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Colchicine Significantly Reduces Incident Cancer in Gout Male Patients

A 12-Year Cohort Study

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Abstract: Patients with gout are more likely to develop most cancers than subjects without gout. Colchicine has been used for the treatment and prevention of gouty arthritis and has been reported to have an anticancer effect in vitro. However, to date no study has evaluated the relationship between colchicine use and incident cancers in patients with gout. This study enrolled male patients with gout identified in Taiwan's National Health Insurance Database for the years 1998 to 2011. Each gout patient was matched with 4 male controls by age and by month and year of first diagnosis, and was followed up until 2011. The study excluded those who were diagnosed with diabetes or any type of cancer within the year following enrollment. We calculated hazard ratio (HR), aged-adjusted standardized incidence ratio, and incidence of 1000 person-years analyses to evaluate cancer risk. A total of 24,050 male patients with gout and 76,129 male nongout controls were included. Patients with gout had a higher rate of incident all-cause cancers than controls (6.68% vs 6.43%, $P = 0.006$). A total of 13,679 patients with gout were defined as having been ever-users of colchicine and 10,371 patients with gout were defined as being never-users of colchicine. Ever-users of colchicine had a significantly lower HR of incident all-cause cancers than never-users of colchicine after adjustment for age (HR = 0.85, 95% CI = 0.77–0.94; $P = 0.001$). In conclusion, colchicine use was associated with a decreased risk of incident all-cause cancers in male Taiwanese patients with gout.

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Abbreviations: HCC = hepatocellular carcinoma, HID = Health Insurance Database, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision.

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INTRODUCTION

Gout is a disorder of purine metabolism and is characterized by hyperuricemia and acute arthritis. Patients with gout and cancer patients have similar risk factors, including obesity and heavy alcohol consumption, as well as inflammation. Gout has been associated with the cytokine and inflammation genes, including the tumor Tumor necrosis factor-α gene,[1] cyclic Guanosine monophosphate-dependent protein kinase II gene,[2] Interleukin-6,[3] and Transforming growth factor-β1 gene.[4] In a recent study using Taiwan's National Health Insurance Database (HID), we[5] found patients with gout to be more likely to develop most cancers than subjects without gout.

Colchicine is an alkaloid agent that has been used for over a century for the treatment and prevention of gouty arthritis.[6–11] Experimentally, colchicine has been demonstrated to dramatically abrogate the inflammatory response to urate crystal stimulation in humans.[12] Besides having an antiinflammatory effect, colchicine is also a microtubule destabilizer with a strong capacity to bind to tubulin, perturbing the assembly dynamics of microtubules.[13–16] The disruption of microtubule dynamics interferes with the regulation of the mitotic spindle resulting in cell cycle arrest and eventual cell death.[17,18] Previous studies have reported that colchicine had an anticancer effect in vitro and in animal models.[19–21] However, to date no study has evaluated the relationship between colchicine use and incident cancers in patients with gout. Therefore, we examined the association between colchicine use and incident cancers in a representative national cohort obtained from Taiwan's National HID.

MATERIALS AND METHODS

Study Sample

This study collected the records of 1 million outpatients obtained from National HID in the form of a longitudinal cohort from 1998 to 2011. The dataset represents about 5% of the total population of Taiwan. The selection process is shown in Figure 1. We excluded patients diagnosed with gout during years 1998 to 1999, and included male patients newly with diagnosed with gout (International Classification of Diseases, Ninth Revision [ICD-9] code 274) after January 2000 to ensure that we were identifying and following only new cases. The diagnosis was further confirmed by 3 continuous prescriptions of antigout medications. Our control group was composed of individuals with no diagnosis of gout from years 2000 to 2011. We randomly selected about 4 nongout male controls which we matched with each gouty patient by age and time of their outpatient visit, matching the same month and year of first diagnosis of gout in the study patients. The comorbidities of gout included obesity (ICD-9: 278), hyperlipidemia (ICD-9: 272), and hypertension (ICD-9: 4010, 4011, 4019), all diagnosed within 1 year following enrollment. Patients who were prescribed colchicine after entry were defined as ever-users; those who were not prescribed colchicine were defined as

