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Risk of Cancer in Middle-aged Patients With Gout: A Nationwide Population-based Study in Korea

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ABSTRACT. ***Objective.*** Gout is reportedly associated with a higher incidence of cancer. However, patients with gout tend to have several cancer-related factors including obesity, smoking, and alcohol consumption; thus, the precise association between gout and cancer risk remains unclear. We aimed to investigate the risk of cancer in Korean patients with gout.

Methods. Based on the Korea Health Insurance Service database, the subjects comprised patients aged 41–55 years with gout newly diagnosed between 2003 and 2007. We used a multivariable-adjusted Cox proportional hazards model in gout patients and a 1:2 ratio for the matched controls by age, sex, and index year.

Results. We compared 4176 patients with gout with 8352 controls. The mean age and follow-up duration were 48.8 years and 10.1 years in both groups. Overall cancer risk was significantly different between gout patients and controls (HR 1.224, 95% CI 1.073–1.398). The all-cause mortality (HR 1.457, 95% CI 1.149–1.847) and cancer mortality (HR 1.470, 95% CI 1.020–2.136) were higher in patients with gout. In the subgroup analysis, the cancer risks of the stomach (HR 1.710, 95% CI 1.221–2.395), head and neck (HR 1.850, 95% CI 1.071–3.196), and hematologic or lymphoid organ (HR 2.849, 95% CI 1.035–7.844) were higher in patients with gout.

Conclusion. Patients aged 41–55 years with gout have a higher risk of cancer and all-cause and cancer mortality compared with the general population. Therefore, special attention should be paid to higher cancer risk and mortality in these patients who are diagnosed in middle age.

Key Indexing Terms: cancer, gout, mortality, risk

Gout is a common inflammatory disease characterized by hyperuricemia and recurrent acute arthritis.[1] Several studies have reported that hyperuricemia or gout is associated with a higher incidence of cancer.[2,3,4,5] In addition, a metaanalysis and a recent prospective cohort study of crystal-proven gout patients showed that hyperuricemia and gout were associated with increased cancer mortality.[6,7] However, major confounding factors such as obesity, hypertension, diabetes mellitus, and heavy alcohol consumption are common in patients with gout.[8,9,10,11] Metabolic syndrome is a significant risk factor for gout, especially in middle-aged persons,[12] and the incidence of cancer increases with age, with a rapid increase beginning in middle age.[13] It is therefore worthwhile to evaluate the effect of gout on cancer incidence and mortality in middle-aged patients.

Generally, incidence of cancer types associated with smoking, obesity, and alcohol intake, including colon, nasopharyngeal, and pancreatic cancer, has been reported to be higher in patients with gout.[3] Further, in a Taiwan population study, the risk of prostate cancer was reported to be higher in patients with gout than in the general population.[4] In a study of a Danish registry, the incidence of hematologic malignancies including multiple myeloma and leukemia was reported to be higher in patients with gout.[14] This means that the prevalent type of cancer in gout could be dependent on cultures and vary between countries. Here, we investigated the risk of cancer, cancer mortality, and site-specific cancer types in Korean patients with gout, especially in a middle-aged population.

METHODS

Data sources. The present study was conducted using patient records extracted from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) between 2002 and 2015 in Korea.[15] The NHIS-HEALS is a cohort of Korean adults who participated in general

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health screening programs conducted by the NHIS. All subscribers (including medical aid beneficiaries) can receive general health screening biennially or annually (for manual employees) and, in particular, Korean adults aged 40 years or older are eligible for biennial medical checkups.[16] This sample cohort first selected qualified individuals between 2002–2003 who were between the ages of 40–79 years and received general medical screening. This cohort consisted of 514,866 individuals who comprised a 10% simple random sample of all health screening participants in that period. The data collected included information on demographics (such as sex, age, region of residence, type of subscription, socioeconomic status [income], disability, death, cause of death), diagnosis (using the International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10]), medical procedures, prescriptions, and medical checkup data.

