Cancer Risk and Mortality in Patients With Kidney Disease: A Population-Based Cohort Study

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Rationale & Objective: Patients with chronic kidney disease (CKD) may be at increased risk for cancer. CKD may also be associated with worse cancer outcomes. This study examined cancer incidence and mortality across the spectrum of CKD.

Study Design: Population-based cohort study.

Setting & Participants: All adult Ontario residents with data on estimated glomerular filtration rate (eGFR) or who were receiving maintenance dialysis or had received a kidney transplant (2007-2016).

Exposure: Patients were categorized as of the first date they had 2 eGFR assessments or were registered as receiving maintenance dialysis or having received a kidney transplant. eGFR levels were further categorized as ≥60, 45-59, 30-44, 15-29, and <15 mL/min/1.73 m^2; the latter 4 groups are consistent with KDIGO (Kidney Disease: Improving Global Outcomes) CKD categories G3a, G3b, G4, and G5, respectively.

Outcomes: Overall and site-specific cancer incidence and mortality.

Analytical Approach: Fine and Gray subdistribution hazard models.

Results: Among 5,882,388 individuals with eGFR data, 29,809 receiving dialysis, and 4,951 having received a kidney transplant, there were 325,895 cancer diagnoses made during 29,993,847 person-years of follow-up. The cumulative incidence of cancer ranged between 10.8% and 15.3% in patients with kidney disease. Compared with patients with eGFR ≥60 mL/min/1.73 m^2, adjusted hazard ratios (AHRs) for a cancer diagnosis among patients with CKD G3a, G3b, G4, and G5 were 1.08 (95% CI, 1.07-1.10), 0.99 (95% CI, 0.97-1.01), 0.85 (95% CI, 0.81-0.88), and 0.81 (95% CI, 0.73-0.90), respectively. The AHRs for patients receiving dialysis and who had received a transplant were 1.01 (95% CI, 0.96-1.07) and 1.25 (95% CI, 1.12-1.39), respectively. Patients with kidney disease had higher proportions of stage 4 cancers at diagnosis. Patients with CKD G3a, G3b, and G4 and transplant recipients had increased risks of cancer-specific mortality (AHRs of 1.27 [95% CI, 1.23-1.32], 1.29 [95% CI, 1.24-1.35], 1.25 [95% CI, 1.18-1.33], and 1.48 [95% CI, 1.18-1.87], respectively). The risks of bladder and kidney cancers and multiple myeloma were particularly increased in CKD, and mortality from these malignancies increased with worsening kidney function.

Limitations: Possible unmeasured confounding and limited ability to infer causal associations.

Conclusions: Cancer incidence in the setting of kidney disease is substantial. Cancer risk was increased in mild to moderate CKD and among transplant recipients, but not in advanced kidney disease. Cancer-related mortality was significantly higher among patients with kidney disease, particularly urologic cancers and myeloma. Strategies to detect and manage these cancers in the CKD population are needed.

Visual Abstract online

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Chronic kidney disease (CKD) is an increasing global burden, with an estimated 11%-13% prevalence worldwide.[1] Patients with CKD may be at higher risk of cancer than the general population, possibly because of heightened inflammation and immune dysfunction, which may predispose to malignancy.[2-4] However, available clinical data are limited. A small prospective cohort study suggested that, for every 10-mL/min/1.73 m^2 decrement in estimated glomerular filtration rate (eGFR), the risk of cancer increased by 29%.[5] A meta-analysis of patients enrolled in 6 prospective clinical studies reported nonsignificant findings for the association between CKD and overall cancer risk.[6] More recently, in a Swedish cohort, a U-shaped association was observed between eGFR and cancer incidence, driven primarily by increased risk of skin and urogenital cancers.[7] Patients with kidney failure receiving dialysis have also been shown to have increased rates of kidney and other urinary tract malignancies.[8,9]

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Cardiovascular disease has traditionally been viewed as the predominant cause of death in patients with CKD, but the proportion of cancer-related death may be underappreciated in this population, particularly in those with mild to moderate decreases in kidney function. One large US cohort study estimated that 35% of patients with CKD will die of cardiovascular causes and 32% will die of cancer.[10] Patients with CKD may also

PLAIN-LANGUAGE SUMMARY

Patients with kidney disease may have an increased risk of cancer and may be more likely to die of cancer. We used health care databases in Ontario, Canada, to categorize patients according to their kidney function (using blood test data) or records that identify patients receiving dialysis or having received a kidney transplant. We then looked at their risks of being diagnosed with cancer and of dying of cancer. Patients with mild to moderate kidney disease and kidney transplant recipients had a higher risk of cancer than patients with normal kidney function. Patients with kidney disease had a higher risk of dying of cancer than patients with normal kidney function, particularly cancers such as bladder and kidney cancers and multiple myeloma. Our study suggests that improved strategies to detect and treat cancer in patients with kidney disease are needed.

have worse cancer outcomes than patients with normal kidney function.[11]

Despite the increased risks of cancer and potentially worse outcomes, there is a paucity of population-level data on cancer incidence and outcomes in patients across the spectrum of CKD, including those with kidney failure. Also, much of the evidence for cancer screening in this population (including the basis for the current Choosing Wisely recommendations, which advise against routine cancer screening in some dialysis patients) is based on data from the 1990s and earlier.[12-14] Given the advances in cancer treatment (including the advent of targeted and immunologic therapies) and the changing demographic characteristics of the dialysis and transplant populations, there is a need to characterize the incidence of cancer and its outcomes in patients with CKD, including those receiving kidney replacement therapy. We used a population-based cohort of individuals with serum creatinine measurements, as well as linked registries of dialysis and kidney transplant recipients, to assess overall and site-specific cancer incidence and cancer-specific mortality across the spectrum of CKD.

Methods

Study Design and Setting

We conducted a population-based cohort study of all Ontario patients 18 years of age or older with serum creatinine data in the provincewide Ontario Laboratory Information System or registration in the Canadian Organ Replacement Register as maintenance dialysis or kidney transplant recipients between April 1, 2007, and October 31, 2016. We excluded patients with prior cancer diagnoses (10 years before the index date) and non-Ontario residents. Ontario is Canada's most populous province, with 14 million residents who receive single-payer publicly funded health care under the Ontario Health Insurance Plan.

This study was conducted using a prespecified protocol, and the use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act and does not require review by a research ethics board.

