Risk of cancer in middle-aged patients with gout: A nationwide population-based study in Korea

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Conflict of interests

The authors declare that they have no conflict of interests.

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Running head: Gout and cancer risk

Abstract

Objectives: 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 hazard model in gout patients and a 1:2 ratio for the matched controls by age, sex, and index year.

Results: We compared 4,176 patients with gout with 8,352 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 gout patients. In the subgroup analysis, the cancer risk 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) was higher in gout patients.

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.

Introduction

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(2-5). In addition, a meta-analysis 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(8-11). 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, the 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 type in Korean patients with gout, especially in a middle-aged population.

Patients and 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

1   (14 years) in Korea(15). The NHIS-HEALS is a cohort of Korean adults who participated in

2   general health screening programs conducted by the NHIS. All subscribers (including medical

3   aid beneficiaries) can receive general health screening biennially or annually (for manual

4   employees) and, in particular, Korean adults aged 40 years or older are eligible for biennial

5   medical check-up(16). This sample cohort first selected qualified individuals between 2002-

6   2003 who were between the ages of 40-79 who received general medical screening. This cohort

7   consisted of 514,866 individuals who comprised a 10% simple random sample of all health

8   screening participants in that period. The data collected included information on demographics

9   (such as gender, age, region of residence, type of subscription, social-economic variable of

10 income rank, disability, death, cause of death), diagnosis (using the International Classification

11 of Disease and Related Health Problems, 10th revision, ICD-10), medical procedures,

12 prescriptions, and medical check-up data.

13   A profile study of the NHIS-HEALS found that the age-standardized prevalence of

14 anemia, diabetes, hypertension, obesity, and hypercholesterolemia in NHIS-HEALS

15 participants were similar to the results in those aged 40 or older who participated in the Korean

16 National Health and Nutrition Examination Survey (KNHANES)(15,17). The KNHANES was

17 a cross-sectional survey that consisted of nationally representative samples of the Korean

18 population and has information on health, nutrition, physical conditions, laboratory tests, and

19 chronic diseases(18). This indicates that the NHIS-HEALS is representative of the sample

20 cohort of the general Korean population.

21

22 **Study design and study subjects**

23   As shown in Figure 1, we compared gout patients with non-gout individuals as the

24 control group. The study cohort included patients aged 41-55 years with gout that was newly

25 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 anti-inflammatory drugs (NSAIDs), allopurinol, febuxostat, or benzbromarone at the date of its diagnosis. Previous validation studies had reported that the positive predictive value of diagnostic codes for gout was 61% to 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 gout patients 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 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 less than 1 year.

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 less than 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 index date. In the control group, the date of 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 check-up), sex, income, 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 check-up data including smoking, alcohol intake, and body mass index (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-hazard regression models and sub distribution 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 continuous variables are shown as mean with standard deviation or median with interquartile range. 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. A Kaplan–Meier plot was used to show the cumulative incidence of cancer diagnosis by the two groups and to compare differences between them we conducted a log-rank test. A multivariable-adjusted Cox proportional hazards regression model with covariates was also used to assess the association between gout patients and cancer diagnosis, all-cause mortality, presenting hazard ratio (HR) [95% confidence interval (CI)]. When a proportional hazards assumption was violated, we conducted stratified Cox proportional hazards regression 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 sub distribution 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, Inc., Cary, NC, USA) 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. This study 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 check-up cohort of the Korean Health Insurance Service

1 database, 4,176 patients were newly diagnosed with gout. We included 8,352 matched controls

2 in a 1:2 ratio by age, sex, and index year who presented between 2003 and 2007 (Figure 1). As

3 shown in Table 1, patients with gout were more likely to be non-smokers and had a greater

4 alcohol intake and more comorbidities than controls. In addition, BMI, and systolic and

5 diastolic blood pressure were higher than in the control group. The mean age and follow-up

6 duration for cancer patients were 48.8 years and 10.1 years, respectively.