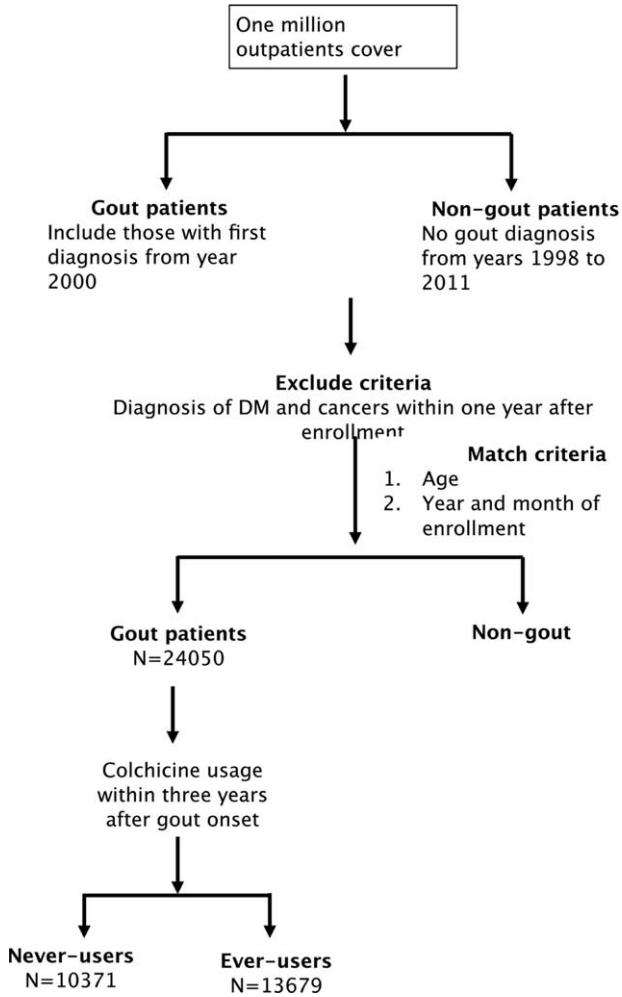

FIGURE 1. The study population inclusion algorithms.

never-users. Benzbromarone, another commonly used gout drug, was used for comparison. Patients who were prescribed benzbromarone after entry were defined as ever-users; those who were not prescribed benzbromarone were defined as never-users. The endpoint was a diagnosis of any cancer (ICD-9: 140–208) after 1 year of enrollment. We excluded any patient who had been diagnosed with type 2 diabetes (ICD-9: 250) and any patient that developed any cancer within 12 months after enrollment both in gout patients and control participants. All participants were followed up from the inclusion date of first diagnosis until 2011. Our matching criteria and exclusion criteria ensured that the follow-up started from the same baseline period and avoided confounding effects of sex and age on the incident cancers. The approval for the analysis of the database was obtained from the Institutional Review Board of Changhua Christian Hospital (CCH IRB 121213).

Statistical Analyses

The mean difference for age and follow-up time were estimated by *t*-test, and the frequency difference for obesity, hyperlipidemia, hypertension, and all-cause cancers were estimated by Chi-square test between gout patients and controls. The risk of incident all-cause cancers between gout and control groups as well as between ever-users and never-users of colchicine was calculated by hazard ratio (HR), standardized incidence ratio, and 95% confidence intervals (95% CI) after adjustment of age. The significance for cumulative hazard rate was analyzed with Log-Rank test by SAS program (v9.3) after mining the national outpatient records using the PERL (v5.8) program. A *P*-value less than 0.05 were considered significant.

