screening-eligible transplant recipients are presented in Table 1 for the overall cohort, for those always up-to-date (not included in the multivariate analysis), and for those with non-up-to-date periods (included in the multivariate analysis).

The rates of visits to a PCP and transplant specialist by years after transplantation are shown in Figure 3. One fifth of transplant recipients did not have a general assessment visit to a PCP during the first-year post-transplant, and the rates of these visits decreased over time (80% at 1 year vs. 67% at 15 years, $p<0.001$). Although most recipients had a visit with a transplant specialist in the first-year post-transplantation (96%), the involvement of transplant specialists also decreased over time (70% at 15 years, $p<0.001$). Most visits to a transplant specialist occurred at their transplant center (93.0%) during the first-year post-transplant. However, it ranged from 77.7% at 2 years after transplantation to 79.1% at 15 years after transplantation (Supplementary Figure 1)

Our multivariable analyses related to becoming up-to-date with screening are presented in Figure 4. Higher CCS was associated with lower rates of becoming up-to-date with screening. Compared to patients with no hospitalizations in the prior year, recipients with CCS ≥ 4 had lower rates of being up-to-date with breast (RR 0.69 [95% CI: 0.52-0.91]), cervical (RR 0.62 [95% CI: 0.46-0.84]), and colorectal cancer screening (RR 0.82 [95% CI: 0.68-0.97]).

Assessment by a PCP in the prior year was associated with higher rates of being up-to-date with breast (RR 1.40 [95% CI: 1.12-1.76]), cervical (RR 1.29 [95% CI: 1.06-1.57]), and colorectal cancer (RR 1.30 [95% CI: 1.15-1.48]) screening. In contrast, a visit to a transplant specialist in the prior year was not associated with being up-to-date with screening (breast RR 0.92 [95% CI: 0.70-1.21], cervical RR 0.92 [95% CI: 0.68-1.25], and colorectal cancer RR 1.16 [95% CI: 0.96-1.41]). When restricting visits to a transplant specialist to those at their transplant center (Supplementary Figure 2), recipients with a visit to a transplant specialist at their transplant center were more likely to become up to date with breast (RR 1.36 [95% CI: 1.09-1.70]) and colorectal (RR 1.19 [95% CI: 1.01-1.35). Similar results were observed for cervical cancer screening (RR: 1.21 [95% CI: 0.99-1.47), although this was not statistically significant.

Males were less likely to become up-to-date with colorectal cancer screening than women (RR: 0.86 [95% CI: 0.78-0.95]). Compared to kidney transplant recipients, liver recipients had lower rates of becoming up-to-date with breast cancer screening (RR 0.72 [95% CI: 0.59-0.93]), and in the case of colorectal cancer screening, liver and lung transplant recipients had higher rates of becoming up-to-date than kidney transplant recipients (liver RR: 1.60 [95% CI: 1.37-1.86], lung RR: 1.25 [95% CI: 1.02-1.53]). No differences in the risk of becoming up-to-date with cervical cancer screening existed by transplanted organ. The findings multivariable recurrent event models were not altered when increasing the screening intervals by six months for each screening modality (Supplementary Figure 3).

Discussion

This study is the first to evaluate cancer screening in a population-based cohort of SOTR. Cancer screening uptake in our cohort was low; most SOTR had periods when they were non-adherent to screening recommendations during follow up. In fact, many recipients were never screened. Transplant recipients with more comorbidities had lower rates of becoming screen up-to-date, possibly because of a presumed reduced life-expectancy. Visits to a PCP but not a transplant specialist were associated with patients becoming up-to-date with all types of cancer screening. However, one fifth of the recipients did not have an assessment visit to a PCP during the first year after transplantation, and the rate decreased over time. SOTR who had a visit to a transplant specialist at their transplant centre were more likely to become up-to-date with cancer screening.

There are few prior estimates of post-transplant cancer screening uptake in the SOTR population. A population-based study explored the use of screening mammography in 17,090 women aged 50 years or older who started dialysis in 1997, using the US Renal Data System.(35) This study found a 25% rate of biennial screening mammography in this population. However, women who were on the transplant list had higher screening rates (69%)(35). Similar patterns were observed in a population-based cohort of women with chronic kidney disease in Ontario between 2002 – 2013 (36). The incidence of breast cancer screening was 26% for women on dialysis and similar rates were observed for cervical cancer screening (36). These findings are in sharp contrast to the rates of post-transplant breast cancer screening observed in our population, which was never higher than 50% of age-eligible women. A population-based study assessed the uptake of cervical cancer screening by kidney transplant recipients over a 10-year period in Northern Ireland and reported that only 10% of these patients had the recommended number of screening procedures.(37) In contrast, the rates of post-transplant cervical cancer screening observed in our population were never lower than 51%.