7

8 **Overall cancer risk in patients with gout**

9 As shown in table 2, the overall cancer occurrence rates in the gout and control groups

10 were 9.241 and 7.218 per 1000 person-years, respectively. A Cox proportional hazard model

11 showed that the risk of cancer was significantly different between patients with gout and

12 controls (HR =1.224, 95% CI 1.073–1.398). According to the Kaplan–Meier plots (Figure 2

13 A), the proportion of patients who developed cancer was significantly higher in those with gout

14 than in controls (Log-rank test: $p < 0.001$).

15

16 **All-cause mortality and cancer mortality**

17 Table 2 shows the all-cause mortality and cancer mortality in patients with gout

18 compared with controls. The overall all-cause mortality rates in the gout group and control

19 group were 2.997 and 1.970 per 1000 person-years, respectively. The risks of all-cause

20 mortality (HR 1.457, 95% CI 1.149–1.847) and cancer mortality (HR 1.470, 95% CI 1.020–

21 2.136) were significantly higher in patients with gout than in controls. Also, the plot of the CIF

22 (Figure 2B) indicated that death from cancer was significantly higher in those with gout than

23 in controls (Grey's test: p-value = 0.002).

24

25 **Individual cancer risk in patients with gout**

1 Table 3 shows the individual cancer risk in patients with gout compared with controls.

2 The risk for stomach cancer was higher in gout patients than in controls (HR 1.710, CI 1.221–

3 2.395). In addition, the risks of head and neck cancer (HR 1.850, CI 1.071–3.196) and

4 hematologic or lymphoid cancers (HR 2.849, CI 1.035–7.844) were higher than in controls.

5 The risk of other site-specific cancer was not significantly different between patients with gout

6 and controls.

7

8 **Discussion**

9 Cancer is the second leading cause of death in the U.S.(23) and the top cause of death

10 in South Korea(24) and the incidence seems likely to increase in the future(25). Gout is a

11 chronic disease that is preventable and manageable, thus, understanding the relationship

12 between gout and cancer risk is important for the reduction of cancer mortality. In this Korean

13 population-based study, patients aged 41–55 years with gout had a higher risk of cancer

14 compared with the non-gout population. Also, all-cause mortality and cancer mortality were

15 higher in gout patients than in controls. In terms of cancer type, patients with gout have a higher

16 risk of stomach, head and neck, and hematologic or lymphoid cancers compared with the non-

17 gout population.

18 Previous studies have reported that overall cancer risk is higher by 15%–25% in

19 patients with gout than in those without gout(3,4). Most patients with gout have several risk

20 factors for cancer, including heavy alcohol consumption, a smoking habit, obesity, and

21 metabolic syndrome that are confounding factors for evaluating the causal relationship between

22 gout and cancer risk(10). We used multivariable-adjusted Cox proportional-hazard model in

23 the 41-55 age-group to evaluate the relationship between gout and cancer risk more clearly.

24 Patients with gout showed different characteristics compared with controls, however, after

25 adjusting for the risk factors, patients with gout aged 41-55 showed a higher risk of cancer than

1 controls. In addition, there is an association between gout and higher cancer risk in patients

2 with gout aged 56-79 (HR 1.126, CI 1.025–1.237) (supplementary table 1). Thus, all patients

3 with gout over 40 have a higher risk of cancer than those without gout. The results of this study

4 are in line with the aforementioned studies on gout and cancer risk. However, this is the first

5 evidence to demonstrate the effect of gout on incidental cancer, especially in the middle-aged

6 population. According to our findings, cancer screening may be important in middle-aged

7 patients with newly diagnosed gout.

8 Several studies have reported that gout is associated with a higher risk of all-cause

9 mortality which is explained by the elevated risk of death from cardiovascular disease(26,27).