A profile study of the NHIS-HEALS found that the age-standardized prevalence of anemia, diabetes, hypertension, obesity, and hypercholesterolemia in NHIS-HEALS participants was similar to the results in those aged 40 or older who participated in the Korean National Health and Nutrition Examination Survey (KNHANES).[15,17] The KNHANES was a cross-sectional survey that consisted of nationally representative samples of the Korean population and had information on health, nutrition, physical conditions, laboratory tests, and chronic diseases.[18] This indicates that the NHIS-HEALS is representative of the sample cohort of the general Korean population.

Study design and study subjects. As shown in Figure 1, we compared gout patients with non-gout individuals as the control group. The study cohort included patients aged 41–55 years with gout that was newly diagnosed between 2003 and 2007. Patients who were diagnosed with gout (ICD-10, M10.xx) were treated with gout-related medications, including colchicine, glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs), allopurinol, febuxostat, or benzbromarone at the date of diagnosis. Previous validation studies had reported that the positive predictive value of diagnostic codes for gout was 61–86%,[19,20] and that of the diagnostic codes in addition to a prescription claim for gout-related medications including colchicine, NSAIDs, or oral glucocorticoids was up to 99%.[21] The cohort entry date of patients with gout was the date of the first diagnosis of gout and prescription for gout-related medications. Patients who were diagnosed with gout in 2002 were excluded. Subjects who had no uric acid test information, no measurement data, and who had measurement outliers were excluded. Patients were also excluded if they were diagnosed with a malignancy before or within 1 year of the index date, or if their follow-up duration was < 1 year.

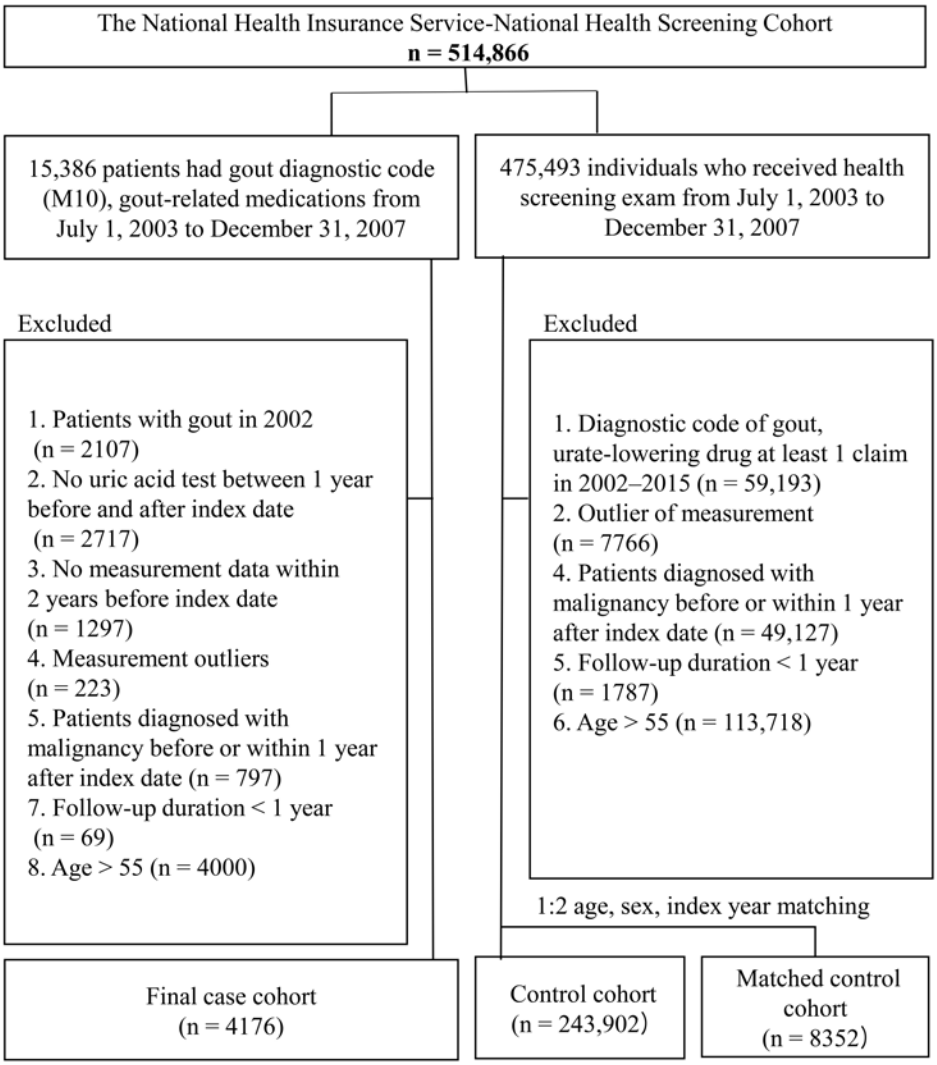

Figure 1. Selection of study population from the National Health Insurance Service-National Health Screening Cohort.

