Risk of Kidney Failure in Patients With Cancer: A South Korean Population-Based Cohort Study

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Rationale & Objective: Reduced kidney function is associated with an increased risk of cancer; however, it is unclear if cancer increases the risk of kidney failure with replacement therapy (KFRT). We assessed the risk of KFRT among patients with various types of cancer collectively and with specific types of cancer.

Study Design: Retrospective population-based cohort study.

Setting & Participants: A total of 2,473,095 participants with (n = 824,365) or without (n = 1,648,730) cancer registered in the Korean National Health Insurance Service database.

Predictors: Cancer and cancer subtypes defined using International Classification of Diseases, 10th Revision, Clinical Modification, codes.

Outcomes: Primary outcome was KFRT defined as the initiation of hemodialysis or peritoneal dialysis or kidney transplantation.

Analytical Approach: For each patient with cancer, 2 controls matched for age, sex, estimated glomerular filtration rate, diabetes, and hypertension were included. To address the competing risk of death, a competing risk survival analysis was conducted using the Fine and Gray method.

Results: Occurrence of KFRT was higher in patients with cancer than in controls without cancer (incidence rates of 1.07 vs 0.51 cases per 1,000 person-years). Competing risk analysis showed that cancer was significantly associated with an increased risk of KFRT after adjusting for other potential predictors (adjusted hazard ratio, 2.29 [95% CI, 2.20-2.39]). Multiple myeloma, leukemia, lymphoma, and kidney, ovarian, and liver cancer were most significantly associated with an increased KFRT risk, with multiple myeloma conferring the highest risk across age and sex groups. All subgroups of patients with cancer (based on age, sex, smoking, alcohol, exercise, obesity, and comorbid conditions) exhibited a higher risk of KFRT.

Limitations: Causal association between cancer and kidney outcomes could not be confirmed.

Conclusions: Patients with cancer, particularly those with multiple myeloma, exhibited an increased risk of KFRT after accounting for the competing risk of death.

Visual Abstract online

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Am J Kidney Dis. 79(4):507-517. Published online August 17, 2021.

doi: 10.1053/j.ajkd.2021.06.024

Cancer is a major cause of disability and mortality worldwide.[1,2] According to the GLOBOCAN report, the global cancer burden is estimated to have reached 18.1 million new cases, with 9.6 million deaths in 2018.[3] However, mortality rates associated with most common cancers are reaching a plateau or decreasing in developed countries as a result of a reduction in known risk factors, screening and early detection, and improved treatment.[4] The 2016 national cancer statistics report in Korea showed that cancer survival had increased 1.3-fold in the previous 10 years; consequently, the number of patients with cancer in Korea is estimated to be 1.74 million.[5] The increasing prevalence of cancer emphasizes the need for comprehensive management of cancer-associated complications.

Onconephrology, which highlights the interaction between cancer and kidney disease, has emerged as a new clinical concept in recent years.[6] Several studies have reported an increased risk of cancer in dialysis and kidney transplant populations compared with the general population.[7-9] Moreover, albuminuria or moderately reduced glomerular filtration rate may be associated with a higher risk of cancer; however, this relationship varies for different types of cancer.[10-13] The link between cancer and the risk of developing kidney failure with replacement therapy (KFRT) has not been well defined. A previous study showed that cancer did not accelerate the rate of kidney disease progression; however, this study was performed with a relatively small cohort of patients with chronic kidney disease (CKD).[14]

In the present study, we hypothesized that patients with cancer may have a higher risk of KFRT and that the risk would differ according to cancer type. We used data from the large National Health Insurance Service (NHIS) database to test this hypothesis. Determining whether there is a robust association between cancer and the risk of developing KFRT can have important public health implications in the prevention and early detection of kidney disease progression in patients with cancer.

Methods

NHIS Data Source

Anonymized data are publicly available from the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do). In this study, we used the national health insurance claims database established by the Korean NHIS, which includes all claims data provided

PLAIN-LANGUAGE SUMMARY

Previous studies have shown an increased cancer risk within the dialysis and kidney transplant populations compared with the general population. However, it is unclear whether cancer increases the risk of kidney failure. This population-based cohort study was conducted using the Korean National Health Insurance Service database and compared approximately 825,000 patients with cancer versus twice as many patients without cancer but matched on other characteristics. This study found that cancer was associated with an increased risk of kidney failure, even after adjusting for potential confounders and addressing the competing risk of death. Types of cancer that were most significantly associated with kidney failure included multiple myeloma, leukemia, lymphoma, kidney cancer, ovarian cancer, and liver cancer.

by the NHIS and Medical Aid programs. The Korean NHIS database includes, for the entire Korean population, sociodemographic data and all medical expenses for inpatient and outpatient services, pharmacy dispensing claims, and mortality data.[15,16] All insured Korean individuals older than 40 years of age undergo a biannual health checkup supported by the NHIS, and employed Koreans older than 20 years are required to undergo an annual health checkup. Body weight (in kilograms), height and waist circumference (in centimeters), and systolic and diastolic blood pressure (in millimeters of mercury) are measured during these checkups. In this study, we used a subset of NHIS health checkup data corresponding to the period between 2009 and 2018.

The study protocol was approved by the institutional review board of Chonnam National University Hospital (CNUH-EXP-2020-007). Patient identification numbers were anonymized to protect individual privacy. Anonymized and deidentified data were used for analysis, so the institutional review board waived the need for informed consent.