Exposure (Kidney Function Status)

Patients were categorized according to kidney function status using serum creatinine values in the Ontario Laboratory Information System or registration as a maintenance dialysis or kidney transplant recipient in the Canadian Organ Replacement Register (Table S1). The Ontario Laboratory Information System captures ambulatory and inpatient laboratory studies that are covered by the Ontario Health Insurance Plan from January 1, 2007, onward, and is estimated to capture 95% of laboratory tests within the province.[15] The Canadian Organ Replacement Register is a validated national registry that captures the incidence, prevalence, and outcomes of >99% of patients who received maintenance dialysis or solid-organ transplants.[16]

In those who had not received dialysis or a kidney transplant, we categorized patients as having an eGFR ≥60 mL/min/1.73 m^2 or into one of 4 CKD categories according to KDIGO (Kidney Disease: Improving Global Outcomes): G3a, G3b, G4, and G5 for 45-59, 30-44, 15-29, and <15 mL/min/1.73 m^2, respectively. eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (without race adjustment).[17]

We required that patients have 2 eGFR assessments (within ±10 mL/min/1.73 m^2 or 10%) separated by at least 3 months (but <1 year) to permit accurate categorization of baseline kidney function. The first date at which patients had 2 eligible eGFR assessments (ie, the date of the second eGFR assessment) or were registered as maintenance dialysis or kidney transplant recipients served as the index date (ie, time origin for follow-up). Patients who initiated maintenance dialysis or received a kidney transplant during follow-up were censored, and subsequent person-time follow-up was attributed to their new treatment exposure status (ie, dialysis or transplant), with the new time origin (index date) being the date of the start of dialysis or the transplant date. As such, patients who transitioned to the dialysis or kidney transplant categories were permitted to have multiple (independent) entries within the cohort.

Data Sources

Data from multiple linked administrative health care databases stored at ICES were used. ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data without consent for health system evaluation and improvement.[18] The datasets were linked using unique

encoded identifiers and analyzed at ICES. Patient characteristics, including demographic data, vital status, and socioeconomic data, were obtained from the Registered Persons Database. Cancer diagnoses were identified using the Ontario Cancer Registry. This registry contains data on all incident cancers in Ontario since 1964, and has been estimated to be >95% complete.[19] Classification of 25 cancer diagnoses was done per the *International Classification of Diseases for Oncology, Third Edition* definitions used by the 2018 Ontario Cancer Statistics report (Table S2).[20]

Mortality and cause of death were determined using death certificate data from the Ontario Registrar General Death database. Strong agreement between database-reported cause of death and patients receiving intensive prospective follow-up has been reported,[21] and this dataset has been previously employed in studies assessing cause of death in Ontario.[22-24]

Comorbidity data were obtained from the Canadian Institutes of Health Information Discharge Abstract Database (using *International Classification of Diseases, Tenth Revision* codes) and Ontario Health Insurance Plan diagnostic codes. Health care use was obtained from the Ontario Health Insurance Plan and the National Ambulatory Care Reporting System (Table S3).

Outcomes

The primary outcome was time to any new cancer diagnosis within the Ontario Cancer Registry (all diagnoses are ascribed to a specific site or categorized as "unknown/other"). Patients were followed from the index date to the first new cancer diagnosis (of any site), censoring events (transition to dialysis, kidney transplant status, or the end of follow-up, December 31, 2017) or death, whichever came first. We assessed total incidence for all cancers and 25 site-specific cancers (because patients were censored after the first new cancer diagnosis, other site-specific cancers were not treated as competing risks). Secondary outcomes included time to overall cancer-specific mortality, cancer-specific mortality related to the 5 most common solid tumor malignancies (breast, bladder, colon, lung, and prostate cancers), as well as kidney cancers and multiple myeloma (because prognosis and management of these particular malignancies may be associated with kidney function) and cardiovascular mortality. Additionally, we assessed cancer stage at diagnosis (categorized as 1-4).

We also assessed the association between selected CKD-related risk factors and time to cancer incidence. We assessed the association between albuminuria via urinary albumin-creatinine ratio (categorized as normal to mild [<3 mg/mmol], moderate [3-30 mg/mmol], severe [>30 mg/mmol], or not measured) and time to overall cancer incidence. In patients who initiated dialysis or received a kidney transplant, we also assessed the association between time from dialysis initiation and time from transplant with overall cancer incidence.

Statistical Analyses

We calculated 5-year and overall cumulative incidence of total and individual cancer types and reported event rates per 1,000 patient-years. We used multivariable Fine and Gray models to assess the association between kidney function and cancer incidence (while accounting for the competing risk of death).[25] Model covariates included age at index date (per 5-year increment), sex (female referent), income quintile, urban versus rural residence, Charlson comorbidity index (per unit increment), and the presence of one or more comorbid conditions (including previous acute kidney injury, myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes, chronic liver disease, gastrointestinal hemorrhage, HIV infection, peripheral vascular disease, ischemic heart disease, and hypertension). We constructed cumulative incidence function curves for overall cancer incidence and mortality, with truncation of the curves when <10% of individuals remained in each kidney function group (to avoid overinterpretation of sparse data in later follow-up).[26]

Because inclusion of the total cohort of more than 5 million individuals was too large for the available computing resources to handle in a timely manner, we used a random subset of 1 million individuals with eGFR ≥60 mL/min/1.73 m^2 as the referent group for the reported subdistribution hazard ratios. To address repeatedness/clustering related to multiple patient entries (ie, from transitions to the dialysis or kidney transplant exposure groups), we used robust sandwich variance estimation. We assessed the proportional hazards assumption using graphical plots of the Schoenfeld residuals. To compare cancer stage at diagnosis across kidney function categories, we used χ^2 testing. We considered a 2-sided P value less than 0.05 as statistically significant. We performed all analyses using SAS version 9.4 (SAS Institute).

Sensitivity Analyses

To assess the possibility of "reverse causality" (ie, reduced kidney function being caused by undiagnosed cancer), we repeated the cancer incidence analysis for all cancers, kidney cancer, and multiple myeloma, with the exclusion of cancer diagnoses that occurred within the first year following the index date. We also repeated the analysis for overall cancer incidence excluding cancers that may cause CKD (eg, bladder, kidney, and myeloma).

Additional sensitivity analyses to compare results from a cause-specific hazard model and to assess for the potential effect of immortal-time bias on our results are described in Item S1.