A control cohort included individuals aged 41–55 years who received health checkups between 2003 and 2007 with no diagnostic code for gout and no medical claim for urate-lowering medications. We excluded outlier cases, those diagnosed with cancer before or within 1 year of the index date, and those with a follow-up duration of < 1 year. The cohort entry date of the control group was the date the individual received general medical screening.

Cohort follow-up. In the group with gout, the date of the first gout diagnosis and prescription for gout-related medications was defined as the index date. In the control group, the date of the health checkup was defined as the index date.

If the outcome was a diagnosis of cancer, follow-up started the day after the index date and continued until the occurrence of cancer, death, or end of the study. In case of a mortality outcome, follow-up began from the index date and continued until death or the end of the study.

Study outcome. The primary outcome was newly diagnosed cancer between 2004 and 2015 that required cancer as the main diagnostic code. The secondary outcome was all-cause mortality, cancer mortality, and cancer by site-specific cancer type. In the case of cancer mortality, we worked out the cause of death through "death_code1" and "death_code2" that indicated why the subjects died.

Baseline covariates. All covariates were assessed during the baseline. The following covariates were collected from demographic information including age at diagnosis of gout (or date of medical checkup), sex, income, and region of residence; and comorbid medical conditions including hypertension, diabetes mellitus, kidney disease, chronic obstructive pulmonary disease, and *Helicobacter pylori*-related diseases, including peptic ulcer (only for stomach cancer). In addition, medical checkup data including smoking, alcohol intake, and BMI, and examination and laboratory data including systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, and levels of hemoglobin, were collected.

Statistical analyses. We created a matched control group by conducting age, sex, and index year 1:2 matching to balance these factors. Then, multivariable-adjusted Cox proportional hazards models and subdistribution hazard models with the other covariates except age, sex, and index year were used to minimize potential confounding factors.

Categorical variables in baseline characteristics are presented as frequencies with percentages, and continuous variables are shown as mean with SD or median with IQR. Categorical variables were compared using the chi-square test, and continuous variables were compared using *t* tests.

The incidence of outcomes (including cancer, all-cause mortality, cancer mortality, and incident cancer by site-specific cancer type) was calculated as a rate per 1000 person-years (PY). A Kaplan–Meier plot was used to show the cumulative incidence of cancer diagnosis by the 2 groups and to compare differences between them, we conducted a log-rank test. A multivariable-adjusted Cox proportional hazards model with covariates was also used to assess the association between gout and cancer diagnosis and all-cause mortality (HR [95% CI]). When a proportional hazards assumption was violated, we conducted stratified Cox proportional hazards only for covariates to solve this problem. To estimate the crude incidence of cancer mortality and competing mortality, we used the cumulative incidence function (CIF).[22] We also conducted a subdistribution hazards model to assess the effect of covariates on the CIF for cancer mortality and mortality from other causes.

All statistical analyses were performed using SAS Enterprise Guide software (version 7.13; SAS Institute) and R software version 3.6.2 (The R Foundation). $P < 0.05$ was considered statistically significant.

Ethical approval. This study fulfilled the ethical guidelines of the Declaration of Helsinki, and was approved by the Institutional Review Board of Asan Medical Center (number: 2018-0299). The requirement for informed consent was waived because an existing database was used.

RESULTS

Baseline characteristics. According to the medical checkup cohort of the Korean Health Insurance Service database, 4176 patients were newly diagnosed with gout. We included 8352 matched controls in a 1:2 ratio by age, sex, and index year, who presented between 2003 and 2007 (Figure 1). As shown in Table 1, patients with gout were more likely to be nonsmokers and had a greater alcohol intake and more comorbidities than controls. In addition, BMI and systolic and diastolic blood pressure were higher than in the control group. The mean age and follow-up duration for cancer were 48.8 years and 10.1 years, respectively.