RESULTS

A total of 24,050 male gout patients and 76,129 male nongout controls were included in this study. The mean age of the gout patients was 44.63 ± 14.84 years old and controls 44.74 ± 14.69 years ($P = 0.287$) (Table 1). Gout patients had a significantly higher prevalence of obesity, hypertension, and hyperlipidemia than controls (all $P < 0.001$). The prescription rate of colchicine was significantly higher in gout patients than controls (56.88% vs 3.41%, $P < 0.001$). The prescription rate of benzbromarone was significantly higher in gout patients than controls (54.03% vs 1.90%, $P < 0.001$). Gout patients had a higher rate of incident all-cause cancers (6.68% vs 6.43%, $P < 0.006$) compared with controls. The mean follow-up time for gout patients was 100.70 months (±29.72), which was significantly lower than that for controls (103.00 ± 29.18, $P < 0.001$; Table 1).

All gout patients were categorized into those with or without incidental cancers (Table 2). In total, 1606 gout patients were diagnosed with incidental cancers during the 12-year follow-up period. Patients with incidental cancers were older and had a significantly lower prescription rate for colchicine (48.9% vs 57.4%) as compared to those without incidental cancers. The prevalence rates of obesity, hypertension, and hyperlipidemia

TABLE 1. Baseline Characteristics, Comorbidities, Colchicine Use and Incident All-Cause Cancers in Gout Patients and Controls

Variables	Gout	Control	*P*-Values*
No.	24,050	76,129	
Age (years; mean ± SD)	44.63 ± 14.84	44.74 ± 14.69	0.287
Colchicine			
Use	13,679 (56.88)	2593 (3.41)	<0.001
Nonuse	10,371 (43.12)	73,536 (96.59)	
Benzbromarone			
Use	12,994 (54.03)	143 (1.90)	<0.001
Nonuse	11,056 (45.97)	74,686 (98.10)	
Obesity			
Yes	704 (2.93)	729 (0.96)	<0.001
No	23,346 (97.07)	75,400 (99.04)	
Hyperlipidemia			
Yes	13,101 (54.47)	19,237 (25.27)	<0.001
No	10,943 (45.53)	56,892 (74.73)	
Hypertension			
Yes	12,112 (50.36)	24,751 (32.51)	<0.001
No	11,938 (49.64)	51,378 (67.43)	
All-cause cancers			
Yes	1606 (6.68)	4893 (6.43)	0.006
No	22,444 (93.32)	71,236 (93.57)	
Follow-time for all-cause cancers, months	100.70 (29.72)	103.00 (29.18)	<0.001

* The values were estimated by *t*-test for age and follow-time, and by Chi-square test for the other variables.

TABLE 2. The Hazard Ratios of Incidental All-Cause Cancers Among Gout Patients

	All-Cause Cancers			
	Yes	**No**	**HR (95% CI)**	***P*-Values**
No.	1606 (6.68)	22,444 (93.32)		
Age (years; mean ± SD)	55.28 ± 14.30	43.86 ± 14.58	1.05 (1.04–1.05)	<0.001
Colchicine, %				
Never-users	820 (7.91)	9551 (92.09)	1.0	
Ever-users	786 (5.75)	12,893 (94.25)	0.85 (0.77–0.94)*	0.001
Use-days, days	39.69 ± 110.40	38.04 ± 95.34	1.00 (1.00–1.00)	0.380
Benzbromarone				
Never-users	710 (44.21)	10,346 (46.10)	1.0	
Ever-users	896 (55.79)	12,098 (53.90)	1.01 (0.91–1.11)*	0.870
Use-days	68.32 ± 137.90	62.59 ± 132.90	1.00 (1.00–1.00)	0.133
Obesity				
Yes	34 (2.12)	670 (2.99)	0.99 (0.71–1.39)	0.961
No	1572 (97.88)	21,774 (97.01)	1.0	
Hypertension				
Yes	1096 (68.24)	11,016 (49.08)	1.11 (0.99–1.24)	0.072
No	510 (31.76)	11,428 (50.92)	1.0	
Hyperlipidemia				
Yes	982 (61.15)	12,119 (54.00)	1.09 (0.99–1.21)	0.090
No	624 (38.85)	10,325 (46.00)	1.0	