Results

Baseline Characteristics

We identified 5,882,388 individuals with eGFR data, of whom 439,554 (7.4%) had CKD G3a-G5. In addition,

Table 1. Baseline Characteristics of Cohort According to Kidney Function Status

Characteristic	Full cohort (N = 5,882,388)	eGFR ≥ 60 (n = 5,432,283)	CKD G3a (n = 260,639)	CKD G3b (n = 128,233)	CKD G4 (n = 41,273)	CKD G5 (n = 9,409)	Dialysis (n = 29,809)	Transplant (n = 4,951)
Age								
Mean ± SD	53.8 ± 17.2	52.0 ± 16.3	75.3 ± 11.0	78.5 ± 11.0	77.8 ± 12.8	66.8 ± 16.6	63.1 ± 15.8	51.8 ± 13.5
Median [IQR]	54 [42-66]	52 [41-63]	77 [69-83]	80 [73-86]	80 [72-87]	69 [56-80]	65 [53-75]	53 [42-62]
Sex								
Female	3,342,680 (56.6%)	3,073,112 (56.6%)	150,050 (57.6%)	77,204 (60.2%)	24,069 (58.3%)	4,598 (48.9%)	11,793 (39.6%)	1,854 (37.4%)
Male	2,563,917 (43.4%)	2,359,171 (43.4%)	110,589 (42.4%)	51,029 (39.8%)	17,204 (41.7%)	4,811 (51.1%)	18,016 (60.4%)	3,097 (62.6%)
eGFR								
Mean ± SD	95.2 ± 21.8	95.2 ± 17.1	53.2 ± 4.3	38.6 ± 4.2	24.3 ± 4.1	9.4 ± 3.6	–	–
Median [IQR]	93 [79-106]	95 [83-107]	53 [50-57]	39 [35-42]	25 [21-28]	10 [6-13]	–	–
UACR								
Median [IQR]	1 [0-3]	1 [0-2]	2[0-5]	3 [1-13]	9 [2-57]	96 [20-267]	–	–
Undetectable	169,239 (2.9%)	151,903 (2.8%)	11,342 (4.4%)	4,581 (3.6%)	937 (2.3%)	58 (0.6%)	–	–
Normal-mild	104,560 (1.8%)	75,266 (1.4%)	13,876 (5.3%)	9,529 (7.4%)	3,680 (8.9%)	413 (4.4%)	–	–
Moderate	308,019 (5.2%)	269,425 (5.0%)	24,849 (9.5%)	10,636 (8.3%)	2,450 (5.9%)	95 (1.0%)	–	–
Severe	35,260 (1.6%)	14,102 (0.3%)	4,307 (1.7%)	4,543 (3.5%)	3,508 (8.5%)	1,300 (13.8%)	–	–
Unmeasured	5,289,519 (89.6%)	4,921,587 (90.6%)	206,265 (79.1%)	98,945 (77.3%)	30,698 (74.4%)	7,543 (80.2%)	–	–
SES								
Quintile 1	1,133,171 (19.2%)	1,028,591 (18.9%)	54,673 (21.0%)	28,822 (22.5%)	9,798 (23.7%)	2,481 (26.4%)	7,681 (25.8%)	1,125 (22.7%)
Quintile 2	1,184,211 (20.0%)	1,082,461 (19.9%)	55,155 (21.2%)	27,884 (21.7%)	9,018 (21.8%)	2,066 (22.0%)	6,592 (22.1%)	1,035 (20.9%)
Quintile 3	1,217,307 (20.6%)	1,120,503 (20.6%)	53,445 (20.5%)	26,103 (20.4%)	8,488 (20.6%)	1,863 (19.8%)	5,890 (19.8%)	1,015 (20.5%)
Quintile 4	1,214,217 (20.6%)	1,126,289 (20.7%)	49,299 (18.9%)	23,523 (18.3%)	7,322 (17.7%)	1,629 (17.3%)	5,200 (17.4%)	955 (19.3%)
Quintile 5	1,157,691 (19.6%)	1,074,439 (19.8%)	48,067 (18.4%)	21,901 (17.1%)	6,647 (16.1%)	1,370 (14.6%)	4,446 (14.9%)	821 (16.6%)
Rural residence	596,839 (10.1%)	534,598 (9.8%)	34,141 (13.1%)	17,184 (13.4%)	5,664 (13.7%)	1,128 (12.0%)	3,615 (12.1%)	509 (10.3%)
Index date								
2007	19,950 (0.3%)	10,963 (0.2%)	2,040 (0.8%)	1,569 (1.2%)	914 (2.2%)	554 (5.9%)	3,438 (11.5%)	472 (9.5%)
2008	397,256 (6.7%)	325,086 (6.0%)	36,904 (14.2%)	21,188 (16.5%)	8,807 (21.3%)	2,011 (21.4%)	2,797 (9.4%)	463 (9.4%)
2009	908,074 (15.4%)	803,497 (14.8%)	58,225 (22.3%)	30,554 (23.8%)	10,587 (25.7%)	1,870 (19.9%)	2,821 (9.5%)	520 (10.5%)
2010	984,375 (16.7%)	904,255 (16.6%)	47,557 (18.2%)	21,788 (17.0%)	6,033 (14.6%)	939 (10.0%)	3,306 (11.1%)	497 (10.0%)
2011	826,177 (14.0%)	777,979 (14.3%)	28,136 (10.8%)	12,967 (10.1%)	3,337 (8.1%)	577 (6.1%)	2,702 (9.1%)	479 (9.7%)
2012	663,732 (11.2%)	622,382 (11.5%)	23,214 (8.9%)	10,874 (8.5%)	3,109 (7.5%)	800 (8.5%)	2,845 (9.5%)	508 (10.3%)
2013	655,917 (11.1%)	617,343 (11.4%)	21,360 (8.2%)	9,588 (7.5%)	2,802 (6.8%)	1,179 (12.5%)	3,175 (10.7%)	470 (9.5%)
2014	605,127 (10.2%)	570,614 (10.5%)	19,034 (7.3%)	8,623 (6.7%)	2,429 (5.9%)	593 (6.3%)	3,269 (11.0%)	565 (11.4%)
2015	548,046 (9.3%)	518,146 (9.5%)	15,698 (6.0%)	7,309 (5.7%)	2,160 (5.2%)	649 (6.9%)	3,487 (11.7%)	597 (12.1%)
2016	297,943 (5.0%)	282,018 (5.2%)	8,471 (3.3%)	3,773 (2.9%)	1,095 (2.7%)	237 (2.5%)	1,969 (6.6%)	380 (7.7%)
CCI								
Mean ± SD	0.15 ± 0.64	0.10 ± 0.48	0.42 ± 1.02	0.70 ± 1.37	1.18 ± 1.80	2.09 ± 2.06	2.52 ± 2.06	2.06 ± 1.65
Median [IQR]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-1]	0 [0-2]	2 [0-4]	2 [0-4]	2 [0-3]

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Cohort According to Kidney Function Status