Overall cancer risk in patients with gout. As shown in Table 2, the overall cancer occurrence rates in the gout and control groups were 9.241 and 7.218 per 1000 PY, respectively. A Cox proportional hazards model showed that the risk of cancer was significantly different between patients with gout and controls (HR 1.224, 95% CI 1.073–1.398). According to the Kaplan-Meier plots (Figure 2A), the proportion of patients who developed cancer was significantly higher in those with gout than in controls (log-rank test: $P < 0.001$).

All-cause mortality and cancer mortality. Table 2 shows the all-cause mortality and cancer mortality in patients with gout compared with controls. The overall all-cause mortality rates in the gout group and control group were 2.997 and 1.970 per 1000 PY, respectively. The risks of all-cause mortality (HR 1.457, 95% CI 1.149–1.847) and cancer mortality (HR 1.470, 95% CI 1.020–2.136) were significantly higher in patients with gout than in controls. Also, the plot of the CIF (Figure 2B) indicated that death from cancer was significantly higher in those with gout than in controls (Gray test: $P = 0.002$).

Individual cancer risk in patients with gout. Table 3 shows the individual cancer risk in patients with gout compared with controls. The risk for stomach cancer was higher in patients with gout than in controls (HR 1.710, 95% CI 1.221–2.395). In addition, the risks of head and neck cancer (HR 1.850, 95% CI 1.071–3.196) and hematologic or lymphoid cancers (HR 2.849, 95% CI 1.035–7.844) were higher than in controls. The risk of other site-specific cancers was not significantly different between patients with gout and controls.

DISCUSSION

Cancer is the second-leading cause of death in the United States[23] and the foremost cause of death in South Korea[24]; the incidence seems likely to increase in the future.[25] Gout is a chronic disease that is preventable and manageable; thus, understanding the relationship between gout and cancer risk is important for the reduction of cancer mortality. In this Korean population-based study, patients aged 41–55 years with gout had a higher risk of cancer compared with the non-gout population. Also, all-cause mortality and cancer mortality were higher in patients with gout than in controls. In terms of cancer type, patients with gout have a higher risk of stomach, head and neck, and hematologic or lymphoid cancers compared with the non-gout population.

Previous studies have reported that overall cancer risk is higher by 15–25% in patients with gout compared to those without gout.[3,4] Most patients with gout have several risk factors for cancer, including heavy alcohol consumption, a smoking habit, obesity, and metabolic syndrome that are confounding

Table 1. Baseline characteristics of study cohort of patients aged 41–55 years matched 1:2 by age, sex, and index date.

	Non-gout, n = 8352	Gout, n = 4176	*P**
Follow-up duration, cancer, yrs	10.1 ± 2	10.1 ± 2.3	0.49
Follow-up duration, mortality, yrs	10.5 ± 1.6	10.5 ± 1.7	0.23
Age, yrs	48.8 ± 3.8	48.8 ± 3.8	> 0.99
Sex, female	2488 (29.8)	1244 (29.8)	> 0.99
Income[a]			< 0.0001
Group 1 (1–3)	1601 (19.2)	633 (15.1)	
Group 2 (4–7)	2629 (31.5)	1251 (30.0)	
Group 3 (8–10)	4122 (49.4)	2292 (54.9)	
Urban			0.003
Seoul	1366 (16.4)	677 (16.2)	
Metropolitan city	2607 (31.2)	1186 (28.4)	
Other	4379 (52.4)	2313 (55.4)	
Smoking			0.03
None	4665 (55.9)	2378 (56.9)	
Ex-smoker	980 (11.7)	542 (13.0)	
Current	2306 (27.6)	1067 (25.6)	
Unknown	401 (4.8)	189 (4.5)	
Alcohol, no. drinks			< 0.0001
None	3787 (45.3)	1814 (43.4)	
2–3/month	1545 (18.5)	735 (17.6)	
1–2/week	1931 (23.1)	955 (22.9)	
3–4/week	673 (8.1)	434 (10.4)	
Daily	283 (3.4)	177 (4.2)	
Unknown	133 (1.6)	61 (1.5)	
Comorbidities			
Diabetes mellitus	654 (7.8)	549 (13.1)	< 0.0001
Hypertension	1162 (13.9)	1170 (28.0)	< 0.0001
Kidney disease	83 (1.0)	142 (3.4)	< 0.0001
COPD	58 (0.7)	60 (1.4)	< 0.0001
H. pylori–related diseases[b]	1924 (23)	1528 (36.6)	< 0.0001
Measurements			
BMI	24.0 ± 2.7	24.8 ± 2.73	< 0.0001
SBP, mmHg	124.8 ± 15.7	126.7 ± 16.8	< 0.0001
DBP, mmHg	79.2 ± 10.7	80.5 ± 11.5	< 0.0001
Fasting glucose, mg/dL	96.4 ± 23	96.4 ± 21.6	0.88
Total cholesterol, mg/dL	198.1 ± 35.3	200.8 ± 38	0.001
Hemoglobin, g/dL	14.3 ± 1.5	14.3 ± 1.5	0.18

