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Original Article

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Long-Term Low-Dose Aspirin Use Reduces Gastric Cancer Incidence: A Nationwide Cohort Study

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Purpose

The aim of this study was to investigate whether aspirin use can reduce the incidence of gastric cancer in patients with hypertension or type 2 diabetes.

Materials and Methods

A total of 200,000 patients with hypertension or type 2 diabetes were randomly selected from the Korean National Health Insurance claim database. Of these, 3,907 patients who used 100 mg of aspirin regularly (regular aspirin users) and 7,808 patients who did not use aspirin regularly (aspirin non-users) were selected at a frequency of 1:2, matched by age, sex, comorbid illnesses (type 2 diabetes and hypertension), and observation periods. The incidence of gastric cancer in this cohort was then assessed during the observation period of 2004 to 2010.

Results

In the matched cohort, the incidence rates of gastric cancer were 0.8% (31/3,907) for regular aspirin users and 1.1% (86/7,808) for aspirin non-users, but the cumulative incidence rates were not significantly different between groups (p=0.116, log-rank test). However, in multivariate analysis, regular aspirin users had a reduced risk of gastric cancer (adjusted hazard ratio [aHR], 0.71; 95% confidential interval [CI], 0.47 to 1.08; p=0.107). Duration of aspirin use showed significant association with reduction of gastric cancer risk (aHR for each year of aspirin use, 0.85; 95% CI, 0.73 to 0.99; p=0.044), particularly in patients who used aspirin for more than 3 years (aHR, 0.40; 95% CI, 0.16 to 0.98; p=0.045).

Conclusion

Long-term low-dose aspirin use was associated with reduced gastric cancer risk in patients with hypertension or type 2 diabetes.

Key words
Aspirin, Low-dose, Stomach neoplasms, Risk

Introduction

Aspirin has been widely used as an anti-platelet drug for the primary or secondary prevention of cardiovascular (CV) events, including ischemic heart disease and stroke. Guidelines recommend prescription of low-dose aspirin for hypertensive patients with history of or at high risk for CV events [1], as well as diabetic patients, who are at a chronically elevated risk for CV events [2].

In addition to its preventive effects against CV events, aspirin has been widely investigated as an anti-cancer drug since the first report of its reduction of colorectal cancer incidence [3]. Indeed, two recent meta-analyses reported association of aspirin use with a reduced risk of various gastrointestinal cancers, particularly colorectal cancer [4,5]. This anti-cancer activity of aspirin is mainly associated with blockage of the cyclooxygenase (COX) pathway, an action also associated with the anti-inflammatory capacity of aspirin [6,7]. Chronic inflammation plays an important role in development of gastric cancer, and considerable experimental studies have reported on the association between the COX-2 pathway and gastric carcinogenesis [8]. In systematic reviews, epidemiological data corroborate these laboratory findings, reporting a negative association between gastric cancer incidence and the use of COX pathway-inhibiting drugs, including aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). However, the effects of aspirin and NSAID use on the reduction of gastric cancer risk were inconsistent according to study types [4,5].

Thus, we investigated the association between long-term, low-dose aspirin use and gastric cancer incidence using data from a large cohort of patients with hypertension or type 2 diabetes obtained from the Korean National Health Insurance (KNHI) claim database.

Materials and Methods

1. Study population

Because a large number of regular aspirin users were necessary to achieve statistical power, only patients with hypertension or type 2 diabetes were considered; use of regular aspirin was above average for both groups due to their increased risk of CV events. The KNHI Corporation provided data on 200,000 patients randomly sampled from all claimants with a diagnosis of hypertension or type 2 diabetes (100,000 patients with hypertension and 100,000 with type 2 diabetes) from its database using SAS ver. 9.2 software (SAS Institute Inc., Cary, NC). Using drug codes, patients prescribed 100 mg of commercially available aspirin products for at least 6 consecutive months were selected. A control group of aspirin non-users, defined as patients who had never made claims for aspirin prescription or those who had claimed payments for less than 6 months of aspirin prescriptions was also identified. However, to avoid the possible confounding effects of NSAIDs, patients who had claims for regular use of NSAIDs (6 or more consecutive months) were excluded from both groups. To match aspirin non-users with regular aspirin users, a frequency-matched sampling with regular aspirin users was performed, grouped by the distribution of hypertension and type 2 diabetes, age, sex, and starting time of observation periods and death at a ratio of 1:2 (regular aspirin users: aspirin non-users). Matched sampling enabled selection of units from a large reservoir of potential controls to produce a control group of modest size with covariate distributions similar to that of the focal case group [9]. From this pool of patients, 3,913 regular aspirin users and 7,822 aspirin non-users were selected. Patients diagnosed with gastric cancer prior to the start of the observation periods were then excluded. Ultimately, 3,907 regular aspirin users and 7,808 aspirin non-users were included in the final cohort (Fig. 1).