Study Population and Follow-up

We identified participants who were newly diagnosed with cancer using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), codes (C00-C99) during the identification period from January 2009 to December 2016. Among the 1,677,227 patients with cancer aged ≥20 years, those who had not completed a health checkup within 2 years before cancer diagnosis (n = 806,445) were excluded. We also excluded patients who had a history of KFRT before the diagnosis of cancer (n = 1,962) and those with missing data (n = 10,327). For comparison between patients with and without cancer, we selected a control group without cancer that was matched for age, sex, estimated glomerular filtration rate (eGFR), diabetes, and hypertension (2 control participants for every patient with cancer). Patients with cancer who were not matched with controls without cancer were excluded (n = 34,128). A total of 2,473,095 participants with (n = 824,365) and without (n = 1,648,730) cancer were followed from baseline to the date of KFRT diagnosis, the date of death before KFRT during the follow-up period, or the last checkup before December 31, 2017, which was the end of follow-up. The detailed enrollment flow chart is shown in Figure 1.

Study Outcomes

The study endpoint was incident KFRT, which was defined as a status of requiring hemodialysis, peritoneal dialysis, or kidney transplant. Patients with KFRT were identified using a combination of the ICD-10-CM codes (N18-N19, Z49, Z94.0, and Z99.2) and a special code assigned to patients receiving maintenance hemodialysis or peritoneal dialysis for ≥3 months or those with a transplant kidney (V001, procedure-related outpatient care or inpatient treatment on the day of hemodialysis; V003, peritoneal dialysis; and V005, kidney transplant). We excluded individuals who had a kidney transplant or dialysis code on the same date as an acute kidney failure code (N17.9). Individuals receiving continuous kidney replacement therapy or short-term peritoneal dialysis were also excluded. The Korean Health Insurance Review and Assessment Service database can be used for the reimbursement of medical expenses for dialysis. Moreover, maintenance dialysis and kidney transplant recipients are registered as special Medical Aid program beneficiaries. Therefore, we were able to use this combined information to identify every patient with KFRT in the South Korean population when analyzing study outcomes.

Measurements and Definitions

Information on patients' smoking status, alcohol consumption, body mass index (BMI), and waist circumference was obtained during health examinations. Participants were additionally categorized into 3 groups according to smoking

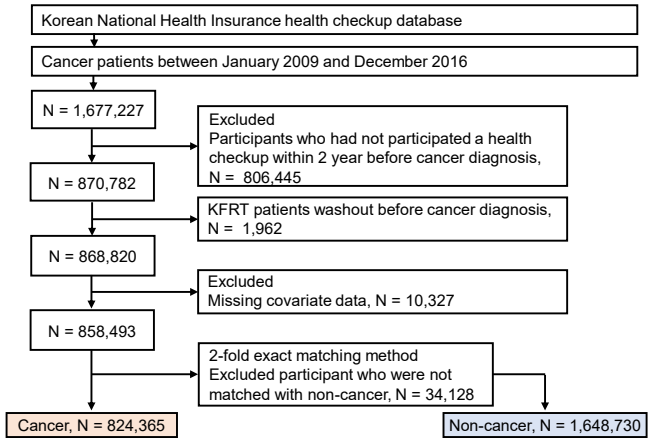

Figure 1. Flow chart of participant enrollment. KFRT, kidney failure with replacement therapy.

status (nonsmokers, former smokers, or current smokers) and 3 categories according to alcohol consumption (none or moderate or heavy drinking [≥30 g alcohol per day]). For each participant, BMI was calculated by dividing the body weight (in kilograms) by the square of the height (in meters). We defined obesity as a BMI ≥25 kg/m^2. The waist circumference of each participant was also measured at the midpoint between the rib cage and iliac crest by a trained examiner. Abdominal obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women according to the definition of the Korean Society for the Study of Obesity.[17] Participation in regular exercise was determined by the response to the question, "Did you exercise moderately for >30 minutes until you were substantially short of breath on more than 5 days during the past week?" Residence in an urban area was also determined. The participants were divided according to income into quartiles of 1 (lowest) through 4 (highest) to assess the effects of socioeconomic status. A low income was defined by classification into quartile 1 or the receipt of Medical Aid benefits.

During the health examination, blood pressure was measured at least twice using a mercury or automatic sphygmomanometer after a minimum rest period of 5 minutes, with the individual in a sitting position. Hypertension was defined as a previous hypertension diagnosis (ICD-10-CM codes I10-I13, I15) and a history of taking ≥1 antihypertensive drug or a recorded systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg in the health examination database. Diabetes was defined as a previous clinical diagnosis (ICD-10-CM codes E11-E14) and a medical history of diabetes or a recorded fasting serum glucose concentration ≥126 mg/dL in the health examination database. Dyslipidemia was identified using the appropriate diagnostic code (ICD-10-CM code E78) and a history of lipid-lowering drug use or a total serum cholesterol concentration ≥240 mg/dL in the health examination database. CKD was defined as an eGFR <60 mL/min/1.73 m^2 and was calculated using the MDRD Study equation.[18] Previous ischemic heart disease and peripheral artery disease were defined based on the diagnostic code (codes I20-I25 and I70, and I73, respectively). Stroke was defined using ICD-10-CM codes I63 and I64 and prescription of brain imaging.