* Hazard ratio was estimated after adjustment of age.

were not significantly different between gout patients with and without incidental cancers. Colchicine ever-users had significantly lower incidence of all cause cancers after adjustment for age, compared with colchicine never-users (HR: 0.85, 95% CI = 0.77–0.94; $P = 0.001$). The incidence of all cause cancers was not significantly different between benzbromarone ever-users and never-users (HR: 1.01, 95% CI = 0.91–1.11; $P = 0.870$).

A total of 13,679 gout patients were ever-users of colchicine and 10,371 were never-users of colchicine (Table 3). Ever-users were younger and had a lower prevalence of hyperlipidemia than never-users. Never-users had a significantly higher HR of incident all-cause cancers than ever-users after adjusting for age and hyperlipidemia (HR = 1.15, 95% CI = 1.04–1.28; $P = 0.007$; Table 3).

Figure 2 shows the cumulative hazard risks of incident all-cause cancers in gout patients who ever used colchicine and those who never used it. The incidence of all-cause cancers per 1000-person-years was 6.86 cases in those who used colchicine, showing a significant protective effect compared to the 9.41 cases in the nonusers (aged-adjusted standardized incidence ratio = 0.73, 95% CI = 0.66–0.80).

TABLE 3. The Hazard Ratios of All-Cause Cancers in Colchicine Never-Users and Ever-Users Among Gout Patients

	Colchicine			
	Never-Users	**Ever-Users**	**OR (95%CI)**	***P*-Values**
No	10,371 (43.12)	13,679 (56.88)		
Age (mean ± SD)	46.90 ± 14.62	42.90 ± 14.77	1.02(1.02–1.02)	<0.001
Obesity				
Yes	269 (2.59)	435 (3.18)	0.93(0.79–1.09)	0.348
No	10,102 (97.41)	13,244 (96.82)		
Hypertension				
Yes	5606 (54.05)	6506 (47.56)	1.06 (0.99–1.12)	0.053
No	4765 (45.95)	7173 (52.44)	1.0	
Hyperlipidemia				
Yes	6467 (61.39)	6734 (49.23)	1.56 (1.48–1.65)	<0.001
No	4004 (38.61	6945 (50.77	1.0	
All-cause cancer				
Yes	820 (7.91)	786 (5.75)	1.15 (1.04–1.28)*	0.007
No	9551 (92.09)	12,893 (96.82)	1.0	

* Odds ratios were adjusted by age and hyperlipidemia.

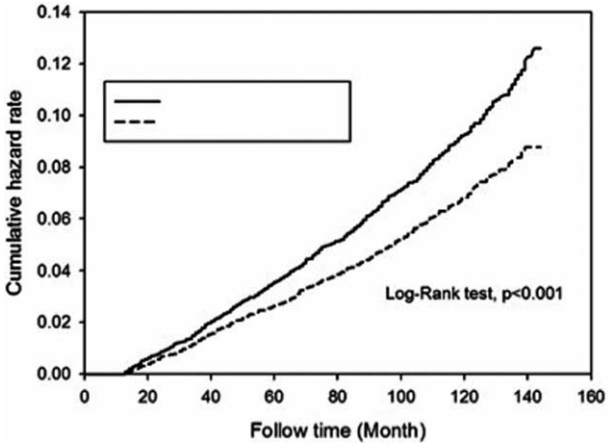

FIGURE 2. Cumulative hazard risk of incident all-cause cancers in colchicine ever-users and never-users among gout patients ($P < 0.001$).