Characteristic	Full cohort (N = 5,882,388)	eGFR ≥ 60 (n = 5,432,283)	CKD G3a (n = 260,639)	CKD G3b (n = 128,233)	CKD G4 (n = 41,273)	CKD G5 (n = 9,409)	Dialysis (n = 29,809)	Transplant (n = 4,951)
Comorbidity								
AKI	60,991 (1.0%)	18,948 (0.3%)	9,227 (3.5%)	11,024 (8.6%)	7,426 (18.0%)	2,686 (28.5%)	10,623 (35.6%)	1,057 (21.3%)
AMI	96,945 (1.6%)	68,745 (1.3%)	11,533 (4.4%)	8,530 (6.7%)	3,827 (9.3%)	919 (9.8%)	3,181 (10.7%)	210 (4.2%)
Arrhythmia	172,487 (2.9%)	111,670 (2.1%)	27,282 (10.5%)	19,244 (15.0%)	7,269 (17.6%)	1,444 (15.3%)	5,169 (17.3%)	409 (8.3%)
AF/flutter	204,272 (3.5%)	135,931 (2.5%)	32,412 (12.4%)	21,622 (16.9%)	7,730 (18.7%)	1,308 (13.9%)	4,948 (16.6%)	321 (6.5%)
CBVD	151,335 (2.6%)	108,556 (2.0%)	21,058 (8.1%)	12,945 (10.1%)	4,672 (11.3%)	989 (10.5%)	2,864 (9.6%)	251 (5.1%)
Chronic liver disease	257,357 (4.4%)	236,722 (4.4%)	8,840 (3.4%)	4,485 (3.5%)	1,720 (4.2%)	738 (7.8%)	4,137 (13.9%)	715 (14.4%)
COPD	68,881 (1.2%)	45,138 (0.8%)	9,829 (3.8%)	7,445 (5.8%)	3,210 (7.8%)	648 (6.9%)	2,521 (8.5%)	90 (1.8%)
CHF	163,727 (2.8%)	86,664 (1.6%)	28,067 (10.8%)	24,245 (18.9%)	11,452 (27.7%)	2,653 (28.2%)	9,883 (33.2%)	763 (15.4%)
Diabetes	435,067 (7.4%)	388,253 (7.1%)	27,171 (10.4%)	12,291 (9.6%)	3,655 (8.9%)	784 (8.3%)	2,602 (8.7%)	311 (6.3%)
GI hemorrhage	174,665 (3.0%)	145,659 (2.7%)	13,104 (5.0%)	7,999 (6.2%)	3,223 (7.8%)	902 (9.6%)	3,331 (11.2%)	447 (9.0%)
HIV	11,571 (0.2%)	10,959 (0.2%)	327 (0.1%)	95 (0.1%)	35 (0.1%)	30 (0.3%)	102 (0.3%)	23 (0.5%)
HTN	670,071 (11.3%)	606,756 (11.2%)	35,736 (13.7%)	14,948 (11.7%)	4,554 (11.0%)	1,487 (15.8%)	5,464 (18.3%)	1,126 (22.7%)
IHD	455,413 (7.7%)	335,588 (6.2%)	56,206 (21.6%)	34,801 (27.1%)	13,170 (31.9%)	3,070 (32.6%)	10,679 (35.8%)	1,899 (38.4%)
PVD	29,323 (0.5%)	16,988 (0.3%)	4,156 (1.6%)	3,275 (2.6%)	1,492 (3.6%)	722 (7.7%)	2,207 (7.4%)	483 (9.8%)

Abbreviations: AKI, acute kidney injury; AMI, acute myocardial infarction; AF, atrial fibrillation; CBVD, cerebrovascular disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HTN, hypertension; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); IHD, ischemic heart disease; PVD, peripheral vascular disease; SES, socioeconomic status (neighborhood income); UACR, urinary albumin-creatinine ratio (in mg/mmol).

there were 29,809 maintenance dialysis patients and 4,951 kidney transplant recipients, for a total follow-up of 29,938,374 person-years (Fig S1). Median follow-up was 5.33 (IQR, 3.2-7.1) years.

Median age was 60 (IQR, 46-74) years, and 57% of participants were female (Tables 1 and S4). Patients with CKD G3-G5 and those receiving dialysis were older than those with eGFR ≥60 mL/min/1.73 m^2 and kidney transplant recipients. Patients with CKD G4-G5 or receiving kidney replacement therapy (maintenance dialysis or transplant) also had a greater burden of comorbidities, with a higher Charlson index, and more frequent hospitalizations and emergency department visits.

Overall and Site-Specific Cancer Incidence

There were 325,895 cancer diagnoses during follow-up. The overall 10-year cumulative incidences of all cancer diagnoses in patients with eGFR ≥60 mL/min/1.73 m^2; patients with CKD G3a, G3b, G4, or G5; patients receiving dialysis; and transplant recipients were 9.0% (95% CI, 8.6%-9.3%), 15.3% (95% CI, 14.4%-16.3%), 13.7% (95% CI, 13.5%-14.0%), 11.5% (95% CI, 11.1%-11.9%), 10.8% (95% CI, 9.5%-12.3%), 11.5% (95% CI, 11.0%-12.1%), and 13.2% (95% CI, 11.6%-14.8%), respectively (Fig 1).

The 10-year cumulative incidences of 25 cancer diagnoses are shown in Tables S5 and S6. The malignancies with the highest cumulative incidences in patients with eGFR ≥60 mL/min/1.73 m^2 were prostate (2.6%), breast (2.5%), lung (1.2%), and colorectal (1.0%) cancers and non-Hodgkin lymphoma (0.4%). In those with CKD G4 or G5, dialysis patients, and transplant recipients, kidney cancers were among the top 5 most frequent cancers. Kidney cancers were the third most common cancer in transplant recipients (following breast and lung cancers) and the fourth most common among dialysis patients.

Relative to patients with eGFR ≥60 mL/min/1.73 m^2, the adjusted hazard ratios (AHRs) for all cancer diagnoses among patients with CKD G3a, G3b, G4, or G5, patients receiving dialysis, and transplant recipients were 1.08 (95% CI, 1.07-1.10), 0.99 (95% CI, 0.97-1.01), 0.85 (95% CI, 0.81-0.88), 0.81 (95% CI, 0.73-0.90), 1.01 (95% CI, 0.96-1.07), and 1.25 (95% CI, 1.12-1.39), respectively (Fig 2; Table S7).

Specific cancers with increased risks among patients with kidney disease included bladder cancer (in CKD G3a-G4), kidney cancer, and multiple myeloma. The risks of kidney cancers and multiple myeloma diagnoses increased progressively with worsening eGFR. Patients with kidney disease were noted to have a lower hazard of breast and prostate cancer.