The participants' hemoglobin (in g/dL) and fasting blood glucose, total cholesterol, triglyceride, and high- and low-density lipoprotein cholesterol (all in in mg/dL) concentrations were measured in the fasting state. Proteinuria was measured by the dipstick test. The quality of all laboratory tests was confirmed by the Korean Association for Laboratory Medicine, and the NHIS certified that the hospitals participate in the National Health Insurance health checkup programs.

Statistical Analyses

Data are presented as means ± standard deviation for continuous variables and as the number and proportion for categorical variables. Nonnormally distributed variables are presented as medians (interquartile ranges). To compare the characteristics of interest between groups, paired-samples t tests were applied to continuous variables, and the McNemar χ^2 test was used to assess binary and categorical variables. The mortality rate was calculated per 1,000 person-years. To calculate the attributable risk, the risk for the control group without cancer was subtracted from the risk for the presence of any cancer.[17] To identify the risk of KFRT according to the presence of any cancer and the presence of cancer subtypes, we calculated the hazard ratios (HRs) with 95% CIs and analyzed these data using Fine and Gray models under the matched analyses. Because a mortality event could compete with our outcome of interest, we performed competing risk analysis using the Fine and Gray model,[19,20] which estimates the proportional subdistribution hazard of the event of interest. The proportional hazards assumption was tested visually with Schoenfeld residual plots. In model 1, these calculations were adjusted for age and sex. Model 2 was additionally adjusted for smoking, alcohol consumption, regular exercise, and low income. Model 3 included all covariates from model 2 plus BMI, proteinuria, and a history of diabetes, hypertension, dyslipidemia, ischemic heart disease, peripheral artery disease, stroke, and CKD. Subgroup analyses were conducted based on age, sex, smoking status, heavy alcohol consumption, regular exercise, obesity, diabetes, hypertension, dyslipidemia, CKD, and proteinuria. For subgroup analysis by age, participants were classified into groups aged <65 and ≥65 years. In the assessment of subgroup analyses, the control group was considered as the reference group. Interaction terms were added to test for effect modification across subgroups. Sensitivity analyses were performed while excluding patients with KFRT occurring within 1 and 5 years of follow-up. In addition, we also performed the analyses in which KFRT occurrence during 1 and 5 years of follow-up were included as a competing event alongside death. All statistical tests were 2-tailed, and P values <0.05 were considered statistically significant. All data analyses were conducted using SAS software (version 9.4; SAS Institute).

Results

Baseline Characteristics

The mean baseline age of patients with cancer was 57.6 years, and 47% of the patients were men (Table 1). After matching based on age, sex, eGFR, diabetes, and hypertension with control participants without cancer from the health checkup database and subsequent comparison, patients with cancer were more likely to be former smokers, be frequent alcohol consumers, perform regular exercise, and have proteinuria, ischemic heart disease, and peripheral artery disease. However, they were less likely to have a low income and had lower prevalences of dyslipidemia and stroke.

Table 1. Descriptive Baseline Characteristics of the Study Population

Characteristics	No Cancer	Cancer	*P*
No. of patients	1,648,730 (66.67%)	824,365 (33.33%)	
Age, y	57.59 ± 12.47	57.59 ± 12.47	0.9
Age ≥ 65 y	490,792 (29.77%)	245,396 (29.77%)	0.9
Male sex	774,304 (46.96%)	387,152 (46.96%)	0.9
Smoking			
Never	1,068,388 (64.80%)	528,596 (64.12%)	<0.001
Former	248,999 (15.10%)	133,172 (16.15%)	<0.001
Current	331,343 (20.10%)	162,597 (19.72%)	<0.001
Alcohol consumption			
None	1,023,554 (62.08%)	504,538 (61.20%)	<0.001
Moderate	528,849 (32.08%)	269,974 (32.75%)	<0.001
Heavy	96,327 (5.84%)	49,853 (6.05%)	<0.001
Regular exercise	727,741 (44.14%)	393,319 (47.71%)	<0.001
Diabetes mellitus	272,640 (16.54%)	136,320 (16.54%)	0.9
Hypertension	700,040 (42.46%)	350,020 (42.46%)	0.9
Dyslipidemia	473,165 (28.70%)	223,817 (27.15%)	<0.001
Stroke	56,070 (3.40%)	25,139 (3.05%)	<0.001
Ischemic heart disease	173,468 (10.52%)	95,055 (11.53%)	<0.001
Peripheral artery disease	161,205 (9.78%)	83,995 (10.19%)	<0.001
Low income	421,119 (28.70%)	173,873 (21.09%)	<0.001
CKD	117,394 (7.12%)	58,697 (7.12%)	0.9
eGFR, mL/min/1.73 m^2	87.89 ± 37.10	87.89 ± 37.10	0.9
BMI, kg/m^2	23.92 ± 3.27	23.94 ± 3.23	<0.001
Waist circumference, cm	81.45 ± 9.21	81.58 ± 9.09	<0.001
SBP, mm Hg	125.34 ± 16.17	124.61 ± 15.56	<0.001
DBP, mm Hg	77.20 ± 10.34	76.75 ± 10.05	<0.001
Fasting glucose, mg/dL	102.77 ± 28.17	102.28 ± 26.81	<0.001
Total cholesterol, mg/dL	197.13 ± 38.54	193.71 ± 38.09	<0.001
Triglyceride, mg/dL	112 [78-164]	109 [76-158]	<0.001
HDL, mg/dL	54.72 ± 15.81	54.02 ± 15.71	<0.001
LDL, mg/dL	115.88 ± 35.13	114.12 ± 34.59	<0.001
Hemoglobin, g/dL	13.72 ± 1.57	13.60 ± 1.66	<0.001
Proteinuria			<0.001
Negative	1,159,844 (96.79%)	795,548 (96.5%)	
Positive	52,886 (3.21%)	28,817 (3.50%)	