10 In regard to cancer mortality, a previous study reported that patients with gout have increased

11 cancer mortality, compared with the general population(6). Similar to the previous study, the

12 all-cause and cancer mortalities were higher in the middle-aged gout patients than the control

13 cohort in the present study. There are several studies reporting that hyperuricemia is associated

14 with an increased risk of cancer mortality(2,28); thus, the increased cancer mortality in gout

15 patients may be associated with hyperuricemia. However, the precise relationship between

16 serum uric acid and cancer mortality is still inconclusive and pharmacological modulation of

17 hyperuricemia may have a role in reducing cancer mortality, but this remains unknown.

18 There are diverse results in the increased risk of site -specific cancers in patients with

19 gout or hyperuricemia(4,29). In the present study, a higher risk of stomach, head and neck, and

20 hematologic or lymphoid cancers was observed in patients with gout compared with controls.

21 These diverse results may be influenced by methodology, ethnicity, and environmental

22 exposure. Korea has the highest incidence of stomach cancer worldwide(30) and the crude

23 incidence rate of stomach cancer was 59.7 per 100,000 in 2016(24). Thus, the increased

24 probability of developing the prevalent type of cancer in gout could be considered. On the other

25 hand, a previous study reported that patients with *Helicobacter pylori* infections showed a

higher incidence of gout and hyperuricemia than those without infection(31). Indeed, the incidence of *Helicobacter pylori*-related diseases, including peptic ulcers, is higher in patients with gout than without it in the present study. However, the risk of stomach cancer was still higher in patients with gout after adjusting for *Helicobacter 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 meta-analysis study 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). Other study reported that gout medications are associated with an increased risk of leukemia and non-Hodgkin lymphoma(32). Taken together, the association 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-hazard 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 check-up 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 cancers in patients with gout should be interpreted carefully.

1   In conclusion, patients with gout have a higher risk of cancer as well as both all-cause

2   and cancer mortality compared with general population aged 41–55 years. Therefore, special

3   attention should be paid to higher cancer risk and cancer mortality in patients with gout who

4   are diagnosed in middle age.

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1 **Figure Legends**

2 **Figure 1.** Selection of study population from the National Health Insurance Service-National

3 Health Screening Cohort.

4

5 **Figure 2.** A, Kaplan-Meier curve for the cumulative incidence of cancer in a 1:2 age-, sex-,

6 and index year-matched cohort. B, Plot of the cumulative incidence function for cancer

7 mortality and mortality from other causes in a 1:2 age-, sex-, and index year-matched cohort.

8

Table 1. Baseline characteristics, 1:2 age, sex, and index date matched cohorts aged 41-55 years

Characteristic	Non-gout (n = 8,352)	Gout (n = 4,176)	p-value*
Follow-up duration, cancer (years)	10.1 ± 2	10.1 ± 2.3	0.493
Follow-up duration, mortality (years)	10.5 ± 1.6	10.5 ± 1.7	0.233
Age (year)	48.8 ± 3.8	48.8 ± 3.8	1
Sex, Female	2488 (29.8)	1244 (29.8)	1
Income†			<0.0001
Group 1 (1–3)	1601 (19.2)	633 (15.1)	
Group 2 (4–7)	2629 (31.5)	1251 (30)	
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			0.030
None	4665 (55.9)	2378 (56.9)	
Ex-smoker	980 (11.7)	542 (13)	
Current	2306 (27.6)	1067 (25.6)	
Unknown	401 (4.8)	189 (4.5)	
Alcohol			<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)	
Everyday	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)	<0.0001
Kidney disease	83 (1.0)	142 (3.4)	<0.0001
COPD	58 (0.7)	60 (1.4)	<0.0001
Helicobacter pylori related diseases, including peptic ulcers	1924 (23)	1528 (36.6)	<0.0001
Measurements			
Body mass index	24.0 ± 2.7	24.8 ± 2.73	<0.0001
Systolic blood pressure (mmHg)	124.8 ± 15.7	126.7 ± 16.8	<0.0001
Diastolic blood pressure (mmHg)	79.2 ± 10.7	80.5 ± 11.5	<0.0001
Glucose, fasting (mg/dL)	96.4 ± 23	96.4 ± 21.6	0.876
Total cholesterol (mg/dL)	198.1 ± 35.3	200.8 ± 38	0.001
Hemoglobin (g/dL)	14.3 ± 1.5	14.3 ± 1.5	0.184