Overall and Site-Specific Cancer Mortality

There were 72,143 deaths attributed to cancer (Fig 3). Patients with CKD G3a, G3b, and G4 and transplant recipients had an increased risk of cancer-specific mortality (AHRs of 1.27 [95% CI, 1.23-1.32], 1.29 [95% CI, 1.24-1.35], 1.25 [95% CI, 1.18-1.33], and 1.48 [95% CI, 1.18-

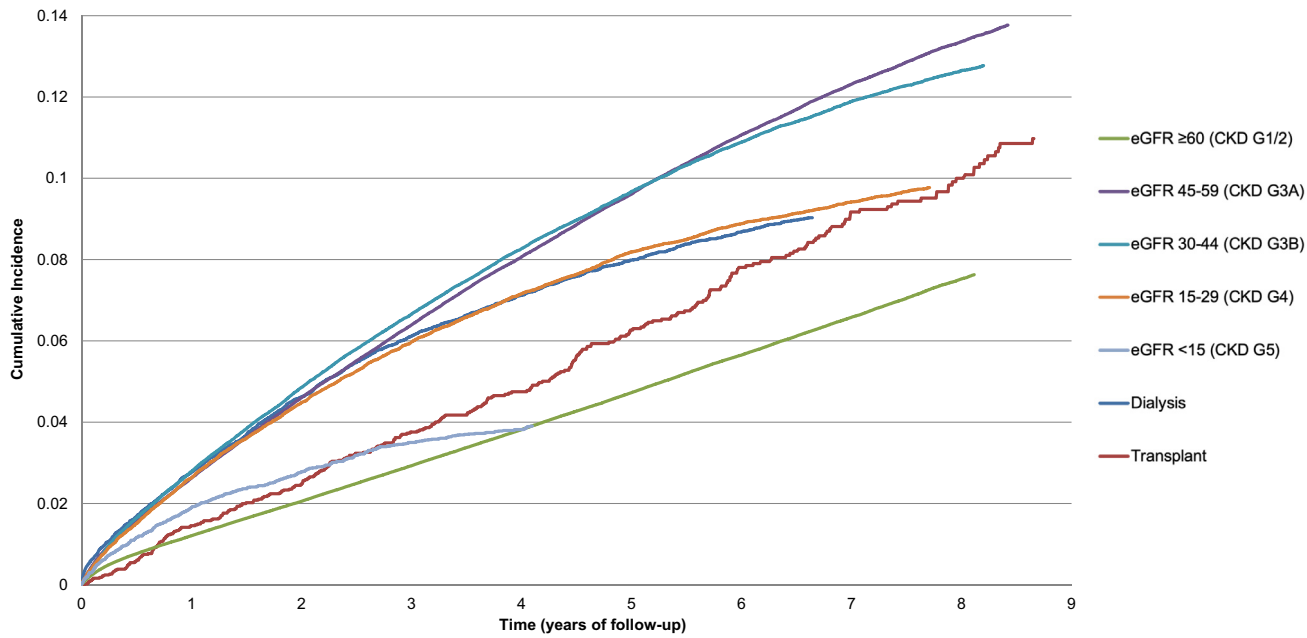

Figure 1. Cumulative incidence function curves for overall cancer incidence by kidney function status. Cumulative incidence function curves truncated when <10% of individuals in each kidney function category remain. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

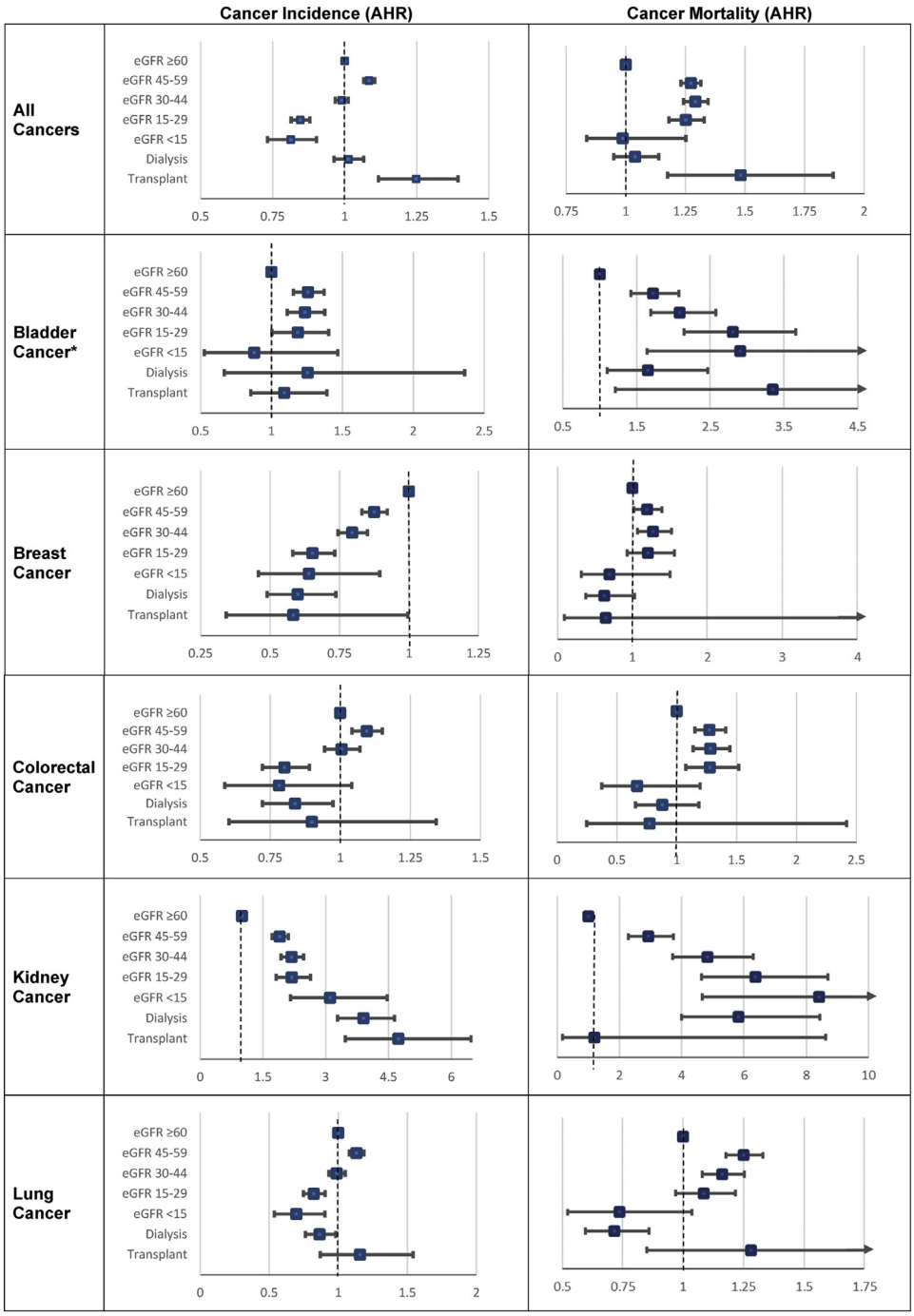

Figure 2. Adjusted hazard ratios (AHRs) for overall and site-specific cancer incidence and cancer mortality across kidney function categories. *Schoenfeld residual plots for the subdistribution hazard models for bladder cancer mortality and myeloma incidence and mortality may suggest a violation of the proportional hazards assumption. The reported subdistribution AHR for these outcomes should therefore be interpreted as average AHR over the follow-up period. Abbreviation: eGFR, estimated glomerular filtration rate.

1.87], respectively; Fig 2). Patients with CKD G5 and those receiving dialysis did not have significantly increased risks of cancer-specific mortality.