Values given for continuous variables as mean ± standard deviation or median [interquartile range] and for categorical variables as number (proportion). Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR; estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Presence of Any Cancer and Risk of KFRT

The median follow-up period was 5.2 (IQR, 3.3-7.1) years, with a total of 12,877,386 person-years of follow-up in the whole population: 4.7 years (3,911,542 person-years) and 5.4 years (8,965,844 person-years) for those with and without cancer, respectively (Table 2). During follow-up, KFRT developed in 4,188 participants with cancer and 4,534 without cancer. The attributable risk associated with cancer was 0.56 (95% CI, 0.26-0.87) cases of KFRT per 1,000 person-years of follow-up; 52.8% (95% CI, 23.9%-81.6%) of these cases were among individuals with cancer. Compared with individuals without cancer, those with cancer showed an increased incidence of KFRT (incidence rates of 0.51 vs 1.07 cases per 1,000 person-years). Competing risk analysis with death as a competing event for KFRT progression showed that the risk of KFRT was significantly higher in the cancer group than in the control group, even after completely adjusting for other potential predictors of KFRT (adjusted HR [AHR], 2.29 [95% CI, 2.20-2.39]; Table 2). Moreover, competing risk analysis consistently showed that cancer was significantly associated with an increased risk of KFRT, even after excluding newly developed cancer cases in the group without cancer during the follow-up period (Table S1).

Presence of Cancer Subtypes and Risk of KFRT

Cancers diagnosed for the first time during the follow-up period were classified according to type. The analysis showed that multiple myeloma (incidence rate, 29.1 cases per 1,000 person-years; AHR, 18.97 [95% CI, 14.31-

Table 2. Incidence Rates and Adjusted Hazard Ratios of KFRT According to Any Cancer and Cancer Subtype

Group	N	KFRT	Follow-up, Person-Years	Incidence per 1,000 Person-Years	Adjusted Hazard Ratio (95% CI)		
					Model 1[a]	Model 2[b]	Model 3[c]
Cancer							
No	1,648,730	4,534	8,965,844	0.506	1.000 (reference)	1.000 (reference)	1.000 (reference)
Yes (all)	824,365	4,188	3,911,542	1.071	2.097 (2.025-2.172)	2.129 (2.054-2.206)	2.292 (2.200-2.387)
Yes (excluding MM, kidney cancer)	805,685	3,548	3,824,556	0.928	1.830 (1.763-1.899)	1.855 (1.787-1.925)	2.007 (1.923-2.094)
Cancer subtype							
Stomach	125,895	470	636,919	0.738	1.254 (1.140-1.380)	1.270 (1.154-1.398)	1.328 (1.192-1.479)
Colon and rectum	102,693	495	521,061	0.950	1.721 (1.560-1.898)	1.764 (1.599-1.947)	1.787 (1.600-1.997)
Liver	47,167	592	173,470	3.413	3.297 (2.961-3.672)	3.322 (2.980-3.703)	3.892 (3.464-4.372)
Pancreas	15,134	54	42,505	1.270	0.948 (0.722-1.243)	0.947 (0.718-1.250)	1.005 (0.739-1.365)
Lung	50,222	182	179,544	1.014	1.101 (0.949-1.278)	1.082 (0.931-1.259)	1.135 (0.964-1.335)
Breast	81,408	103	404,648	0.255	1.469 (1.191-1.812)	1.486 (1.206-1.831)	1.642 (1.300-2.072)
Cervix uteri	15,272	65	77,526	0.838	3.707 (2.610-5.266)	3.719 (2.616-5.288)	3.864 (2.674-5.582)
Thyroid	154,673	200	869,472	0.230	1.397 (1.205-1.620)	1.428 (1.230-1.658)	1.459 (1.240-1.718)
Lymphoma	12,300	111	54,694	2.030	4.432 (3.355-5.854)	4.607 (3.479-6.101)	5.508 (4.106-7.389)
Ovary	7,409	30	33,680	0.891	2.717 (1.723-4.286)	2.805 (1.776-4.432)	3.902 (2.499-6.092)
Prostate	29,651	208	161,097	1.291	1.589 (1.369-1.844)	1.643 (1.414-1.909)	1.826 (1.541-2.163)
Lip and oral cavity	7,539	28	34,278	0.817	1.240 (0.833-1.847)	1.289 (0.861-1.930)	1.262 (0.807-1.975)
Esophagus	6,706	38	26,047	1.459	1.790 (1.263-2.538)	1.826 (1.282-2.600)	2.076 (1.412-3.052)
Bile duct	12,296	55	44,383	1.239	1.642 (1.233-2.188)	1.666 (1.247-2.225)	1.902 (1.383-2.617)
Larynx	3,357	12	17,058	0.704	0.978 (0.539-1.773)	1.027 (0.566-1.864)	1.117 (0.605-2.064)
Corpus uteri	8,602	24	41,805	0.574	2.626 (1.616-4.268)	2.587 (1.589-4.210)	2.911 (1.726-4.910)
Testis	746	0	3,774	0	–	–	–
Kidney	14,603	205	72,012	2.847	4.723 (3.806-5.860)	4.901 (3.943-6.093)	4.899 (3.873-6.197)
Bladder	14,241	175	72,996	2.397	3.134 (2.575-3.815)	3.157 (2.586-3.854)	3.264 (2.603-4.092)
Nervous system	8,370	24	34,428	0.697	1.114 (0.731-1.697)	1.110 (0.731-1.688)	1.430 (0.935-2.188)
MM	4,077	435	14,974	29.051	18.752 (14.102-24.934)	19.232 (14.486-25.534)	18.969 (14.305-25.153)
Leukemia	8,646	139	31,797	4.372	6.419 (4.776-8.627)	6.621 (4.921-8.908)	8.223 (6.033-11.209)
Skin	1,992	6	9,052	0.663	0.752 (0.315-1.797)	0.806 (0.341-1.904)	0.678 (0.238-1.931)
Others	91,366	537	354,323	1.516	1.917 (1.743-2.108)	1.930 (1.754-2.123)	2.078 (1.873-2.307)