Table 4 shows the colchicine exposure days and HR for incident all-cause cancers in gout patients. All analyses showed that colchicine ever-users had a significantly lower risk of incident all cause cancers. Table 5 shows the age-adjusted HR of specific cancers between colchicine ever-users and never-users for gout patients. Compared to never-users of colchicine, ever-users of the drug had a significantly lower risk of prostate cancer (HR = 0.68, 95% CI = 0.52–0.89, $P = 0.004$) and colorectal cancer (HR = 0.75, 95% CI = 0.60–0.94; $P = 0.012$). There were no significant differences in incidence of other specific cancers between the 2 groups (all $P > 0.05$).

DISCUSSION

This study found a significant association between reduced risk of incident cancers, particularly in prostate and colorectal cancers, and use of colchicine in male patients with gout.

Gout became the most common inflammatory joint disease in males because the prevalence of gout has increased in recent decades. There are several comorbidities, including but not limited to hypertension, obesity, and type 2 diabetes, associated with gout.[22] Choi et al[23] found that men with gout had 34% to 66% increased risk of type 2 diabetes compared with those without gout. Many studies have reported patients with type 2 diabetes to be at higher risk of developing cancers.[24–29] In addition to one of our previous national database studies finding gout patients to have increased risk of most cancers,[5] Kuo et al[30] also reported an association between gout and increased risk of cancer, particularly prostate cancer in men. However, those 2 previous studies did not exclude patients with type 2 diabetes who are typically at higher risk of developing cancers. In the current study, we excluded patients with type 2 diabetes, confirming that gout was independently associated with higher risk of incident cancer.

To the best of our knowledge, this study represents the first to report a significant association between colchicine use and lower risk of incidental cancers in male gout patients, who are known to be at higher risk of developing cancers. Colchicine has been found to exhibit an anticancer effect on hepatocellular carcinoma (HCC) by a study using a cell model.[19] That study attributed the inhibition of HCC development on the drug's antiproliferative effects. Furthermore, the administration of colchicine has been found to inhibit the development of tumors and impair tumor-free survival in pressure activation of malignant cells in an animal model.[20] In a retrospective study of 186 patients, Arrieta et al[31] found that long-term colchicine administration in patients with viral hepatitis-related cirrhosis prevented and delayed the development of HCC. Our study, which included more than a hundred thousand male gout patients, found a significant association between colchicine use and a decreased risk of cancer after adjustment (HR = 0.85, 95% CI = 0.77–0.94; $P = 0.001$, Table 2).

Colchicine use was most significantly associated with a decreased risk of prostate and colorectal cancers in our male gout patients in this study. One well-known anticancer mechanism for colchicine is the direct colchicine–tubulin interaction, which perturbs the assembly dynamics of microtubules.[32–34] Fakih et al[21] showed that colchicine inhibited the growth prostate adenocarcinoma cells implanted into Dunning rats. Other studies have reported that the antitumor effect of paclitaxel, an anticancer agent, in castrate resistant prostate cancer may be due to its inhibition of androgen receptor activity via its inhibition of microtubule dynamics.[35–37] These favorable outcomes which were achieved using microtubule targeted agents have rekindled interest in such therapies for the clinical management of prostate cancer.[38] Li et al[39] found 2,3′,4,4′,5′-pentamethoxy-trans-stilbene, which targeted microtules, to be a potent inducer of apoptosis in colon cancer cells. Chopra et al[40] reported that novel piperazine-based compounds inhibited microtubule dynamics and sensitized colon cancer cells to tumor necrosis factor-induced apoptosis. Although these studies are enlightening, the effects of colchicine on prostate and colorectal cancers need to be further clarified in future studies.