Bladder and kidney cancer mortality risk became progressively greater across the kidney disease categories of CKD G3a, G3b, G4, and G5, dialysis patients, and transplant recipients. Mortality related to multiple myeloma was also increased in all groups except those with CKD G5.

Compared with those with eGFR ≥60 mL/min/1.73 m^2, the incidences of breast, colorectal, and prostate cancer diagnoses were lower in most categories of kidney disease; however, cancer-specific mortality was greater in CKD G3a and G3b and similar in other categories of kidney disease.

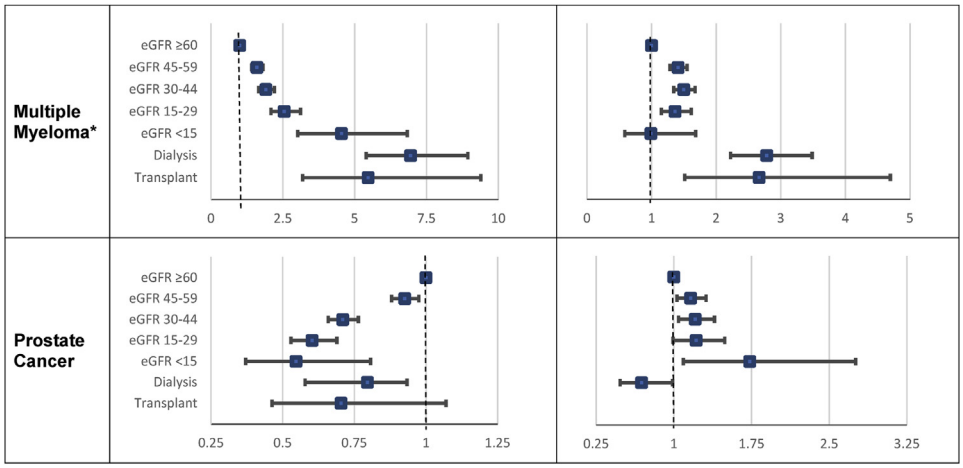

Figure 2. *Continued*

Cancer Stage at Diagnosis and CKD-Related Risk Factors for Cancer

Compared with those with eGFR ≥60 mL/min/1.73 m^2, patients in all kidney disease categories had a higher proportion of stage 4 cancers at the time of diagnosis (Tables 2 and S8). The median cancer stage at diagnosis was 2 in all kidney function categories. In dialysis and transplant recipients, time from dialysis initiation and time since transplant were not associated with increased risk of cancer diagnosis.

Cancer Mortality Versus All-Cause and Cardiovascular Mortality

In patients with CKD G3a-G5, death attributed to cardiovascular causes exceeded cancer-related mortality, whereas, in those with eGFR ≥60 mL/min/1.73 m^2 and kidney transplant recipients, cancer and cardiovascular mortality were comparable (Figs 4 and S2).

Sensitivity Analyses

When we repeated analyses of kidney cancer and multiple myeloma incidence with the exclusion of diagnoses within the first year of follow-up (to mitigate the possibility of reverse causation), the AHRs were attenuated but remained significantly increased in all CKD categories (Fig S3). Also, exclusion of bladder and kidney cancers and myeloma diagnoses resulted in similar associations as the primary analysis. Additional sensitivity analyses to assess a cause-specific hazard model and to address potential immortal-time bias are reported in Figure S4 and Tables S9 and S10.

Discussion

In a population-wide cohort of more than 5 million patients, the cumulative incidence of cancer ranged between 10.8% and 15.3% in patients with kidney disease. Compared with those with eGFR ≥60 mL/min/1.73 m^2, the risk of incident cancer was higher in those with CKD G3a and kidney transplant recipients and lower in those with CKD G4-G5. In contrast, the risk of death due to cancer was higher in patients with CKD G3a-G4 and transplant recipients, but not in those with CKD G5 or those receiving dialysis. Patients with CKD G3a-G4 had a 25%-29% increased risk of cancer-related mortality compared with those with eGFR ≥60 mL/min/1.73 m^2. Our findings demonstrate a disparity between cancer incidence and cancer-related mortality in patients with kidney disease, suggesting shortcomings in early cancer detection and/or treatment in this population.

Our estimates for increased cancer mortality in patients with CKD align with the findings of prior smaller studies.[11,27,28] Iff et al found that patients with eGFR <60 mL/min/1.73 m^2 had an 18% increase in the risk of cancer death for every 10-mL/min/1.73 m^2 decrease in eGFR.[11] More recently, Au et al observed a >2.5-fold increased risk of cancer death in dialysis and kidney transplant recipients.[27] The increased risk of cancer death in the population with kidney disease is likely multifactorial. Reduced kidney function may preclude patients from treatments that are nephrotoxic (eg, platinum-based chemotherapies, ifosfamide, pemetrexed) as well as therapies that are cleared by the kidney that confer systemic toxicities (eg, bleomycin, capecitabine, cytarabine).[29,30] Moreover, patients with CKD are frequently excluded from trials of cancer therapy, which may deter clinicians from administering effective cancer therapies to patients with CKD.[31,32] Importantly, we also found that patients with CKD had greater proportions of stage 4 cancers at diagnosis, which would substantially impact treatment options and survival outcomes.

Although cancer mortality was heightened among patients with CKD, we did not find a uniformly higher incidence of cancer diagnosis across the spectrum of