Continuous variables are presented as the mean ± SD or median (IQR). Categorical variables are presented as n (%). * Chi-square test was conducted for categorical variables and *t* test for continuous variables. [a]Income divided into 10 grades and grouped by 3 categories, where group 3 is the highest grade. [b] *Helicobacter pylori*–related diseases, including peptic ulcers. COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; SBP: systolic blood pressure.

factors for evaluating the causal relationship between gout and cancer risk.[10] We used a multivariable-adjusted Cox proportional hazards model in the 41- to 55-year age group to evaluate the relationship between gout and cancer risk more clearly. Patients with gout showed different characteristics compared with controls; however, after adjusting for the risk factors, patients with gout aged 41–55 years showed a higher risk of cancer than controls. In addition, there is an association between gout and higher cancer risk in patients with gout aged 56–79 years (HR 1.126, 95% CI 1.025–1.237; Supplementary Table 1, available with the online version of this article). Thus, all patients with gout aged over 40 years have a higher risk of cancer than those without gout. The results of this study are in line with the aforementioned studies on gout and cancer risk. However, to our knowledge, this is the first evidence to demonstrate the effect of gout on incidental cancer, especially in the middle-aged population. According to our findings, cancer screening may be important in middle-aged patients with newly diagnosed gout.

Several studies have reported that gout is associated with a higher risk of all-cause mortality, which is explained by the elevated risk of death from cardiovascular disease.[26,27] In regard to cancer mortality, a previous study reported that patients with gout have increased cancer mortality, compared with the general population.[6] Similar to the previous study, the all-cause and cancer

Table 2. Incidence and HR for cancer and mortality in 1:2 matched cohorts aged 41-55 years.

	Non-gout	Gout
Cancer incidence		
Patients, n	8352	4176
PY	84,645	42,202.5
Events	611	390
Rate per 1000 PY	7.218	9.241
HR (95% CI)[a]	Ref	1.224 (1.073–1.398)*
All-cause mortality		
PY	87,316.38	44,038.43
Events	172	132
Rate per 1000 PY	1.970	2.997
HR (95% CI)[a]	Ref	1.457 (1.149–1.847)*
Death from cancer		
PY	87,316.38	44,038.43
Events	68	49
Rate per 1000 PY	0.779	1.113
HR (95% CI)[b]	Ref	1.470 (1.020–2.136)*
Death from other causes		
PY	87,316.38	44,038.43
Events	104	83
Rate per 1000 PY	1.191	1.885
HR (95% CI)[b]	Ref	1.440 (1.074–1.931)*

* Significant. [a] HR from the stratified Cox proportional hazards regression model, adjusted for residence, income, smoking, drinking, comorbidities (DM, hypertension, kidney disease, COPD), BMI, SBP, DBP, glucose, total cholesterol, and hemoglobin. [b] HR from subdistribution hazards model, adjusted for residence, income, smoking, drinking, comorbidities (DM, hypertension, kidney disease, COPD), BMI, SBP, DBP, glucose, total cholesterol, and hemoglobin. COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; DM: diabetes mellitus; PY: person-years; SBP: systolic blood pressure.

mortalities were higher in the middle-aged gout patients than the control cohort in the present study. There are several studies reporting that hyperuricemia is associated with an increased risk of cancer mortality[2,28]; thus, the increased cancer mortality in gout patients may be associated with hyperuricemia. However, the precise relationship between serum uric acid and cancer mortality is still inconclusive, and pharmacological modulation of hyperuricemia may have a role in reducing cancer mortality, but this remains unknown.