This study has several limitations. First, the potentially important clinical covariates, such as smoking status, alcohol consumption, and the levels of uric acid, were lacked in our

TABLE 4. The Colchicine Exposure Days and Hazard Ratio for Incident All-Cause Cancers

	Age-Adjusted		Adjusted for Age and Propensity Score	
Colchicine Use	**HR (95% CI)***	***P*-Values**	**HR (95% CI)***	***P*-Values**
Ever-users	0.85 (0.77–0.94)	0.001	0.77 (0.69–0.86)	<0.001
Cumulative duration, days				
<30	0.87 (0.78–0.99)	0.028	0.85 (0.75–0.96)	0.001
30–90	0.82 (0.71–0.90)	0.011	0.77 (0.66–0.90)	<0.001
>90	0.84 (0.72–0.99)	0.041	0.76 (0.64–0.90)	0.001

* HR was estimated by comparing to the gout patients who did not use colchicine.

TABLE 5. The Age-Adjusted Hazard Ratios of Specific Cancers Between Colchicine Ever-Users and Never-Users Among Gout Patients

	Colchicine			
	Ever-Users	Never-Users	HR (95% CI)*	*P*-Values
Prostate cancer				
Yes	93 (0.68)	132 (1.27)	0.68 (0.52–0.89)	0.004
No	13,586 (99.32)	10,239 (98.73)		
Colorectal cancer				
Yes	143 (1.05)	172 (1.66)	0.75 (0.60–0.94)	0.012
No	13,536 (98.95)	10,199 (98.34)	1.0	
Kidney cancer				
Yes	26 (0.19)	38 (0.37)	0.62 (0.38–1.02)	0.060
No	13,653 (99.81)	10,333 (99.63)	1.0	
Liver cancer				
Yes	122 (0.89)	131 (1.26)	0.79 (0.62–1.02)	0.068
No	13,557 (99.11)	10,240 (98.74)	1.0	
Nasopharynx cancer				
Yes	49 (0.36)	40 (0.39)	0.96(0.63–1.46)	0.837
No	13,630 (99.64)	10,331 (99.61)	1.0	
Lung cancer				
Yes	107 (0.78)	103 (0.99)	0.98 (0.75–1.29)	0.890
No	13,572 (99.22)	10,268 (99.01)	1.0	
Brain cancer				
Yes	10 (0.07)	15 (0.14)	0.53 (0.24–1.19)	0.126
No	13,669 (99.93)	10,356 (99.86)	1.0	
Pancreas cancer				
Yes	16 (0.12)	13 (0.13)	1.12 (0.54–2.33)	0.772
No	13,663 (99.88)	10,358 (99.87)		
Stomach cancer				
Yes	23 (0.17)	25 (0.24)	0.87 (0.49–1.53)	0.617
No	13,656 (99.83)	10,346 (99.76)		
Thyroid cancer				
Yes	9 (0.07)	8 (0.08)	0.87 (0.33–2.26)	0.768
No	13,670 (99.93)	10,363 (99.92)		
Non-Hodgkin lymphoma				
Yes	17 (0.12)	17 (0.16)	0.87 (0.44–1.71)	0.691
No	13,662 (99.88)	10,354 (99.84)	1.0	
Oral cancer				
Yes	93 (0.68)	67 (0.65)	1.14 (0.83–1.56)	0.429
No	13,586 (99.32)	10,304 (99.35)	1.0	
Esophageal cancer				
Yes	17 (0.12)	22 (0.21)	0.67 (0.36–1.27)	0.225
No	13,662 (99.88)	10,349 (99.79)	1.0	
Bladder cancer				
Yes	46 (0.34)	49 (0.47)	0.90 (0.60–1.35)	0.610
No	13,633 (99.66)	10,322 (99.53)	1.0	

* Hazard ratio was estimated after adjustment of age between those used colchicine and the nonusers.

study. Second, the numbers of some specific incident cancers were relatively small, so the power of our analysis was limited.

In conclusion, the present study suggests that colchicine use in male patients with gout may decrease the risk of incident cancers, particularly in prostate and colorectal cancers, in this population.

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