Evidence of the efficacy of cancer screening in SOTR is limited; randomized controlled screening trials have not been performed in this population and are unlikely to be undertaken because of major feasibility issues.(17) Extrapolation from the general population and decision-analysis studies provide the best guidance to formulate recommendations. Modeling studies have demonstrated that screening for breast, colorectal, and cervical cancer following the recommendations for the general population would be cost-effective in the kidney transplant population.(38, 39) Although such studies have not been conducted in other SOTR populations, similar recommendations are included in clinical practice guidelines for post-transplant care of these recipients. It is important to note that recipients with a decreased life expectancy (less than 5 to 10 years), such as those with many comorbidities or with failing transplants, are unlikely to benefit from screening.(15, 38, 39)

Rates of individuals up-to-date with cancer screening were lower in SOTR compared to those reported for the general Ontario population. In a population-based cohort study of patients identified as screen-eligible in 2009 living in Ontario, Canada, the screening prevalence was 61.6% (95% CI: 61.4 – 61.9) for FOBT or endoscopy, 63.4% (95% CI: 63.2 – 63.7) for pap smears, and 59.9 (95% CI: 59.6 – 60.0) for mammogram (40). The rates of being up-to-date for SOTR varied with time since transplantation, however at no point were the rates in this group as

high as that reported in the general population of Ontario during this time period (40). Although there is evidence that cancer screening rates are reduced in patients with other chronic diseases (e.g. patients with obesity and diabetes)(41), the screening uptake in SOTR is lower than that observed in these populations (42-44). Chan *et al*. reported that between 1999 and 2010 only 60.3% of eligible women with diabetes in Ontario had a screening mammography compared to 65.8% of women without diabetes (44). In contrast, the highest rate of eligible SOTR up-to-date with breast cancer screening was 51% at year 15 after transplantation.

Most SOTR in our cohort were followed regularly at their transplant centre. Although approximately 15% were transferred to the care of transplant specialist not at their transplant center during the first year of transplantation, the proportion of SOTR seen at their transplant centre by a transplant specialist remained stable during the duration of the cohort follow-up. Visits to a transplant specialist at their transplant center were associated with becoming up-to-date with cancer screening. This finding highlights the importance of continuity of care, both with PCP and transplant specialist, for the uptake of cancer screening in SOTR. Coordination of transfer of care between transplant specialist during the first year after transplantation and involvement of PCP are strategies that could improve the uptake of cancer screening.

Screening for malignancies in SOTR is generally considered to be a component of primary care. A survey of liver units in the US indicated that hepatologist believe PCP should be involved in the management of non-liver-related transplant complications.(45, 46) Most respondents to the survey stated that responsibility for the over-all care of patients beyond 1 year after transplantation predominantly belonged to PCP. However, the survey also reported that the majority of hepatologists felt that the involvement of PCP occurred infrequently and only 35.8% were satisfied with the PCPs' level of involvement.(45) The American Transplant Society has developed guidelines for the long-term management of the liver transplant recipients directed to PCP. These guidelines recommend that the screening for most malignancies in transplant recipients should be performed at the appropriate sex, age and frequency as per the American Cancer Society guidelines for the general population.(20) However, it is likely that PCP are unaware of guidelines issued by transplant organizations. Our results indicated that visits to a PCP were associated with a higher rate of becoming up-to-date with screening. Visits to a PCP have been previously associated with the uptake of cancer screening, especially in the elderly.(47, 48) Therefore, it is important to increase the involvement of PCP in post-transplant

care and increase their awareness of the recommendations for cancer screening in this population.

The major strengths of this study are its population-based nature and the completeness of the billing claims for the use of screening tests since Ontario is a single payer system. In addition, our analytical approach was well suited to explore factors associated with screening events as these have discontinuous risk intervals, and it represents a novel approach to the study of factors associated with repeated screening events. Moreover, although the Andersen-Gill recurrent event model requires forming complex data structures, it easily allows for the incorporation of time-dependent variables.

It is important to note that using the billing codes for screening test from the OHIP database has some limitations, including the inability to differentiate between tests done for screening or for diagnosis. Thus, we have likely overestimated the rate of screening in this population. Although strict screening intervals were employed in this analysis to define patients being up-to-date, a sensitivity analysis increasing the screening interval by six months did not alter our findings. Another limitation of this study is the difficulty disentangling the role of transplant specialists vs. PCP. Transplant specialists may have prompted patients to request cancer screening from their PCP but this could not be inferred from the data since the screening event occurred after the PCP visit at which the patient made the request. Transplant specialists counsel patients routinely to request cancer screening as per general population guidelines from their PCP. In addition, it is possible that covariate selection and model misspecification might lead to residual confounding. Lastly, although our findings generalizability to other countries is potentially limited, lower screening uptake could be expected in health care systems without universal access.

In conclusion, cancer screening of SOTR in Ontario is low. Assessment by a PCP was associated with a higher rate of SOTR becoming up-to-date with cancer screening. Continuity of care, both for PCP and transplant programs, are associated with the uptake of cancer screening in SOTR. Increasing knowledge of cancer screening among PCP and their involvement in post-transplant care could improve the uptake of the cancer screening recommendations. Moreover, enhancing communication between PCP and transplant specialist may help improve cancer screening. A framework to guide individualized cancer screening decisions in SOTR is needed.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure Legends

Figure 1: Cohort selection and solid organ transplant recipient's eligibility.

Figure 2: Cancer screening up-to-date recipients per all eligible SOTR for cancer screening by year since transplantation. SOTR, solid organ transplant recipients.

Figure 3: Post-transplant assessment visits to primary care physicians and visits to transplant specialists by year since transplantation for all patients eligible for cancer screening.