Aspirin use or non-use from 1 January 2004, to 31 December 2010 was investigated. For aspirin users, the observation period for gastric cancer was started only when patients had claimed payments for aspirin use for 6 consecutive months. Those observation periods were continued until 31 December 2010 (Fig. 2). In our analyses age, sex, residential area, co-morbid illnesses (hypertension or type 2 diabetes), and duration of aspirin use were included as covariates potentially affecting gastric cancer incidence. "Residential area" was assigned to one of three categories (rural, urban, or metropolitan), according to postal code.

This study was approved by the Institutional Review Board of the National Cancer Center, Korea (NCCRE-11-003). Informed consent was waived because the study was based only on routinely collected administrative data.

2. Database

All data used in the current study were obtained from the KNHI claim database. In Korea, medical services are provided by healthcare providers on a fee-for-service basis, with reimbursement by the KNHI Corporation, a single payer, after a claim has been submitted. Therefore, all data necessary for reimbursement for the claimed payments of medical services were recorded in the KNHI claim database. Those data included patients' socio-demographic information, including sex, age, residential area, disease for which payment is claimed, costs incurred, comorbid diseases, a detailed

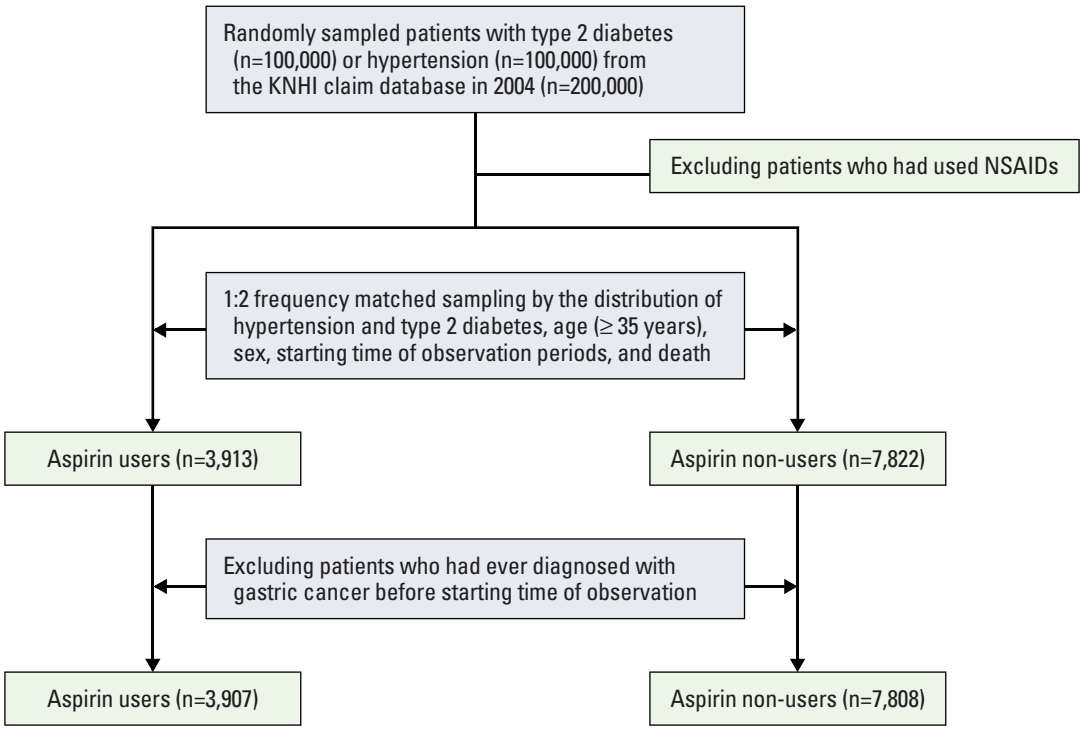

Fig. 1. Study flowchart. Patients with hypertension or type 2 diabetes (100,000 patients each) were classified as aspirin users or non-users. Non-users were matched with users based on demographic and comorbidity covariates. KNHI, Korean National Health Insurance; NSAIDs, non-steroidal anti-inflammatory drugs.