There are diverse results in the increased risk of site-specific cancers in patients with gout or hyperuricemia.[4,29] In the present study, a higher risk of stomach, head and neck, and hematologic or lymphoid cancers was observed in patients with gout compared with controls. These diverse results may be influenced by methodology, ethnicity, and environmental exposure. Korea has the highest incidence of stomach cancer worldwide,[30] and the crude incidence rate of stomach cancer was 59.7 per 100,000 in 2016.[24] Thus, the increased probability of developing the prevalent type of cancer in gout could be considered. On the other hand, a previous study reported that patients with *H. pylori* infections showed a higher incidence of gout and hyperuricemia than those without infection.[31] Indeed, the incidence of *H. pylori*-related diseases, including peptic ulcers, is higher in patients with gout than those without it in the present study. However, the risk of stomach cancer was still higher in patients with gout after adjusting for *H. pylori*–related diseases, including peptic ulcers. Thus, other factors, including hyperuricemia, gout-related medication, or environmental exposure, could contribute to the increased risk of stomach cancer in patients with gout. For hematologic or lymphoid cancers, a previous metaanalysis reported a significant association between hyperuricemia and the risk of lymphoid and hematopoietic system cancers, suggesting that serum uric acid itself has a role in carcinogenesis.[28] Another study reported that gout medications are associated with an increased risk of leukemia and non-Hodgkin lymphoma.[32] Taken together, the association

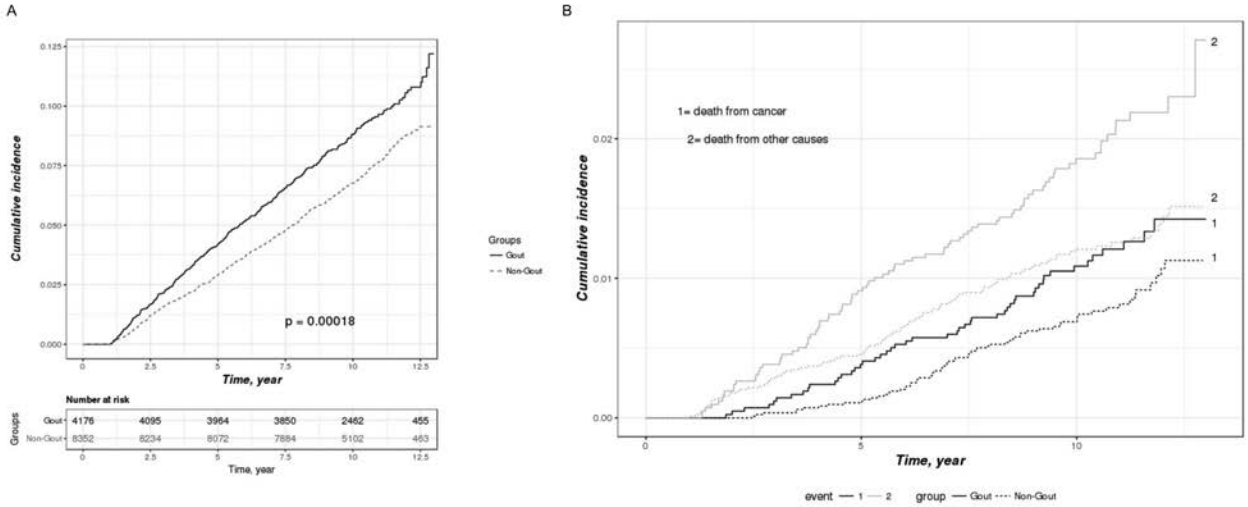

Figure 2. (A) Kaplan-Meier curve for the cumulative incidence of cancer in a 1:2 age-, sex-, and index year–matched cohort. (B) Plot of the cumulative incidence function for cancer mortality and mortality from other causes in a 1:2 age-, sex-, and index year-matched cohort.