Abbreviations: CI, confidential interval; KFRT, kidney failure with replacement therapy; MM, multiple myeloma.
[a]Fine and Gray model 1 is adjusted for age and sex.
[b]Fine and Gray model 2 is adjusted for age, sex, smoking, alcohol consumption, regular exercise, and low income.
[c]Fine and Gray model 3 is adjusted for age, sex, smoking, alcohol consumption, regular exercise, low income, body mass index, proteinuria, and previous histories of diabetes, hypertension, dyslipidemia, ischemic heart disease, stroke, peripheral artery disease, and chronic kidney disease.

25.15]) was associated with the highest risk of KFRT among all cancer types (Table 2), followed by leukemia, lymphoma, kidney cancer, ovarian cancer, and liver cancer. The AHRs for KFRT were higher for patients with hematologic malignancies than for those with solid cancers. Among the solid cancers, those originating in the kidney, liver, ovary, cervix, bladder, uterus, and esophagus led to a relatively higher risk of KFRT. However, there was no significant association between cancers of the pancreas, lung, skin, oral cavity, larynx, and nerves and the risk of KFRT.

The effect modification of cancer subtypes by age or sex was evaluated based on exploratory data analysis because the incidence and prevalence of cancer subtypes differ by age and sex.[5] We performed a subgroup analysis according to patient age <65 or ≥65 years (Table S2). Multiple myeloma was associated with the greatest risk of KFRT in both age groups (age <65 y: AHR, 35.58 [95% CI, 20.68-61.22]; age ≥65 y: AHR, 12.50 [95% CI, 8.98-17.41]). Furthermore, leukemia, lymphoma, and cancers of the liver, kidney, cervix, uterus, ovary, and bladder showed a higher HR for the risk of KFRT in both age groups. However, whereas patients aged <65 years with pancreas, lung, breast, oral cavity, or biliary cancer showed an increased risk of KFRT, those aged ≥65 years did not.

On subgroup analysis stratified by sex, multiple myeloma, leukemia, lymphoma, and cancers of the liver, kidney, and bladder were associated with a higher risk of KFRT progression in both sexes compared with individuals without cancer (Table S3). Additionally, pancreas, thyroid, and bile duct cancer increased the risk of KFRT in women but not in men.

Subgroup Analyses

When performing subgroup analyses stratified by age, sex, health behavior–related factors, obesity, and comorbidities, patients with cancer still showed a higher risk of KFRT (Table 3). Compared with the control group without cancer, the risk of KFRT among patients with cancer was higher in those aged <65 years than in those aged ≥65 years. In addition, in terms of interaction, higher AHRs for incident KFRT were observed in several subgroups, such as women, current smokers, and those performing regular exercise. On the contrary, compared with control participants without cancer, patients with cancer who had a high waist circumference and/or a history of diabetes, hypertension, dyslipidemia, CKD, or proteinuria were at a relatively lower risk for KFRT than those without these comorbidities. However, the association between cancer and the risk of KFRT was not significantly different among heavy drinkers and those with high BMI.

Sensitivity Analyses

To account for the possibility of reverse causation, a sensitivity analysis was performed that excluded participants in whom KFRT developed within 1 and 5 years of follow-up (Tables S4-S9). The results showed that fully adjusted HRs for incident KFRT were 2.29 (95% CI, 2.19-2.39) and 2.08 (95% CI, 1.89-2.28), respectively, in patients with cancer even after competing risk analysis; this therefore indicated no impact on the overall association between cancer and the risk of KFRT. Additionally, analyses were repeated in which KFRT events that occurred within 1 and 5 years of follow-up were included as a competing event in addition to death, and the results were similar to the overall results. The adjusted HRs were 2.07 (95% CI, 1.98-2.16) and 1.14 (95% CI, 1.06-1.23), respectively (Tables S10 and S11).