Continuous variables are presented as the mean ± standard deviation or median (interquartile range)

Categorical variables are presented as number (%)

COPD, chronic obstructive pulmonary disease

*t-test is conducted for continuous variables and chi-square test is conducted for categorical variables.

†Income divided into 10 grades is grouped by 3 categories where group 3 is the highest grade

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

Value	Non-gout	Gout
Cancer incidence		
Patients	8352	4176
Person-years	84645	42202.5
Events	611	390
Rate per 1000 person-years	7.218	9.241
HR (95% CI)†	Reference	1.224 (1.073, 1.398)*
All-cause mortality		
Person-years	87316.38	44038.43
Events	172	132
Rate per 1000 person-years	1.970	2.997
HR (95% CI)†	Reference	1.457 (1.149, 1.847)*
Death from cancer		
Person-years	87316.38	44038.43
Events	68	49
Rate per 1000 person-years	0.779	1.113
HR (95% CI)‡	Reference	1.470 (1.02, 2.136)*
Death from other causes		
Person-year	87316.38	44038.43
Events	104	83
Rate per 1000 person-years	1.191	1.885
HR (95% CI)‡	Reference	1.440 (1.074, 1.931)*

HR, hazard ratio; CI, confidence interval

*Significant

†HR from the stratified Cox proportional-hazards regression model, adjusted for residence, income, smoking, drinking, comorbidities (diabetes mellitus, hypertension, kidney disease, chronic obstructive pulmonary disease), body mass index, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, and hemoglobin.

‡HR from sub distribution hazards model, adjusted for residence, income, smoking, drinking, comorbidities (diabetes mellitus, hypertension, kidney disease, chronic obstructive pulmonary disease), body mass index, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, and hemoglobin.

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

Site	Non-gout (n = 8,352)	Gout (n = 4,176)
Stomach		
Events	82	69
Rate per 1000 person-years	0.943	1.579
HR (95% CI)†	Reference	1.710 (1.221, 2.395)*
Esophagus		
Events	6	3
Rate per 1000 person-years	0.069	0.068
HR (95% CI)‡	Reference	0.839 (0.194, 3.629)
Colon, rectum		
Events	91	38
Rate per 1000 person-years	1.047	0.866
HR (95% CI)‡	Reference	0.697 (0.469, 1.035)
Liver		
Events	69	35
Rate per 1000 person-years	0.792	0.797
HR (95% CI)‡	Reference	0.995 (0.649, 1.524)
Urologic		

Events	30	21
Rate per 1000 person-years	0.344	0.478
HR (95% CI)‡	Reference	1.246 (0.696, 2.232)
Gallbladder, biliary tract, pancreas		
Events	18	18
Rate per 1000 person-years	0.206	0.409
HR (95% CI)‡	Reference	1.851 (0.939, 3.648)
Lung		
Events	56	42
Rate per 1000 person-years	0.643	0.958
HR (95% CI)‡	Reference	1.494 (0.985, 2.267)
Head and neck		
Events	29	26
Rate per 1000 person-years	0.333	0.593
HR (95% CI)‡	Reference	1.850 (1.071, 3.196)*
Thyroid		
Events	86	55
Rate per 1000 person-years	0.99	1.257

HR (95% CI)‡	Reference	1.274 (0.898, 1.806)

Sex-specific organs, female [1)]