Figure 4: Multivariable recurrent event analysis for recipients not up-to-date with cancer screening.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1: Post-transplant visits to a transplant specialist and a transplant specialist at their transplant center by year since transplantation for all patients eligible for cancer screening.

Figure S2: Multivariable recurrent event analysis for recipients not up-to-date with cancer screening including visit to a transplant specialist at their transplant center.

Figure S3: Sensitivity analysis extending screening windows by 6 months – Multivariable recurrent event analysis for recipients not up-to-date with cancer screening.

Appendix 1: OHIP Fee codes

References

1. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M et al. Cancer incidence before and after kidney transplantation. JAMA : the journal of the American Medical Association 2006;296(23):2823-2831.
2. Adami J, Gabel H, Lindelof B, Ekstrom K, Rydh B, Glimelius B et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. British journal of cancer 2003;89(7):1221-1227.
3. Vajdic CM, McCaughan GW, Grulich AE. Cancer risk after organ transplantation. JAMA : the journal of the American Medical Association 2012;307(7):663; author reply 663-664.
4. Acuna SA, Fernandes KA, Daly C, et al. Cancer Mortality Among Recipients of Solid-Organ Transplantation in Ontario, Canada. JAMA Oncology 2016:1-8.
5. Na R, Grulich AE, Meagher NS, McCaughan GW, Keogh AM, Vajdic CM. De novo cancer-related death in Australian liver and cardiothoracic transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2013;13(5):1296-1304.
6. Farrugia D, Mahboob S, Cheshire J, Begaj I, Khosla S, Ray D et al. Malignancy-related mortality following kidney transplantation is common. Kidney international 2013.

7. Kiberd BA, Rose C, Gill JS. Cancer mortality in kidney transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009;9(8):1868-1875.
8. Papaconstantinou HT, Sklow B, Hanaway MJ, Gross TG, Beebe TM, Trofe J et al. Characteristics and survival patterns of solid organ transplant patients developing de novo colon and rectal cancer. Diseases of the colon and rectum 2004;47(11):1898-1903.
9. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Critical reviews in oncology/hematology 2005;56(1):155-167.
10. Ajithkumar TV, Parkinson CA, Butler A, Hatcher HM. Management of solid tumours in organ-transplant recipients. The lancet oncology 2007;8(10):921-932.
11. Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: what is the evidence? Clinical journal of the American Society of Nephrology : CJASN 2008;3 Suppl 2:S87-S100.
12. Wong G, Li MW, Howard K, Hua DK, Chapman JR, Bourke M et al. Health benefits and costs of screening for colorectal cancer in people on dialysis or who have received a kidney transplant. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2013;28(4):917-926.
13. Spier BJ, Walker AJ, Cornett DD, Pfau PR, Halberg RB, Said A. Screening colonoscopy and detection of neoplasia in asymptomatic, average-risk, solid organ transplant recipients: case-control study. Transplant international : official journal of the European Society for Organ Transplantation 2010;23(12):1233-1238.
14. Collins MG, Teo E, Cole SR, Chan CY, McDonald SP, Russ GR et al. Screening for colorectal cancer and advanced colorectal neoplasia in kidney transplant recipients: cross sectional prevalence and diagnostic accuracy study of faecal immunochemical testing for haemoglobin and colonoscopy. Bmj 2012;345:e4657.
15. Kiberd BA, Keough-Ryan T, Clase CM. Screening for prostate, breast and colorectal cancer in renal transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2003;3(5):619-625.

16. Knoll GA, Blydt-Hansen TD, Campbell P, Cantarovich M, Cole E, Fairhead T et al. Canadian Society of Transplantation and Canadian Society of Nephrology commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. American journal of kidney diseases : the official journal of the National Kidney Foundation 2010;56(2):219-246.
17. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009;9 Suppl 3:S1-155.
18. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2010;29(8):914-956.
19. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2013;19(1):3-26.
20. McGuire BM, Rosenthal P, Brown CC, Busch AM, Calcatera SM, Claria RS et al. Long-term management of the liver transplant patient: recommendations for the primary care doctor. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009;9(9):1988-2003.
21. Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2001 to 2010 Ottawa, Ont.: Canadian Institute for Health Information; 2011.
22. McLaughlin JR, Kreiger N, Marrett LD, Holowaty EJ. Cancer incidence registration and trends in Ontario. European journal of cancer 1991;27(11):1520-1524.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 1987;40(5):373-383.

24. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of clinical epidemiology 1992;45(6):613-619.
25. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA : the journal of the American Medical Association 2009;302(11):1179-1185.
26. Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 1955;11(3):375-386.
27. Andersen PK, Gill RD. Cox's Regression Model for Counting Processes: A Large Sample Study. 1982:1100-1120.
28. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer, 2000.
29. Arneson TJ, Liu J, Qiu Y, Gilbertson DT, Foley RN, Collins AJ. Hospital treatment for fluid overload in the Medicare hemodialysis population. Clinical journal of the American Society of Nephrology : CJASN 2010;5(6):1054-1063.
30. Guo Z, Gill TM, Allore HG. Modeling repeated time-to-event health conditions with discontinuous risk intervals. An example of a longitudinal study of functional disability among older persons. Methods of information in medicine 2008;47(2):107-116.
31. Cook RJ, Lawless JF. Analysis of repeated events. Statistical methods in medical research 2002;11(2):141-166.
32. Twisk JW, Smidt N, de Vente W. Applied analysis of recurrent events: a practical overview. Journal of epidemiology and community health 2005;59(8):706-710.
33. Sorup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. JAMA : the journal of the American Medical Association 2014;311(8):826-835.
34. Barbera L, Sutradhar R, Howell D, Sussman J, Seow H, Dudgeon D et al. Does routine symptom screening with ESAS decrease ED visits in breast cancer patients undergoing adjuvant chemotherapy? Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2015.