Discussion

The present real-world, population-based study investigated the association of cancer with the risk of KFRT progression, with a specific focus on a large Asian population. To our knowledge, no previous studies have reported the increased risk of KFRT due to cancer in a population-based cohort. In the present study, patients with cancer, particularly those with multiple myeloma, experienced a higher risk of KFRT even after accounting for the competing risks of death.

A large retrospective cohort study was conducted by Butler et al in patients with KFRT who were undergoing hemodialysis[7]; they showed a higher burden of cancer in the KFRT population than in the general population. The 5-year cumulative incidence of any cancer was 9.48%, with kidney and bladder cancers being the most common. Another population-based study of kidney transplant candidates and recipients found that, for kidney failure–related cancer, particularly kidney and thyroid cancer, the risk was higher during dialysis following kidney failure.[8] Although several population-based cohort studies[7-9,21] have demonstrated that dialysis is independently associated with a higher risk of urinary and thyroid cancers, a parallel association between cancer and cancer-related KFRT was not observed.

A recent retrospective CKD cohort study[14] using the Salford Kidney Study data showed that cancer was an independent risk factor for all-cause mortality. However, cancer status was not significantly associated with progression to KFRT; this is contrary to our results. This difference may be due to the relatively small number of cancer cases (n = 339) in the European study and the fact that enrolled patients had advanced CKD (stages 3-5). Our study demonstrated an increased risk of KFRT in patients with cancer regardless of CKD status using NHIS data of more than 800,000 adults with cancer; this represents a real-world Korean population.

Several pathophysiologic mechanisms may explain the association between cancer and progression to KFRT. Nephrotoxicity associated with anticancer therapy, paraneoplastic kidney injury, electrolyte/metabolic disturbance, contrast medium–associated acute kidney injury (AKI), and obstructive nephropathy due to direct cancer invasion or lymphadenopathy are well-known risk factors for kidney injury in patients with cancer.[22] Moreover, total and partial

Table 3. Fully Adjusted Hazard Ratios for KFRT According to Various Subgroups

Subgroup	N	KFRT	Follow-up, Person-Years	Incidence Per 1,000 Person-Years	AHR (95% CI)[a]	*P* for Interaction
Age						<0.001
<65 y						
No cancer	1,157,938	1,921	6,193,686	0.310	1.000 (reference)	
Cancer	578,969	2,185	2,831,746	0.772	3.114 (2.917-3.324)	
≥65 y						
No cancer	490,792	2,613	2,772,158	0.943	1.000 (reference)	
Cancer	245,396	2,003	1,079,796	1.855	1.801 (1.706-1.901)	
Sex						<0.001
Male						
No cancer	774,304	3,178	4,316,067	0.736	1.000 (reference)	
Cancer	387,152	2,735	1,782,909	1.534	2.158 (2.053-2.268)	
Female						
No cancer	874,426	1,356	4,649,778	0.292	1.000 (reference)	
Cancer	437,213	1,453	2,128,633	0.683	2.616 (2.435-2.810)	
Smoking						0.006
Never/former						
No cancer	1,317,387	3,472	7,220,246	0.481	1.000 (reference)	
Cancer	661,768	3,172	3,188,493	0.995	2.245 (2.135-2.360)	
Current						
No cancer	331,343	1,062	1,745,598	0.608	1.000 (reference)	
Cancer	162,597	1,016	723,049	1.405	2.960 (2.560-3.422)	
Alcohol consumption						0.07
Not heavy						
No cancer	1,552,403	4,329	8,447,117	0.512	1.000 (reference)	
Cancer	774,512	3,939	3,683,917	1.069	2.257 (2.163-2.355)	
Heavy						
No cancer	96,327	205	518,727	0.395	1.000 (reference)	
Cancer	49,853	249	227,625	1.094	3.220 (1.771-5.854)	
Regular exercise						<0.001
No						
No cancer	920,989	2,787	4,934,518	0.565	1.000 (reference)	
Cancer	431,046	2,390	2,017,247	1.185	2.065 (1.943-2.195)	
Yes						
No cancer	727,741	1,747	4,031,327	0.433	1.000 (reference)	
Cancer	393,319	1,798	1,894,295	0.949	2.689 (2.440-2.964)	
BMI						0.9
<25 kg/m^2						
No cancer	1,080,702	2,739	5,887,525	0.465	1.000 (reference)	
Cancer	540,437	2,518	2,553,806	0.986	2.352 (2.207-2.507)	
≥25 kg/m^2						
No cancer	568,028	1,795	3,078,319	0.583	1.000 (reference)	
Cancer	283,928	1,670	1,357,736	1.230	2.453 (2.235-2.691)	
Waist circumference						<0.001
<90/85 cm (M/F)						
No cancer	1,057,590	2,501	5,787,216	0.432	1.000 (reference)	
Cancer	525,069	2,357	2,496,003	0.944	2.613 (2.441-2.798)	
≥90/85 cm (M/F)						
No cancer	591,140	2,033	3,178,628	0.640	1.000 (reference)	
Cancer	299,296	1,831	1,415,539	1.294	2.109 (1.948-2.282)	
Diabetes mellitus						<0.001
No						
No cancer	1,376,090	1,782	7,504,557	0.237	1.000 (reference)	
Cancer	688,045	2,330	3,313,606	0.703	3.166 (2.984-3.358)	

(Continued)