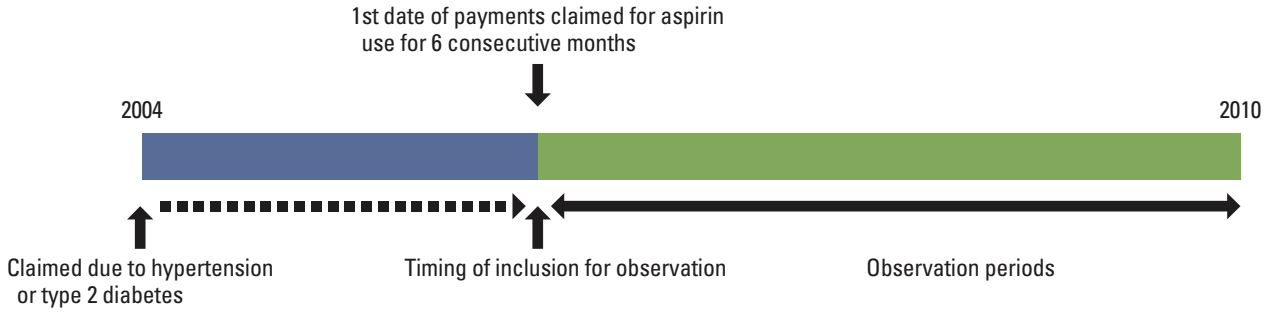

Fig. 2. Observation periods of aspirin users. Claims for aspirin use were investigated in all cohort patients from 2004-2010. For aspirin users, observation periods for gastric cancer began after 6 consecutive months of payment claims for aspirin and ended on 31 December 2010. Non-user observation periods began immediately after any claim was made for hypertension or diabetes. Duration of observation was matched between users and non-users to prevent sampling bias.

list of diagnostic tests, procedures, and prescription provided, and outcomes (deaths). Codes from The International Classification of Diseases 10th edition [10] were used to identify essential hypertension (I10), type 2 diabetes (E11), and gastric cancer (C16).

3. Statistical analyses

Descriptive analyses were performed in order to clarify the distributions of regular aspirin users and aspirin non-users; the chi-square test was used for categorical variables and Student's t test for continuous variables. The Kaplan-Meier

method for life-table estimates and the log-rank test were used for comparison of the incidence of gastric cancer during the observation periods. For regular aspirin users, the duration of aspirin use was calculated as the time between the beginning and end of continuous payment claims for aspirin. Time to gastric cancer occurrence was defined as a period from the first date of observation to the date of gastric cancer diagnosis. All patients were followed until 31 December 2010, except for 1,653 patients who were censored because of death before that date (566 patients [14.5%] in regular aspirin users vs. 1,087 patients [13.9%] in aspirin non-users; p=0.407).

A multivariate Cox proportional hazards regression analysis was performed to evaluate the effects of aspirin use on the incidence of gastric cancer. Before the analysis, the assumption of proportionality was confirmed by plotting the log (-log) hazard estimates against observation periods. In addition, Schoenfeld residuals for each covariate used for adjustment indicated that the assumption for proportional hazards was met ($p > 0.10$ for all covariates). For the multivariate Cox proportional hazards model, the effects of aspirin use were evaluated using three different models. In model 1, status of aspirin use was incorporated as a categorical variable and evaluated according to the regular use of aspirin (regular aspirin users vs. aspirin non-users). In model 2, duration of aspirin use was incorporated as a continuous variable, an approach that meets the assumption of linearity. In model 3, duration of aspirin use was divided into four groups (0.5-1.0 year, 1.1-2.0 years, 2.1-3.0 years, and > 3.0 years) and incorporated as a categorical variable. All statistical analyses were performed using SAS ver. 9.2 software (SAS Institute Inc.). The criterion for statistical significance was $p < 0.05$.

Results

1. Baseline characteristics of the study population

The median age of all included patients was 64 years (interquartile range [IQR], 56 to 70 years) and the percentage of male patients was 50.5%. The proportions of patients with hypertension and type 2 diabetes were 56.9% and 43.1%, respectively. The mean duration of aspirin use was 2.3 years for regular aspirin users. No significant differences in age, sex, or comorbidities were observed between regular aspirin users and non-users. However, higher rates of urban residency were observed for regular aspirin users compared with aspirin non-users (45.0% vs. 42.2%, respectively; p=0.014). Detailed characteristics of cohort patients are summarized in Table 1.