35. Walter LC, Lindquist K, O'Hare AM, Johansen KL. Targeting screening mammography according to life expectancy among women undergoing dialysis. Archives of internal medicine 2006;166(11):1203-1208.
36. Wong G, Hayward JS, McArthur E, Craig JC, Nash DM, Dixon SN et al. Patterns and predictors of screening for breast and cervical cancer in women with CKD. Clinical Journal of the American Society of Nephrology 2017;12(1):95-104.
37. Courtney AE, Leonard N, O'Neill CJ, McNamee PT, Maxwell AP. The uptake of cervical cancer screening by renal transplant recipients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2009;24(2):647-652.
38. Wong G, Howard K, Craig JC, Chapman JR. Cost-effectiveness of colorectal cancer screening in renal transplant recipients. Transplantation 2008;85(4):532-541.
39. Wong G, Howard K, Webster A, Chapman JR, Craig JC. The health and economic impact of cervical cancer screening and human papillomavirus vaccination in kidney transplant recipients. Transplantation 2009;87(7):1078-1091.
40. Borkhoff CM, Saskin R, Rabeneck L, Baxter NN, Liu Y, Tinmouth J et al. Disparities in receipt of screening tests for cancer, diabetes and high cholesterol in Ontario, Canada: a population-based study using area-based methods. Can J Public Health 2013;104(4):e284-e290.
41. Fontana SA, Baumann LC, Helberg C, Love RR. The delivery of preventive services in primary care practices according to chronic disease status. American Journal of Public Health 1997;87(7):1190-1196.
42. Zhao G, Ford ES, Ahluwalia IB, Li C, Mokdad AH. Prevalence and trends of receipt of cancer screenings among US women with diagnosed diabetes. Journal of general internal medicine 2009;24(2):270-275.
43. Ferrante JM, Ohman-Strickland P, Hudson SV, Hahn KA, Scott JG, Crabtree BF. Colorectal cancer screening among obese versus non-obese patients in primary care practices. Cancer detection and prevention 2006;30(5):459-465.
44. Chan W, Yun L, Austin P, Jaakkimainen R, Booth G, Hux J et al. Impact of socio-economic status on breast cancer screening in women with diabetes: a population-based study. Diabetic Medicine 2014;31(7):806-812.

45. Heller JC, Prochazka AV, Everson GT, Forman LM. Long-term management after liver transplantation: primary care physician versus hepatologist. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2009;15(10):1330-1335.
46. Wagoner LE. Management of the cardiac transplant recipient: roles of the transplant cardiologist and primary care physician. The American journal of the medical sciences 1997;314(3):173-184.
47. Finkelstein MM. Preventive screening. What factors influence testing? Canadian Family Physician 2002;48(9):1494-1501.
48. Sutradhar R, Gu S, Glazier R, Paszat L. The association between visiting a primary care provider and uptake of periodic mammograms as women get older. Journal of Medical Screening 2015.

Appendix 1. OHIP Fee codes

For cancer screening test

Screening	Type	Fee code	Description
Colorectal	Fecal Occult Blood Test (FOBT)	L181	Laboratory Medicine - Biochemistry - Occult Blood
		L179	Tracking Code - Colon Cancer Check
		G004	D./T. Proc - Laboratory Medicine - Occult Blood
	Flexible sigmoidoscopy	Z580	Intestine - Endoscopy - Using 60 C.M. Flexible Endoscope
	Colonoscopy	Z496	Presence of Signs or Symptoms - Sigmoid to Descending Colon
		Z497	Confirmatory Colonoscopy - Sigmoid to Descending Colon
		Z498	Surveillance Colonoscopy - Sigmoid to Descending Colon
		Z499	Colonoscopy - Absence of Signs or Symptoms, Family History of Colon Cancer in a First Degree Relative - Sigmoid to Descending Colon
		Z555	Intestines - Endoscopy - Colonoscopy into Descending Colon
Breast	Mammography	X185	Diagnostic Radiology - Mammogram - Bilateral
		X178	Mammogram - No Signs or Symptoms - Bilateral
Cervical	PAP test	G365	D./T. Proc. - Gynaecology - Papanicolaou Smear
		G394	Additional Pap Smear for Follow-up of Abnormal or Inadequate Smears
		L812	Laboratory Medicine - Cytology - Cervicovaginal Specimen
		E430	D./T. Proc - Pap Smear Performed Outside of Hospital
		L713	Laboratory Medicine - ANAT, PATH, HIST, CYT-Cytol-Gynaecological Specimen