Table 3 (Cont'd). Fully Adjusted Hazard Ratios for KFRT According to Various Subgroups

Subgroup	N	KFRT	Follow-up, Person-Years	Incidence Per 1,000 Person-Years	AHR (95% CI)[a]	*P* for Interaction
Yes						
No cancer	272,640	2,752	1,461,288	1.883	1.000 (reference)	
Cancer	136,320	1,858	597,936	3.107	1.653 (1.560-1.751)	
Hypertension						<0.001
No						
No cancer	948,690	591	5,140,340	0.115	1.000 (reference)	
Cancer	474,345	1,188	2,303,090	0.516	4.990 (4.518-5.511)	
Yes						
No cancer	700,040	3,943	3,825,504	1.031	1.000 (reference)	
Cancer	350,020	3,000	1,608,452	1.865	1.843 (1.761-1.929)	
Dyslipidemia						<0.001
No						
No cancer	1,175,565	2,083	6,472,155	0.322	1.000 (reference)	
Cancer	600,548	2,479	2,880,886	0.861	3.025 (2.823-3.242)	
Yes						
No cancer	473,165	2,451	2,493,690	0.983	1.000 (reference)	
Cancer	223,817	1,709	1,030,655	1.658	1.672 (1.546-1.808)	
CKD						<0.001
No						
No cancer	1,531,336	1,775	8,305,421	0.214	1.000 (reference)	
Cancer	765,668	2,512	3,643,113	0.690	3.625 (3.406-3.857)	
Yes						
No cancer	117,394	2,759	660,424	4.178	1.000 (reference)	
Cancer	58,697	1,676	268,429	6.244	1.421 (1.341-1.505)	
Proteinuria						<0.001
Negative						
No cancer	1,595,844	2,481	8,686,793	0.286	1.000 (reference)	
Cancer	795,548	2,963	3,785,684	0.783	2.928 (2.789-3.075)	
Positive						
No cancer	52,886	2,053	279,051	7.357	1.000 (reference)	
Cancer	28,817	1,225	125,858	9.733	1.250 (1.118-1.399)	

Abbreviations: AHR, adjusted hazard ratio; BMI, body mass index; CI, confidential interval; CKD, chronic kidney disease; KFRT, kidney failure with replacement therapy.
[a]Fine and Gray model adjusted for age, sex, smoking, alcohol consumption, regular exercise, low income, body mass index, proteinuria, and previous histories of diabetes, hypertension, dyslipidemia, ischemic heart disease, stroke, peripheral artery disease, and chronic kidney disease.

nephrectomy in patients with kidney cancer can also increase the risk of KFRT.[23] The incidence and severity of AKI varies with cancer type or stage, treatment regimen, and underlying comorbidities; however, AKI and CKD are prevalent in patients with cancer[24,25] and are proposed to be risk factors for KFRT.[26]

Advanced age, obesity, diabetes, hypertension, dyslipidemia, CKD, and proteinuria per se are well-known traditional risk factors for KFRT.[27-29] Therefore, in patients with these risk factors, the relative risk of KFRT attributable to cancer may be attenuated by the presence of comorbidities. In our subgroup analysis, the relative risk of KFRT was lower in patients with cancer with CKD than in those without CKD (AHRs of 1.42 [95% CI, 1.34-1.51] and 3.63 [95% CI, 3.41-3.86] for cancer with vs without CKD, respectively; $P < 0.001$ for interaction). Similarly, the subgroup analysis suggested that patients with cancer who are older, do not exercise regularly, or have comorbid conditions such as proteinuria, diabetes, hypertension, and dyslipidemia have an attenuated relative risk for the development of KFRT. Therefore, cancer may have exerted a relatively stronger effect on the development of KFRT in patients without traditional risk factors than in those with comorbid conditions. In this context, when younger and healthier patients (with no history of diabetes, hypertension, dyslipidemia, CKD, or proteinuria) are diagnosed with cancer, intensive strategies need to be adopted to prevent KFRT.

We investigated AHRs for KFRT according to cancer type, as the association between individual cancer types and risk of KFRT was unclear. In our study, multiple myeloma showed the highest HR for the development of KFRT despite its low incidence in Korea.[5] Our results corroborate those of previous studies that suggested that multiple myeloma is the most common malignancy leading to KFRT.[30,31] A previous study showed that the serum creatinine level was increased in almost half of patients with newly diagnosed multiple myeloma.[32] Even with

aggressive treatment, progression to KFRT occurs in as many as 65% of patients with cast nephropathy within 3 months of diagnosis.[31,33] The pathogenesis of multiple myeloma–induced kidney injury primarily involves cast nephropathy, monoclonal immunoglobulin deposition disease, and hypercalcemia.[34] A report published in 2018 listed liver cancer as the sixth most commonly diagnosed cancer worldwide and the fourth leading cause of cancer death.[3] Among patients with solid cancers, liver cancer was found to increase the risk of KFRT. The reason for this increased risk is unknown, but it may be related to the marked impairment in kidney function that occurs in severe chronic liver disease, acute liver failure, and advanced cirrhosis–induced hepatorenal syndrome. Furthermore, AKI may also occur after transarterial chemoembolization in patients with hepatocellular carcinoma.[35,36] Pancreatic and bile duct cancer significantly increased the risk of KFRT in women and patients aged <65 years, respectively; however, multiple myeloma, leukemia, lymphoma, and cancers of the kidney, bladder, and liver, which conferred the highest risk among all cancers, increased the risk of KFRT across the entire age spectrum and both sexes. Therefore, patients with these cancers require greater kidney failure prevention efforts and closer surveillance.