2. Incidence of gastric cancer according to aspirin use

During the observation periods (median, 6.4 years; IQR, 4.6 to 7.0 years), 117 patients were diagnosed with gastric cancer (31 patients who were regular aspirin users and 86 who were aspirin non-users). The rate of diagnosis with gastric cancer was lower for regular aspirin users (0.8%) than aspirin non-users (1.1%), but without statistical significance (p=0.114) (Table 1). Results of a Kaplan-Meier analysis also showed no significant difference in the cumulative gastric cancer incidence between the two groups (p=0.116, by log-rank test) (Fig. 3). However, according to each year of observation periods the cumulative incidences tended to be lower for regular aspirin users than aspirin non-users after each year of observation periods (Table 2).

3. Factors associated with gastric cancer incidence

Univariate and multivariate analyses were performed to examine the effects of regular aspirin use on gastric cancer incidence in the cohort. In model 1, regular aspirin users tended to have reduced gastric cancer risk in univariate (crude hazard ratio [cHR], 0.72; p=0.117) and multivariate analysis (adjusted HR [aHR], 0.71; p=0.107), but these results were not statistically significant. However, results of multivariate analysis of the duration of aspirin use showed a significant reduction of gastric cancer risk. In model 2, longer duration of aspirin use showed association with a reduced risk of gastric cancer in univariate (cHR for each year of aspirin use, 0.84; 95% confidence interval [CI], 0.72 to 0.98; p=0.028) and multivariate analyses (aHR for each year of aspirin use, 0.85; 95% CI, 0.73 to 0.99; p=0.044). In model 3, regular aspirin users who used aspirin for more than 3 years had significantly reduced risk of gastric cancer in univariate (cHR, 0.37; 95% CI, 0.15 to 0.90; p=0.029) and multivariate analyses (aHR, 0.40; 95% CI, 0.16 to 0.98; p=0.045) (Table 3).

The results of univariate and multivariate analyses for other covariates are shown in Table 3. In multivariate analysis, both male and rural patients had a significantly increased risk of gastric cancer. However, age at the time of inclusion and comorbidities (hypertension or type 2 diabetes) were not significant factors associated with the risk of developing gastric cancer.

Discussion

Historically, studies of the chemopreventive effects of aspirin on gastrointestinal cancers have focused on its prevention of colorectal cancer. In recent meta-analyses of both

Table 1. Baseline characteristics of the study population

Characteristic	Regular aspirin users (n=3,907)	Aspirin non-users (n=7,808)	p-value
Age, median (IQR, yr)	64 (56-70)	64 (56-70)	0.765
Sex			
Male	1,980 (50.7)	3,935 (50.4)	0.774
Female	1,927 (49.3)	3,873 (49.6)	
Residential area			
Metropolitan	2,148 (55.0)	4,513 (57.8)	0.014
Urban	1,168 (29.9)	2,198 (28.2)	
Rural	591 (15.1)	1,097 (14.1)	
Comorbidity			
Hypertension	2,208 (56.5)	4,452 (57.0)	0.603
Type 2 diabetes	1,699 (43.5)	3,356 (43.0)	
Duration of aspirin use (yr)			
0-0.49	0	7,808 (100)	< 0.001
0.50-1.00	1,211 (31.0)	-	
1.01-2.00	1,038 (26.6)	-	
2.01-3.00	586 (15.0)	-	
> 3.00	1,072 (27.4)	-	
Mean±standard deviation	2.323±1.854	0.003±0.031	< 0.001
Observation periods, median (IQR, yr)	6.4 (4.6-7.0)	6.4 (4.6-7.0)	0.977
Gastric cancer occurrence	31 (0.8)	86 (1.1)	0.114

Values are presented as number (%) unless otherwise indicated. IQR, interquartile range.