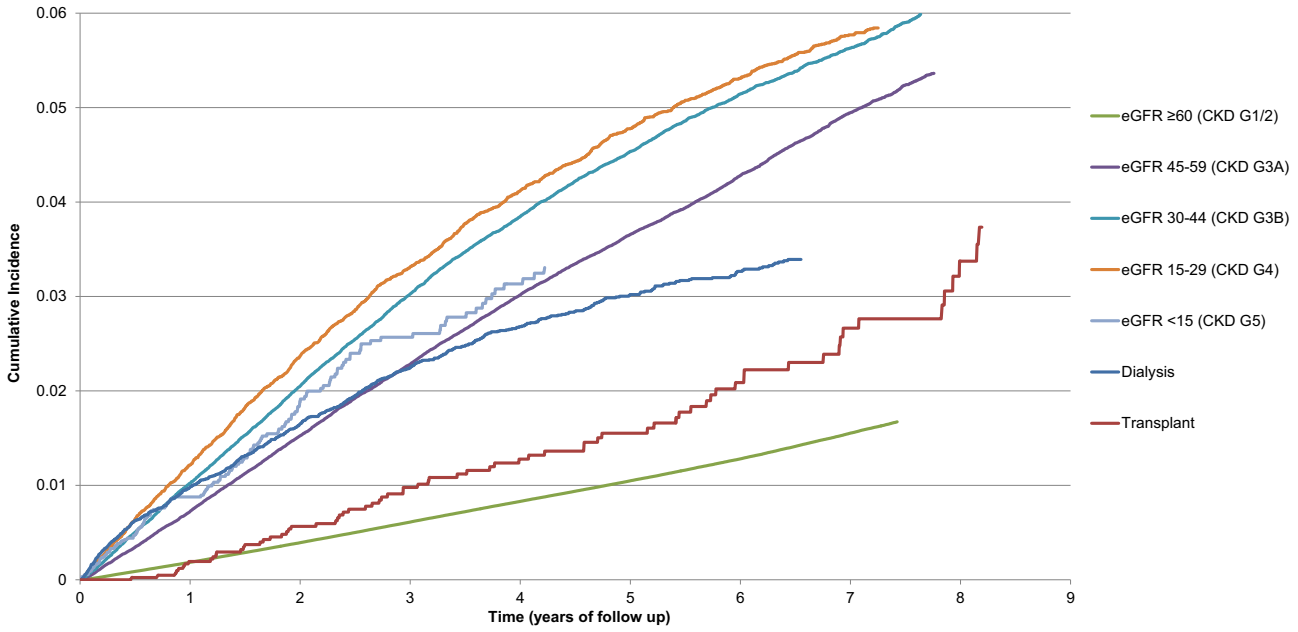

Figure 3. Cumulative incidence function curves for overall cancer mortality by kidney function status. Cumulative incidence function curves truncated when <10% of individuals in each kidney function category remain. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

kidney disease. This is consistent with a meta-analysis by Wong et al that did not demonstrate a higher cancer incidence in patients with CKD.[6] Similarly, Lowrance et al observed no association between severity of kidney dysfunction and incident cancer.[33] These studies, along with our findings, are in contrast to recent reports by Xu et al and Mok et al, which found a modestly increased risk of cancer in patients with CKD.[7,34]

Although cancer diagnoses in aggregate were not clearly associated with kidney disease, certain cancers were strongly associated with kidney function (with respect to incidence and mortality). Kidney and bladder

Table 2. Cancer Stages at Diagnosis Across Kidney Function Categories and Hazard Ratios for Kidney Disease–Related Risk Factors for Cancer Incidence

	Stage 4 Cancer at Diagnosis	Median (IQR) Stage at Cancer Diagnosis	*P*[a]	AHR (95% CI)
Kidney function category			<0.001	–
eGFR ≥60 mL/min/1.73 m^2	20.7%	2 (1-3)		–
CKD 3a: 45-59 mL/min/1.73 m^2	25.1%	2 (1-4)		–
CKD 3b: 30-44 mL/min/1.73 m^2	27.4%	2 (1-4)		–
CKD 4: 15-29 mL/min/1.73 m^2	30.6%	2 (2-4)		–
CKD 5: <15 mL/min/1.73 m^2	20.7%	2 (1-4)		–
Dialysis	26.5%	2 (1-4)		–
Kidney transplant	25.3%	2 (1-3)		–
Risk factor				
Time from dialysis initiation, per 1 y greater	–	–	–	1.00 (0.99-1.06)
Time from kidney transplant, per 1 y greater	–	–	–	1.01 (0.99-1.03)
UACR				
Normal-mild: <3 mg/mmol	–	–	–	1.00 (reference)
Moderate: 3-30 mg/mmol	–	–	–	1.03 (0.99-1.07)
Severe: >30 mg/mmol	–	–	–	0.89 (0.84-0.94)
Not measured	–	–	–	0.94 (0.92-0.96)

Abbreviations: AHR, adjusted hazard ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]The χ^2 test was used to assess for differences in median stage at cancer diagnosis among kidney function groups.

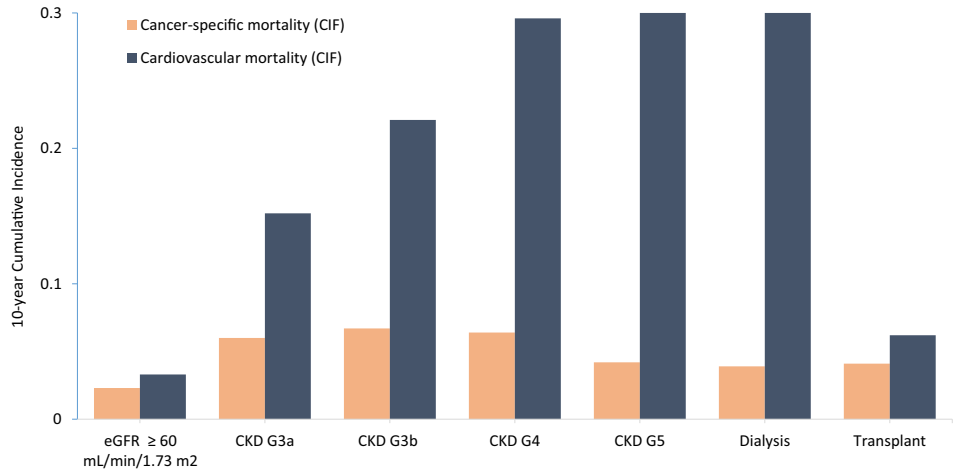

Figure 4. Cumulative (10-year) incidence of cancer-specific and cardiovascular mortality across kidney function categories.

cancer incidences increased significantly with reduced kidney function, even in mild to moderate CKD. The association between kidney dysfunction and urologic malignancy has been observed in previous cohorts, with risks ranging from 1.1- to 2.3-fold.[5,7,33] The magnitude of this association was even higher in our cohort (even in analyses excluding cancer diagnoses in the first year of follow-up). Although newly discovered CKD may precipitate a workup that leads to a cancer diagnosis, a true association is likely, particularly given the progressively greater risk seen with more severely decreased kidney function. Moreover, multiple pathophysiologic causes for the increased incidence of urologic cancers in patients with kidney disease have been postulated, including the presence of uremic and inflammatory toxins[35,36] and immune dysfunction.[37,38] Importantly, patients with reduced kidney function (and particularly kidney transplant recipients) may have impaired control of viral oncogenesis, which may mediate increased risk for multiple cancers.[39,40]

Apart from the increased incidences of bladder and kidney cancers, our data are particularly concerning for the substantially increased risk of mortality from these cancers. Few previous studies have examined site-specific cancer mortality in CKD; however, these estimated a 2-fold increased risk of digestive cancers[6] and a 2.5-fold increased risk for urinary tract cancers[11] and highlighted the need for larger cohorts to examine risk from these particular malignancies. The increased risk of death as a result of these cancers may be related to the delivery of less aggressive treatments because of legitimate or perceived risk in patients with CKD.