Events	43	22
Rate per 1000 person-years	0.494	0.501
HR (95% CI)‡	Reference	1.093 (0.646, 1.847)

Sex-specific organs, male [2)]

Events	61	32
Rate per 1000 person-years	0.701	0.729
HR (95% CI)‡	Reference	0.926 (0.588, 1.456)

Hematologic or lymphoid

Events	7	10
Rate per 1000 person-years	0.08	0.227
HR (95% CI)‡	Reference	2.849 (1.035, 7.844)*

Other sites

Events	33	19
Rate per 1000 person-years	0.379	0.432
HR (95% CI) ‡	Reference	0.977 (0.542, 1.761)

HR, hazard ratio; CI, confidence interval

*Significant

† HR from the Cox proportional-hazards regression model, adjusted for residence, income, smoking, drinking, comorbidities (diabetes mellitus, hypertension, kidney disease, chronic obstructive pulmonary disease,

Helicobacter pylori disease or peptic ulcers), body mass index, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, and hemoglobin.

‡ HR from the Cox proportional-hazards regression model, adjusted for residence, income, smoking, drinking, comorbidities (diabetes mellitus, hypertension, kidney disease, and chronic obstructive pulmonary disease), body mass index, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, and hemoglobin.

1) Breast, and female genital organs

2) Prostate, and other male genital organs

The National Health Insurance Service-National Health Screening Cohort
n = 514,866

| 15,386 patients had gout diagnostic code (M10), gout-related medications from July 1, 2003 to December 31, 2007 | 475,493 individuals who received health screening exam from July 1, 2003 to December 31, 2007 |

Excluded

Excluded

1. Patients with gout in 2002 (n = 2,107)
2. No uric acid test between 1 year before and after index date (n = 2,717)
3. No measurement data within 2 years before index date (n = 1,297)
4. Measurement outliers (n = 223)
5. Patients diagnosed with malignancy before or within 1 year after index date (n = 797)
7. Follow-up duration < 1 year (n = 69)
8. Age > 55 (n = 4,000)

1. Diagnostic code of gout, Urate-lowering drug at least one claim in 2002-2015 (n = 59,193)
2. Outlier of measurement (n = 7,766)
4. Patients diagnosed with malignancy before or within 1 year after index date (n = 49,127)
5. Follow-up duration < 1 year (n = 1,787)
6. Age > 55 (n = 113,718)