Used to identify nephrologist

Type	**Fee code**	**Description**
Nephrology	A135	Consult. - Internal Medicine
	A161	Nephrology - Complex Medical Specific Re-assessment
	A163	Nephrology - Medical Specific Assessment
	A164	Nephrology - Medical Specific Re-assessment
	A165	Nephrology - Consultation
	A166	Nephrology - Repeat Consultation

	A168	Nephrology - Partial Assessment
	C101	Visits to I.C.U/C.C.U (Extra)
	C138	Concurrent Care - Internal Medicine - Hospital
	G860	Hospital Hemodialysis
	G323	D./T. Proc. - Dialysis - Haemodialysis - Acute, Repeat
	G333	Home/Self-care dialysis
	E083	Subsequent visits MRP to Subsequent visits, C122/C123/C124/C142 OR C143
	C132	Subsequent visits up to 5 Weeks - Internal Medicine - Hospital
	C135	Consultation - Internal Medicine - Hospital
	C137	Subsequent visit from 6th to 13th Week Including Internal Medicine - Hospital
	C139	Subsequent visit after 13th week - Internal Medicine - Hospital
	H540	Renal Dialysis (Output)
Dialysis	R849	D./T. Proc. - Dialysis - Hemodialysis - Initial and Acute
	G323	D./T. Proc. - Dialysis - Hemodialysis - Acute, Repeat
	G325	D./T. Proc. - Dialysis - Haemodialysis - Medical Componenet
	G326	Dialysis - Chronic, continuing Haemodialysis or Haemofiltration Each
	G860	Hospital Hemodialysis
	G862	Hospital Self Care or Satellite Hemodialysis
	G863	Independent Health Care Facility Hemodialysis
	G865	Home Hemodialysis
	G866	Intermittent Hemodial Auxillary Treat Centre (Per Treat)
	G330	D./T. Proc. - Dialysis - Peritoneal - Acute (Up to 48 Hours)
	G331	D./T. Proc. - Dialysis - Peritoneal - Repeat Acute (Up to 48 Hours)
	G332	Peritoneal dialysis - Chronic
	G861	Hospital Peritoneal Dialysis
	G864	Home Peritoneal Dialysis

Used to identify general assessment visits by general practitioners/family physicians

Fee code	Description
K131	Periodic health visit – adult age 18 to 64 inclusive
K132	Periodic health visit – adult 65 years of age and older

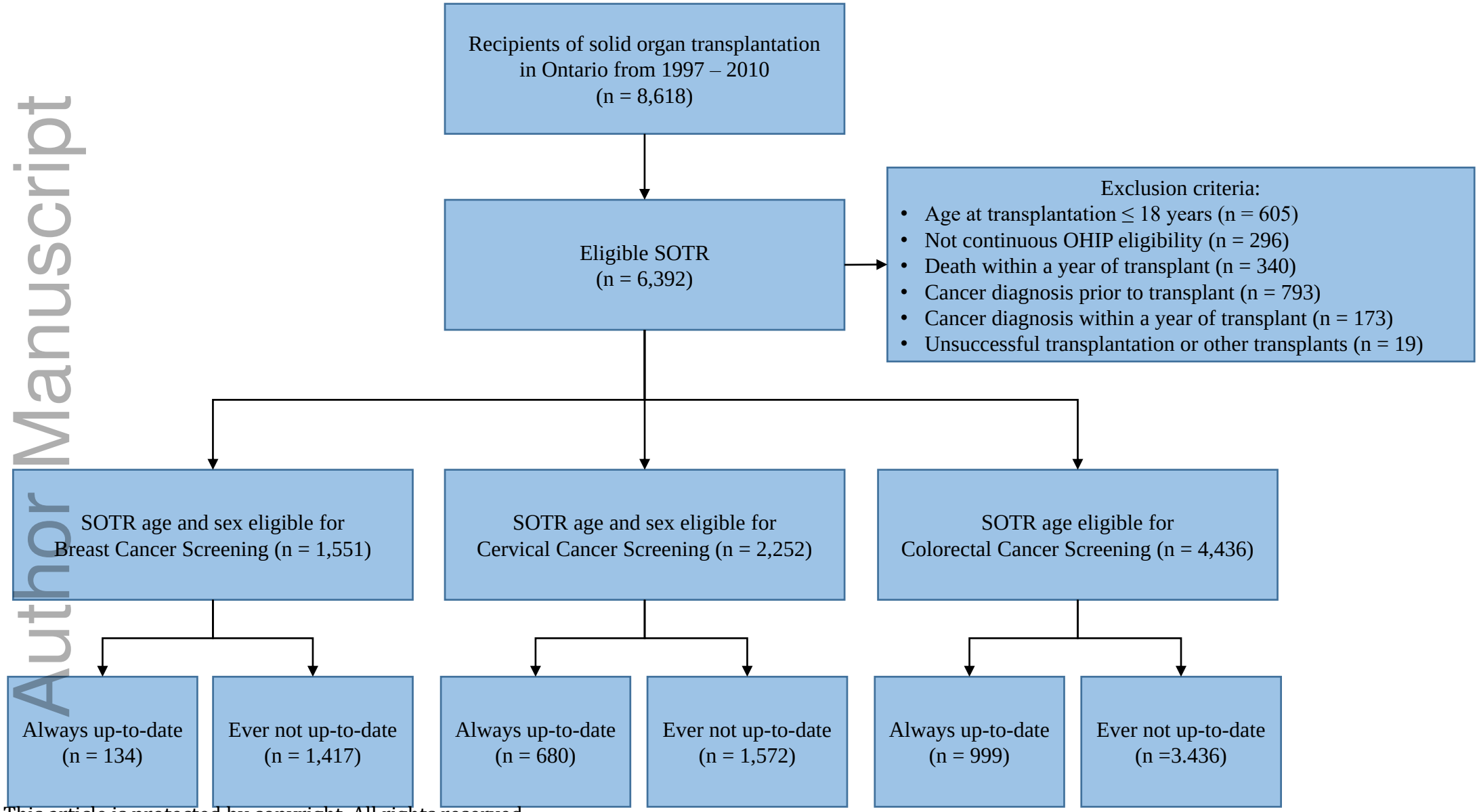
A003	General assessment
A004	General re-assessment
A005	Consultation
A007	Intermediate assessment
A903	Pre-dental/pre-operative general assessment