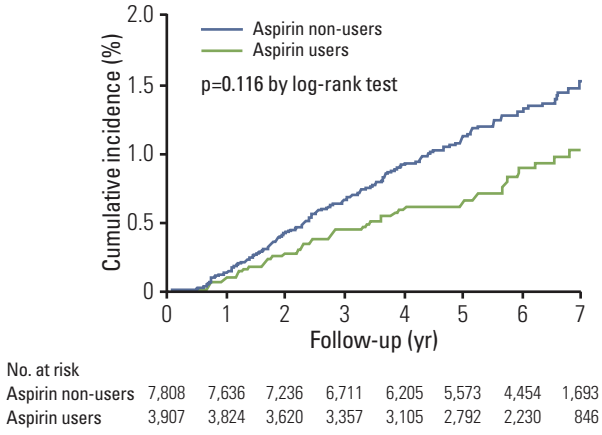

Fig. 3. Cumulative incidence of gastric cancer according to aspirin use. The cumulative gastric cancer incidence rate in aspirin users was not statistically different from that of non-users (p=0.116, log-rank test).

case-control and cohort studies aspirin use was protective against colorectal cancer risk [4,5]. However, results for other gastrointestinal cancers, including gastric cancer, were not consistent between the case-control and cohort studies. In our large, population-based, retrospective cohort study, we found a significant association of duration of regular, low-dose aspirin use with a reduction of gastric cancer incidence in patients with hypertension or type 2 diabetes. In addition, long-term, low-dose aspirin use, particularly that exceeding three years, resulted in significantly reduced gastric cancer incidence, with an aHR of 0.40.

Case-control [11-15] and cohort studies [16-19] have previously evaluated the association between aspirin use and gastric cancer risk. In case-control studies, all studies reported significant association of aspirin use with a reduction in gastric cancer risk, with odds ratios (OR) ranging from 0.3 to 0.7 [11-15]. However, results from cohort studies were inconsistent. Studies evaluating the association between aspirin use more than once [18] or twice [19] per week and gastric cancer incidence showed that its use significantly reduced gastric cancer risk (OR, 0.57 to 0.73). On the contrary, studies examining aspirin use more than once per month [16] or any prescription of aspirin within 1 year of diagnosis [17] did not report reduced gastric cancer incidence. However, those studies have several limitations. First, the aspirin dosages were unclear and associations between aspirin use and cancer incidence were analyzed according to frequency of aspirin use, such as prescriptions of aspirin per day, week, or month [11,13,15,18,19]. Second, the definition of aspirin users varied among studies. Third, most studies

Table 2. Cumulative incidence rate of gastric cancer according to each year of observation periods

	Regular aspirin users (n=3,907)		Aspirin non-users (n=7,808)		p-value
	Cumulative gastric cancer cases	Cumulative rate of gastric cancer (95% CI, %)	Cumulative gastric cancer cases	Cumulative rate of gastric cancer (95% CI, %)	
FU year					
At 1 yr	3	0.08 (0.03-0.24)	13	0.17 (0.10-0.29)	0.028[a]
At 2 yr	10	0.27 (0.14-0.49)	25	0.33 (0.22-0.48)	
At 3 yr	15	0.41 (0.25-0.68)	40	0.54 (0.40-0.74)	
At 4 yr	19	0.53 (0.34-0.83)	56	0.79 (0.61-1.02)	
At 5 yr	22	0.63 (0.42-0.96)	65	0.94 (0.73-1.19)	
At 6 yr	28	0.88 (0.60-1.27)	77	1.17 (0.93-1.46)	
At 7 yr	31	1.05 (0.73-1.51)	86	1.41 (1.13-1.75)	

CI, confidence interval; FU, follow-up. [a]Univariate Cox-proportional hazard regression analysis.

Table 3. Univariate and multivariate Cox proportional hazard model for incidence of gastric cancer