This study has several limitations. First, the study population was from a single country. As the cancer burden and causes of cancer-related deaths vary significantly according to economic, social, and lifestyle factors, it would be difficult to generalize the results of our study to other nations. Second, because of the retrospective cohort design of the study, a causal association between cancer and kidney outcomes could not be confirmed. Therefore, reverse causality is plausible because patients with kidney failure may be at a greater risk of developing cancer. However, to minimize the possible effects of reverse causality, in sensitivity analysis, we excluded patients with preexisting KFRT and those in whom KFRT developed within 1 and 5 years of follow-up. Third, AKI and particular treatments for each cancer could contribute to the development of KFRT. We were unable to investigate this possible association because the information available in the database was limited. However, this study also had some notable strengths. To the best of our knowledge, it is the largest population-based cohort study assessing the association of cancer with the risk of KFRT, and used a well-established and validated longitudinal database of Korean patients with cancer.[37,38] Moreover, we evaluated the risk of KFRT in 23 different cancers to determine how risk varies among specific cancer types.

In conclusion, onconephrology is an emerging and expanding field that is gaining more attention as the prevalence of cancer increases. In this population-based cohort study, we found that cancer is associated with an increased risk of KFRT. In particular, multiple myeloma, leukemia, lymphoma, and kidney, ovarian, and liver cancers conferred an increased risk of KFRT. The presence of kidney failure has significant influence on the treatment options available to patients with cancer, including certain chemotherapeutic agents, hematopoietic stem cell transplant, and surgery, and affects overall cancer-related survival. Therefore, it is crucial for nephrologists and oncologists to be aware of the risk of KFRT in patients with cancer so better preventive strategies can be developed. Future prospective cohort studies are needed to clarify the effect of early detection and management of kidney disease progression on the prevention of kidney failure in patients with cancer.

Supplementary Material

Supplementary File (PDF)

Table S1: HRs of KFRT for any cancer type after excluding newly developed cancer cases in the noncancer group during the follow-up period.

Table S2: Incidence rates and HRs of KFRT according to cancer subtype, stratified by age.

Table S3: Incidence rates and HRs of KFRT according to cancer subtype, stratified by sex.

Table S4: Sensitivity analysis of incidence rates and HRs of KFRT for all cancers and cancer subtypes after excluding KFRT within 1 y of follow-up.

Table S5: Sensitivity analysis of incidence rates and HRs of KFRT for all cancers and cancer subtypes after excluding KFRT within 5 y of follow-up.

Table S6: Sensitivity analysis of incidence rates and HRs of KFRT for all cancers, stratified by age, after excluding KFRT within 1 y of follow-up.

Table S7: Sensitivity analysis of incidence rates and HRs of KFRT according to cancer subtype, stratified by age, after excluding KFRT within 5 y of follow-up.

Table S8: Sensitivity analysis of incidence rates and HRs of KFRT according to cancer subtype, stratified by sex, after excluding KFRT within 1 y of follow-up.

Table S9: Sensitivity analysis of incidence rates and HRs of KFRT according to cancer subtype, stratified by sex, after excluding KFRT within 5 y of follow-up.

Table S10: Sensitivity analysis of HRs of KFRT during 1 y of follow-up included as a competing event alongside death for all cancers and according to cancer subtype.

Table S11: Sensitivity analysis of HRs of KFRT during 5 y of follow-up included as a competing event alongside death for all cancers and according to cancer subtype.

Article Information

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Support: This work was supported by the Bio & Medical Development Program through the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2017M3A9E8023001, NRF-2017M3A9E8023018); by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute funded by the Ministry of Health & Welfare, Republic of Korea (grants HI18C0331, HR20C0021); and by a grant (BCRI21023) from Chonnam National University Hospital Institute for Biomedical Science. The funders had no role in study design; data collection, analysis, or reporting; or the decision to submit for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received August 12, 2020. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form June 9, 2021.

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Risk of Kidney Failure in Patients With Cancer

Setting & Participants

South Korean Population-Based Cohort Study

NHIS database
N = 2,473,095

Cancer
N = 824,365

2-fold matched controls:
age, sex, eGFR, DM, and HTN

Non-Cancer
N = 1,648,730

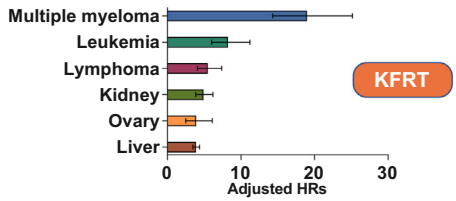
Outcomes & Analysis

Outcomes:
Kidney Failure Requiring Replacement Therapy (KFRT)

Analysis:
Competing risk analysis using the Fine and Gray's model

Results

KFRT	Non-Cancer	Cancer
Incidence rate, per 1,000 PY	0.51	1.07
Adjusted HRs	1 (ref)	2.29



CONCLUSION: Cancer patients, particularly those with multiple myeloma, exhibited an increased risk of KFRT, even after accounting for competing risks of death.

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