Table 1. Baseline characteristic of solid organ transplant recipients eligible for breast or cervical cancer screening

Characteristics	Breast Cancer Screening Eligible			Cervical Cancer Screening Eligible			Colorectal Cancer Screening Eligible		
	All (N=1,551)	Always up-to-date (N=134)	Ever not up-to-date (N=1,417)	All (N=2,252)	Always up-to-date (N=680)	Ever not up-to-date (N=1,572)	All (N=4,436)	Always up-to-date (N=999)	Ever not up-to-date (N=3,437)
Age at transplant, median (IQR)	54 (48-61)	59 (55-65)	54 (48-60)	48 (38-57)	47 (38-55)	49 (38-58)	55 (49-61)	60 (55-65)	53 (48-60)
Female, n (%)	1,551 (100)	134 (100)	1,417 (100)	2,252 (100)	680 (100)	1,572 (100)	1,551 (35.0)	327 (32.7)	1,224 (35.6)
Transplant organ, n (%)									
Kidney	1,041 (67.1)	96 (71.6)	945 (90.8)	1,529 (67.9)	490 (72.1)	1,039 (66.1)	2,909 (65.6)	546 (54.6)	2,363 (68.8)
Liver	314 (20.2)	23 (17.2)	291 (20.5)	415 (18.4)	103 (15.1)	312 (19.8)	865 (19.5)	349 (34.9)	516 (15.0)
Heart	70 (4.5)	≤5	>65	107 (4.8)	28 (4.1)	79 (5.0)	344 (7.8)	54 (5.4)	290 (8.4)
Lung	126 (8.1)	12 (9.0)	114 (8.0)	201 (8.9)	54 (26.9)	147 (73.1)	318 (7.2)	50 (5.1)	268 (7.8)
Income quintile, n (%)									
1 (lowest)	304 (19.6)	27 (20.1)	277 (19.5)	477 (21.2)	119 (17.5)	358 (22.8)	836 (18.8)	176 (17.6)	660 (19.2)
2	309 (19.9)	24 (17.9)	285 (20.1)	440 (19.5)	136 (20.0)	304 (19.3)	912 (20.6)	207 (20.7)	705 (20.5)
3	300 (19.3)	22 (16.4)	278 (19.6)	452 (20.1)	133 (19.6)	319 (20.3)	866 (19.5)	192 (19.2)	674 (19.6)
4	325 (21.0)	28 (20.9)	297 (21.0)	448 (19.9)	129 (19.0)	319 (20.3)	901 (20.3)	191 (19.1)	710 (20.7)
5 (highest)	307 (19.8)	33 (24.6)	274 (19.3)	428 (19.0)	163 (24.0)	265 (16.9)	903 (20.4)	230 (23.0)	673 (19.6)
Missing	6 (0.4)	0 (0.0)	6 (0.4)	7 (0.3)	0 (0.0)	7 (0.40)	18 (0.4)	≤5	>10
Rural residence, n (%)									
Rural	152 (9.8)	13 (9.7)	139 (9.8)	225 (10.0)	62 (9.1)	163 (10.4)	559 (12.6)	125 (12.5)	434 (12.6)
Urban	1,399 (90.2)	121 (90.3)	1,278 (90.2)	2,027 (90.0)	618 (90.9)	1,409 (89.6)	3,877 (87.4)	874 (87.5)	3,003 (87.4)
Year of transplant, n (%)									
1997 – 2001	479 (30.9)	18 (13.4)	461 (32.6)	727 (32.3)	161 (23.7)	566 (36.0)	1,357 (30.5)	141 (14.1)	1,216 (35.4)
2002 – 2006	553 (35.6)	37 (27.6)	516 (36.4)	781 (34.6)	234 (34.4)	547 (34.8)	1,577 (35.5)	315 (31.5)	1,262 (36.6)
2007 – 2010	519 (33.5)	79 (59.0)	440 (31.1)	744 (33.0)	285 (41.9)	459 (29.2)	1,502 (33.8)	543 (54.3)	959 (27.9)
Charlson Score, n (%)									
No hospitalizations	336 (21.7)	25 (18.7)	311 (21.9)	421 (18.7)	139 (20.4)	282 (17.9)	959 (21.6)	180 (18.0)	779 (22.7)
0	56 (3.6)	6 (4.5)	50 (3.5)	92 (4.1)	32 (4.7)	60 (3.8)	145 (3.3)	25 (2.5)	120 (3.5)
1	128 (8.3)	11 (8.2)	117 (8.3)	200 (8.9)	57 (8.4)	143 (9.1)	325 (7.3)	67 (6.7)	258 (7.5)
2	492 (31.7)	61 (45.5)	431 (30.4)	771 (34.2)	264 (38.8)	507 (32.3)	1,317 (29.7)	240 (24.0)	1,077 (31.3)