Table 3. Incidence and HR for site-specific cancers in 1:2 matched cohorts aged 41–55 years.

Site	Non-gout, n = 8352	Gout, n = 4176
Stomach		
Events	82	69
Rate per 1000 PY	0.943	1.579
HR (95% CI)[a]	Ref	1.710 (1.221–2.395)*
Esophagus		
Events	6	3
Rate per 1000 PY	0.069	0.068
HR (95% CI)[b]	Ref	0.839 (0.194–3.629)
Colon, rectum		
Events	91	38
Rate per 1000 PY	1.047	0.866
HR (95% CI)[b]	Ref	0.697 (0.469–1.035)
Liver		
Events	69	35
Rate per 1000 PY	0.792	0.797
HR (95% CI)[b]	Ref	0.995 (0.649–1.524)
Urologic		
Events	30	21
Rate per 1000 PY	0.344	0.478
HR (95% CI)[b]	Ref	1.246 (0.696–2.232)
Gallbladder, biliary tract, pancreas		
Events	18	18
Rate per 1000 PY	0.206	0.409
HR (95% CI)[b]	Ref	1.851 (0.939–3.648)
Lung		
Events	56	42
Rate per 1000 PY	0.643	0.958
HR (95% CI)[b]	Ref	1.494 (0.985–2.267)
Head and neck		
Events	29	26
Rate per 1000 PY	0.333	0.593
HR (95% CI)[b]	Ref	1.850 (1.071–3.196)*
Thyroid		
Events	86	55
Rate per 1000 PY	0.99	1.257
HR (95% CI)[b]	Ref	1.274 (0.898–1.806)
Sex-specific organs, female[c]		
Events	43	22
Rate per 1000 PY	0.494	0.501
HR (95% CI)[b]	Ref	1.093 (0.646–1.847)
Sex-specific organs, male[d]		
Events	61	32
Rate per 1000 PY	0.701	0.729
HR (95% CI)[b]	Ref	0.926 (0.588–1.456)
Hematologic or lymphoid		
Events	7	10
Rate per 1000 PY	0.08	0.227
HR (95% CI)[b]	Ref	2.849 (1.035–7.844)*
Other sites		
Events	33	19
Rate per 1000 PY	0.379	0.432
HR (95% CI)[b]	Ref	0.977 (0.542–1.761)

* Significant. [a] HR from the Cox proportional hazards regression model, adjusted for residence, income, smoking, drinking, comorbidities (DM, hypertension, kidney disease, COPD, *Helicobacter pylori*–related diseases including peptic ulcers), BMI, SBP, DBP, glucose, total cholesterol, and hemoglobin. [b] HR from the Cox proportional hazards regression model, adjusted for residence, income, smoking, drinking, comorbidities (DM, hypertension, kidney disease, and COPD), BMI, SBP, DBP, glucose, total cholesterol, and hemoglobin. [c] Breast and female genital organs. [d] Prostate, and other male genital organs. COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; DM: diabetes mellitus; PY: person-years; SBP: systolic blood pressure.

between the increased risk of site-specific cancer and gout is still inconclusive, and further studies are required to confirm these results.

The present study has several strengths. First, the major confounding factors that contribute to cancer risk were adjusted by the multivariable-adjusted Cox proportional hazards model. Second, the follow-up duration was sufficient to detect the occurrence of cancer. The study also has several limitations. First, the sample cohort included only those aged over 40 years, and the population was relatively small; therefore, there is a limit to the generalization of the results. Second, the serum uric acid level could not be determined in the medical checkup cohort of the Korean Health Insurance Service, and thus the association between hyperuricemia and cancer risk could not be clearly delineated. Third, other potential confounding factors that affect cancer risk, such as medications and various comorbidities, might exist. Indeed, different risk factors for site-specific cancers exist and are difficult to fully evaluate in the present study. Thus, the observed increased risk of site-specific cancer in patients with gout should be interpreted carefully.

In conclusion, patients with gout have a higher risk of cancer, as well as both all-cause and cancer mortality, compared with the general population aged 41–55 years. Therefore, special attention should be paid to higher cancer risk and cancer mortality in patients with gout who are diagnosed in middle age.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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