We submit that, in patients with CKD, special attention should be accorded to advancing treatment options for kidney and urologic cancers, particularly in those with more advanced kidney dysfunction. At present, very few clinical trials include patients with CKD, and no clinical practice guidelines focus on cancer treatment in the CKD population.[31] Evidence for dose modifications of systemic cancer therapies (conventional and targeted) that are cleared by the kidney and/or nephrotoxic is needed to guide optimal cancer therapy.[41,42] In addition, increased uptake and availability of real-world outcomes/safety data from the use of novel immunotherapies may allow patients with CKD and cancer to benefit from recent advances in treatment.[43,44]

Death from multiple myeloma was also strongly associated with kidney disease. Reverse causation may be partially explanatory because patients may have monoclonal gammopathies contributing to kidney dysfunction before a myeloma diagnosis. However, it is plausible that patients with reduced kidney function at baseline would be more susceptible to paraprotein-related kidney injury and therefore more likely to have worse myeloma outcomes.[45,46] Other malignancies, such as lung, breast, and colon cancers, also appeared to have increased mortality risk in CKD of intermediate severity, but not in more advanced kidney disease. Although our analyses attempted to account for the competing risks of non–cancer-related mortality, this finding may in part be explained by the very high risk of cardiovascular mortality in patients with advanced kidney disease and the potential that patients remained in the CKD G4-G5 groups for shorter durations compared with the CKD G3 group.

Certain common malignancies were less frequent in advanced kidney disease, most notably breast, colon, and prostate cancer, and this may contribute to the decreased overall cancer incidence observed in CKD G4-G5. A reduced prostate cancer incidence has also been reported in other CKD cohorts.[6] These cancers are all detectable by routine screening procedures in the age-appropriate general population (ie, mammography, colonoscopy, and prostate-specific antigen testing). It is possible that patients with advanced CKD, including those with kidney failure,

may be screened less frequently for these cancers, resulting in fewer ascertained cases. Prior studies in Ontario have demonstrated substantially lower rates of cancer screening in patients with kidney disease.[47] Our data demonstrate that mortality from these cancers was not reduced versus the general population, suggesting that patients with CKD, including those with kidney failure, should still be considered for screening for these cancers in the appropriate clinical context. Increased adherence to cancer screening guidelines with an individualized approach to patient life expectancy, values, and consideration of kidney transplant candidacy[48] may allow for earlier detection and improved cancer outcomes.

Our study has several strengths. We evaluated a cohort of individuals across the spectrum of kidney function in a jurisdiction with a large and diverse population. We were able to comprehensively ascertain cancer outcomes in a well-validated registry and evaluate cancer incidence and mortality. We were also able to adjust for a large number of demographic parameters, socioeconomic indicators, and relevant comorbidities using linked administrative databases. Moreover, we accounted for competing risks and conducted sensitivity analyses to address the potential for immortal-time bias and reverse causality.

Our study has limitations. Residual confounding related to measured covariates (eg, increased age/comorbidity in patients with CKD) or due to missing cancer risk factors such as family history and smoking status may have biased our effect estimates. Even though we included patients with 2 stable assessments of eGFR, misclassification of kidney function was possible. Although we were able to assess initiation of dialysis and receipt of kidney transplant in a longitudinal manner, given the vast number of serum creatinine measures during the follow-up, we were unable to analyze time variation in nondialysis CKD severity as a result of computational limitations. Small numbers of patients with advanced CKD (particularly CKD G5 not treated with dialysis) may have limited power to detect associations for some site-specific cancer outcomes. Also, despite sensitivity analyses performed in an attempt to address reverse causality, this remains an important potential limitation that may influence the effect estimates for overall cancer risk and the specific risks for urologic cancers and multiple myeloma, among others. Furthermore, although this study is population-based and was conducted in a large, ethnically diverse province, our findings may not be entirely generalizable to other jurisdictions. Finally, although we used validated and previously published approaches to determine cancer mortality, death certificates may misclassify cause of death.

In conclusion, in a population-wide cohort of patients across the spectrum of kidney disease, we found that incident cancer affected as many as 15% of patients with CKD. However, cancer risk did not consistently vary with CKD severity. Specific cancers including kidney and bladder cancers and multiple myeloma were more frequent in patients with kidney disease. Overall cancer mortality rates were significantly higher in those with moderate to severe CKD and in kidney transplant recipients relative to patients with eGFR ≥60 mL/min/1.73 m^2. Efforts to improve cancer treatment strategies in this population are needed, particularly for urologic cancers and multiple myeloma.

Supplementary Material

Supplementary File (PDF)

Figure S1: Study flow diagram.

Figure S2: Cumulative incidence function curves for overall cardiovascular mortality by kidney function status.

Figure S3: Reverse causation analysis.

Figure S4: Adjusted cause-specific HRs for overall cancer incidence and cancer mortality across kidney function categories.

Item S1: Methods for additional sensitivity analyses.

Table S1: Administrative data codes used to identify the cohort of individuals with eGFR data, receiving dialysis, or with kidney transplant.

Table S2: Administrative data codes used to define outcome measures.

Table S3: Administrative data codes used to define baseline characteristics.

Table S4: Baseline characteristics of the full sample of patients with eGFR ≥60 mL/min/1.73 m^2 and the randomly selected subsample used in the subdistribution hazard models.

Table S5: Cumulative incidence of site-specific cancer in patients with CKD G3a-G4.

Table S6: Cumulative incidence of site-specific cancer in those with CKD G5, dialysis patients, and kidney transplant recipients.

Table S7: AHRs for cancer incidence according to kidney function status.

Table S8: Distribution of cancer stage at diagnosis across kidney function groups.

Table S9: AHRs for overall cancer risk using index date–based time scale versus age-based time scale subdistribution hazard models.

Table S10: Comparison of age- and sex-adjusted HRs for cancer incidence from cause-specific hazard models for censoring patients and recategorizing at dialysis initiation and kidney transplant, with dialysis initiation and kidney transplant considered as time-varying exposures.

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Cancer Risk and Mortality in Patients With Kidney Disease

Setting and Participants

Population-based cohort study

Ontario, Canada

To assess cancer incidence & mortality

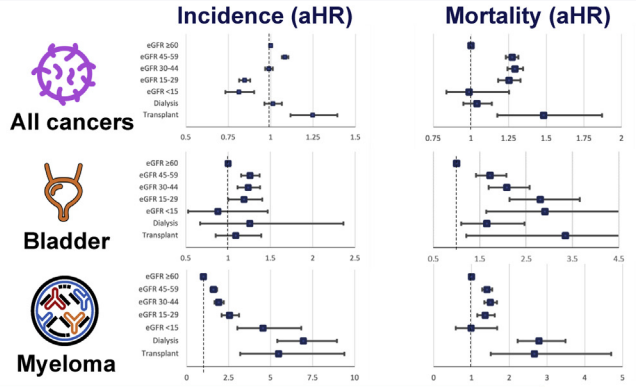
Exposure: CKD stage based on eGFR, dialysis, kidney transplant

Patients w/ eGFR
N = 5,882,388

Dialysis
N = 29,809

Transplant
N = 4,951

Results



Conclusions: Cancer risk was increased in mild-moderate CKD and transplant, but not advanced CKD. Cancer-related mortality was significantly higher in kidney disease, particularly urologic cancers and myeloma.

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