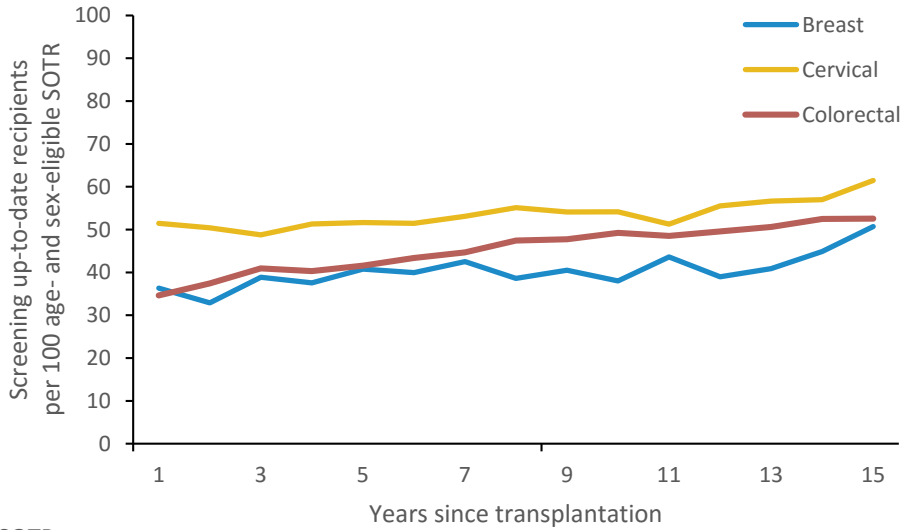
3	264	(17.0)	15	(11.2)	249	(17.6)	382	(17.0)	95	(14.0)	287	(18.3)	745	(16.8)	193	(19.3)	552	(16.1)
4+	275	(17.7)	16	(11.9)	259	(18.3)	386	(17.1)	93	(13.7)	282	(17.9)	945	(21.3)	294	(29.4)	651	(18.9)
Pre-transplant continuous care provided by a PCP	1,464	(94.6)	127	(94.8)	1,337	(94.4)	2,131	(94.6)	663	(97.5)	1,468	(93.1)	4,135	(93.2)	954	(95.5)	3,181	(92.6)

Figure 1. Cohort selection and solid organ transplant recipient's eligibility



Abbreviations: SOTR: Solid Organ Transplant Recipient | OHIP: Ontario Health Insurance Program

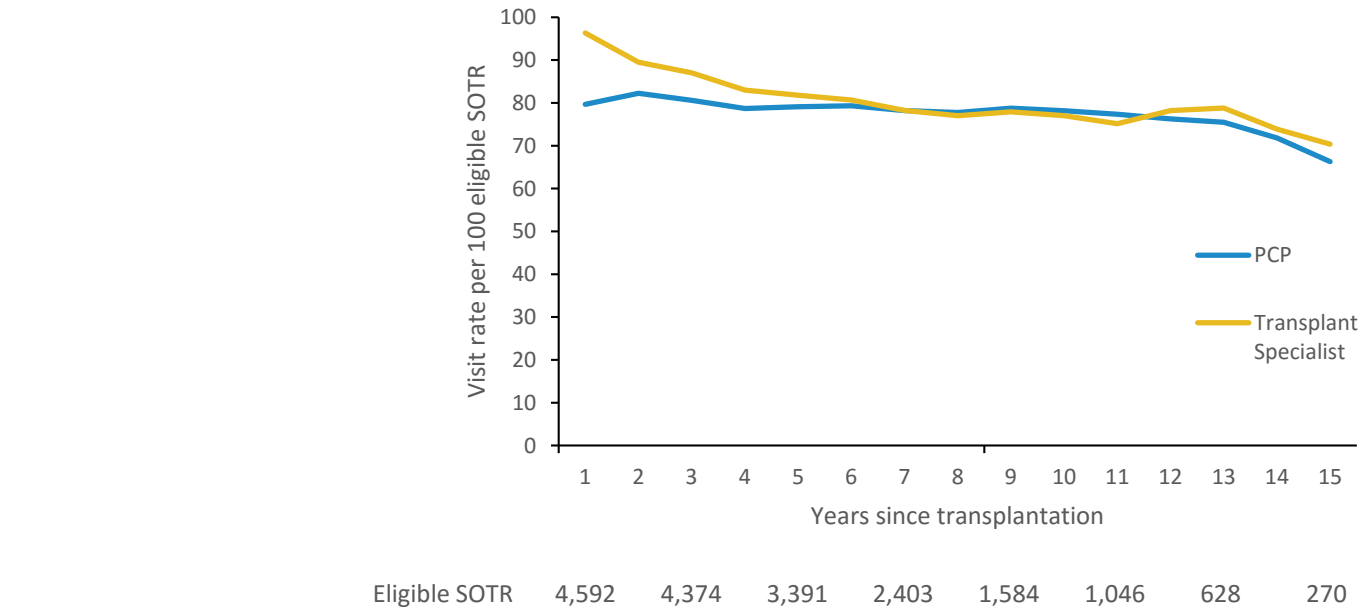
Figure 2. Cancer screening up-to-date recipients per all eligible SOTR for cancer screening by year since transplantation