1:2 age, sex, index year matching

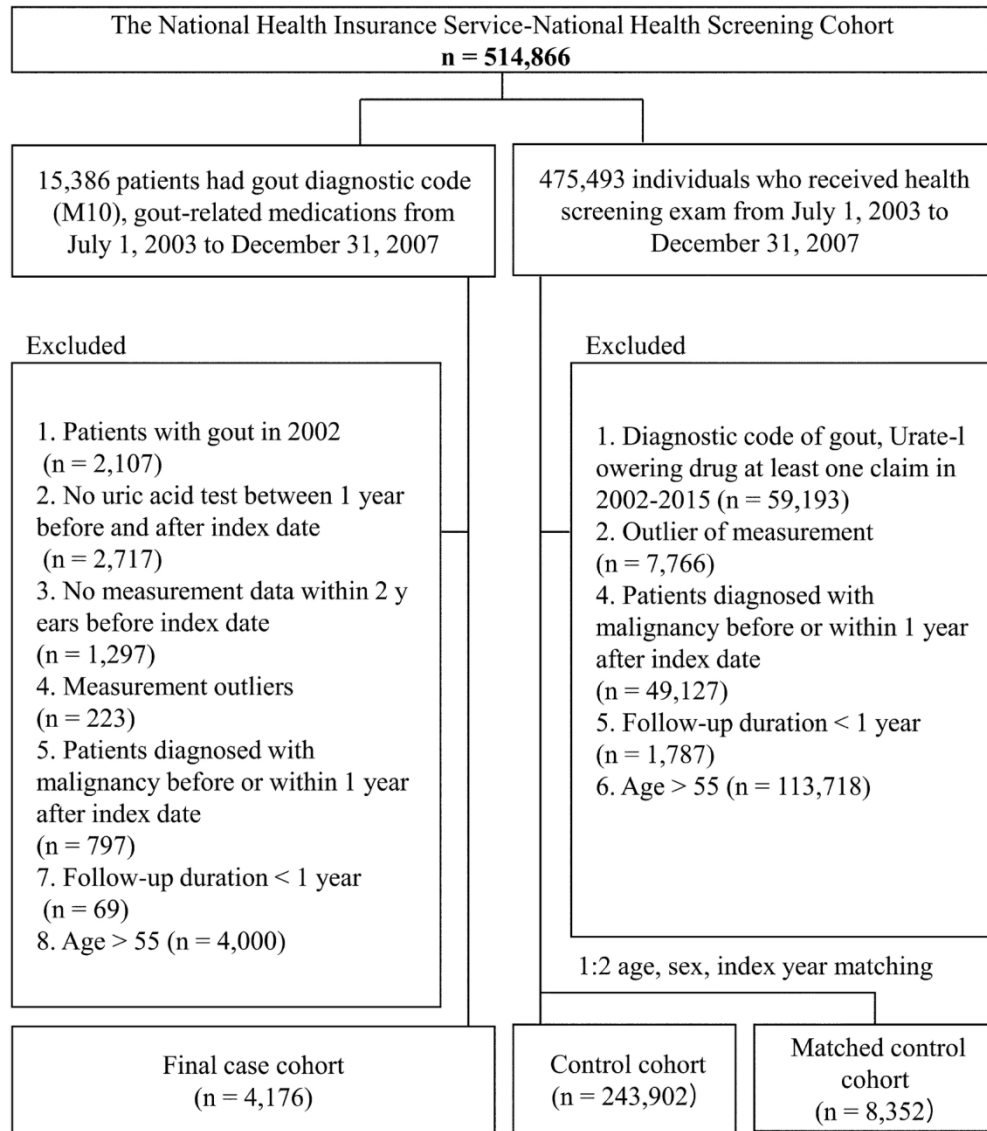| Final case cohort (n = 4,176) | Control cohort (n = 243,902) | Matched control cohort (n = 8,352) |

Figure 1. Selection of study population from the National Health Insurance Service-National Health Screening Cohort.
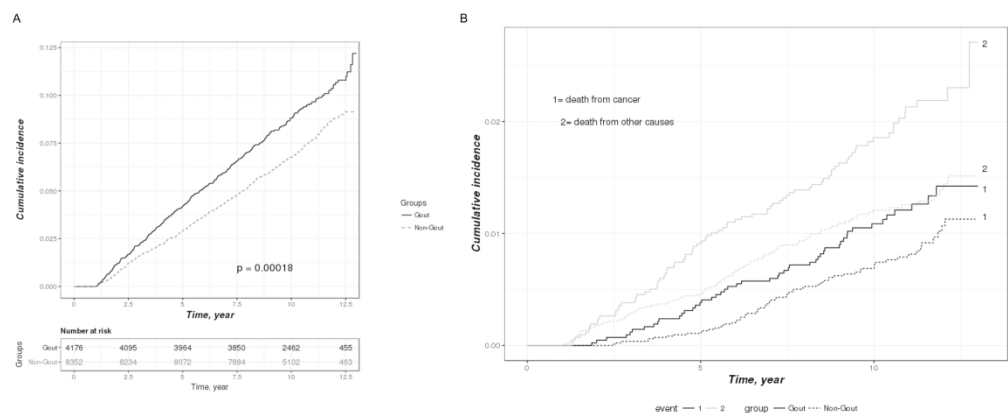
72x82mm (600 x 600 DPI)

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.

169x69mm (600 x 600 DPI)