Eligible SOTR								
Breast	1,154	1,184	979	729	484	328	181	71
Cervical	2,225	2,030	1,545	1,079	719	476	256	96
Colorectal	3,459	3,505	2,806	2,041	1,353	909	561	253

Legend: Cancer screening up-to-date rate for breast (blue) cervical (yellow) and colorectal (red) cancer per 100 eligible solid organ transplant recipients by years since transplantation.

Figure 3. Post-transplant assessment visits to primary care physicians and visits to transplant specialist by year since transplantation for all patients eligible for cancer screening.



Legend: Rate of visits to a primary care physician (PCP, blue) and rate of visits to a transplant specialist (yellow) by year since transplantation for all patients eligible for cancer screening. PCP visits restricted to assessment visits.

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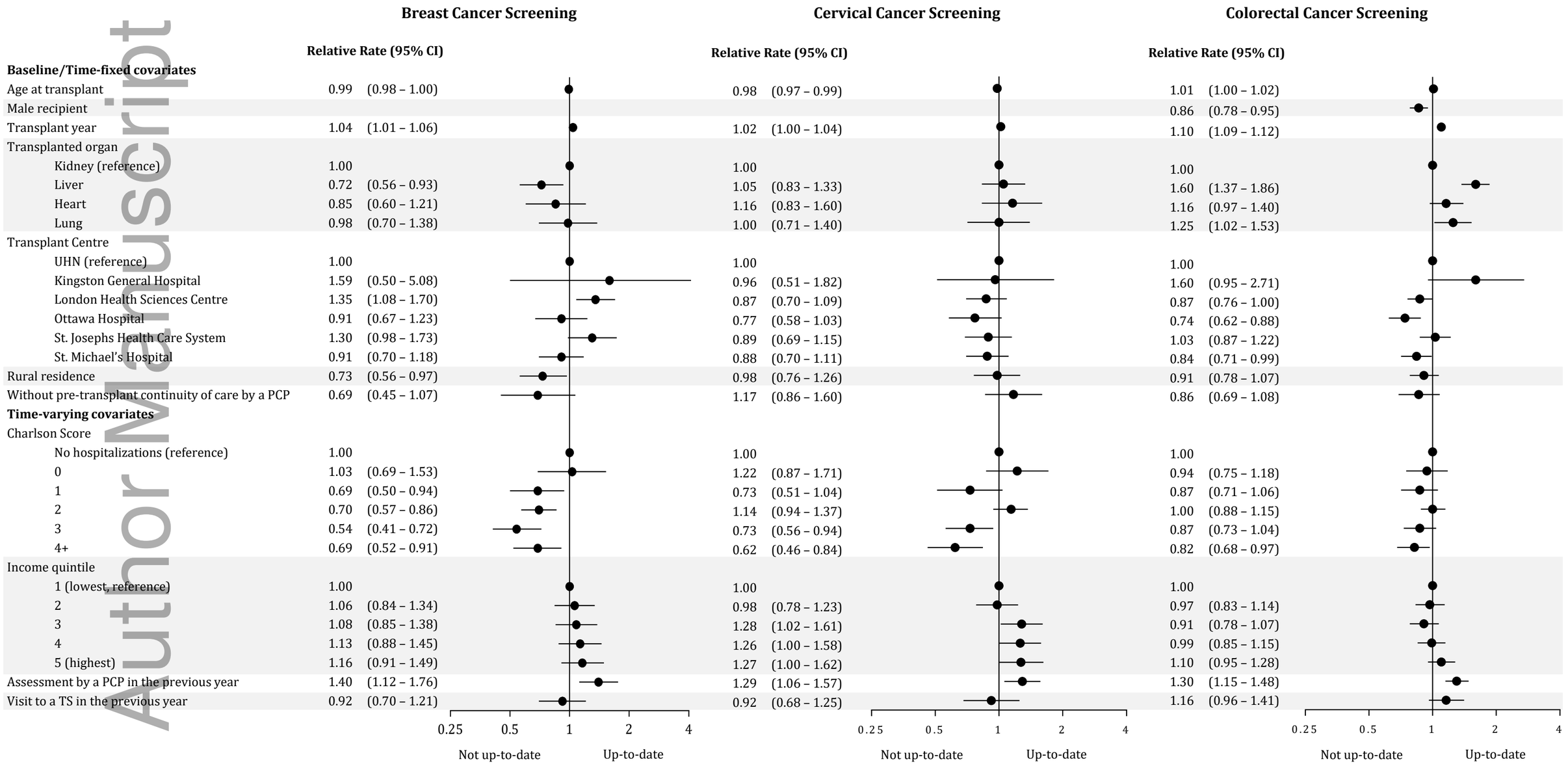
Figure 4. Multivariable recurrent event analysis for recipients not up-to-date with cancer screening.



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