Variable	No.	Person-years	Unadjusted		p-value	Adjusted for Covariates		p-value
			cHR	95% CI		aHR	95% CI	
Sex								
Male	5,915	32,877	1.00			1.00		
Female	5,800	32,054	0.39	0.26-0.58	< 0.001	0.39	0.26-0.59	< 0.001
Age at the time of inclusion (yr)	11,715	64,931	1.02	1.00-1.04	0.066	1.01	0.99-1.03	0.512
Residential area								
Metropolitan	6,661	36,954	1.00			1.00		
Urban	3,366	18,622	1.10	0.71-1.69	0.676	1.07	0.69-1.64	0.773
Rural	1,688	9,355	1.84	1.17-2.91	0.009	1.82	1.15-2.88	0.011
Comorbidity								
Hypertension	6,660	37,351	1.00			1.00		
Type 2 diabetes	5,055	27,580	1.38	0.96-1.98	0.081	1.26	0.87-1.81	0.219
Status of aspirin use								
Model 1 (regular aspirin users)	11,715	64,931	0.72	0.48-1.09	0.117	0.71	0.47-1.08	0.107
Duration of aspirin use								
Model 2 (continuous variable, yr)	11,715	64,931	0.84	0.72-0.98	0.028	0.85	0.73-0.99	0.044
Model 3 (categorical variable)								
0.5-1.0 yr	1,211	6,134	0.91	0.49-1.71	0.769	0.82	0.44-1.54	0.541
1.1-2.0 yr	1,038	5,489	0.74	0.36-1.52	0.410	0.71	0.34-1.46	0.349
2.1-3.0 yr	586	3,234	1.09	0.51-2.36	0.823	1.11	0.52-2.41	0.783
> 3.0 yr	1,072	6,802	0.37	0.15-0.90	0.029	0.40	0.16-0.98	0.045

cHR, crude hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio.

included both aspirin and NSAID users.

In contrast, our study has several comparative strengths. First, only patients who were prescribed 100 mg aspirin were included, and patients prescribed 300-500 mg aspirin or NSAIDs were excluded. Second, our study showed long-term effects of regular aspirin use on gastric cancer incidence, especially when continued for more than 3 years. Our analyses might be sensitive to this phenomenon because we carefully defined aspirin users as patients who made claims for aspirin for at least 6 consecutive months; previous studies have not made this distinction.

Duration and continuity of aspirin use are crucial variables when examining the effect of aspirin on gastrointestinal cancers because several years are necessary for the clinical detection of disease [20]. Indeed, a meta-analysis demonstrated that aspirin use for longer than 5 years reduced col-

orectal cancer risk in both case-control and cohort studies [5]. Our study also showed the importance of controlling for duration of use by demonstrating an association of long-term aspirin use with a significant reduction of gastric cancer risk, especially for aspirin use of more than 3 years. These results were consistent with those of previous studies, in which the duration of aspirin or NSAID treatment significantly reduced the risk of gastric cancer after 2 years [12,19], 5 years [15], or 10 years [11] of use.

The main mechanism of the cancer-preventing properties of aspirin and NSAIDs is associated with the blockade of the COX pathway, which influences various cellular processes, including inflammation, thrombosis, angiogenesis, apoptosis, and cell proliferation and migration [7]. In gastric cancer, the expression of COX-2 is highly elevated compared to normal gastric tissues [21], and elevated COX-2 expression is associated with many elements of gastric carcinogenesis, including the promotion of cell proliferation, inhibition of apoptosis, induction of vessel formation, and metastasis [8]. Therefore, the protective effects of aspirin against gastric cancer may be, in part, associated with the blockade of the COX-2 pathway.

Previous studies on the short-term use of aspirin as a chemotherapeutic agent showed that its activity in gastric cancer depends on anatomic location, *Helicobacter pylori* infection status, and histology. Aspirin significantly reduces the risk of gastric cancer when gastric cancers are located in the non-cardiac or distal portion of the stomach [11,13-15,18,19], when *H. pylori* infection is also present [13], and when the cancer shows an intestinal-type histology [19]. In Korea, the reported rate of cardiac gastric cancer is 7.2%-7.6% [22,23] of all gastric cancer diagnoses; the remaining proportion consists of non-cardiac gastric cancer diagnoses. In addition, the seropositive rate of *H. pylori* among Koreans is high, with a prevalence of 60% among asymptomatic subjects aged 16 years or more with no history of *H. pylori* treatment [24]. The known chemopreventive effects of aspirin on gastric cancer in *H. pylori*–positive tissue might contribute to the protective effects against gastric cancer that we found in our study of diabetic and hypertensive Koreans. However, because those data were not available in the KNHI claim database we were unable to test for differences among *H. pylori* infection status, cardiac versus non-cardiac gastric cancer, or histology type.

The current study has several limitations. First, this study is a retrospective cohort study. Although the results were derived from the analyses of a large, matched population, the possibility of selection bias from the KNHI claim database was unavoidable. Second, our findings may not be applicable to other geographic areas; the incidence of gastric cancer in Korea is the highest in the world [25]. Third, the effect of aspirin use on gastric cancer risk was evaluated in populations with type 2 diabetes or hypertension, which might affect the risk of gastric cancer. Thus, the association between aspirin use and gastric cancer risk reduction could be different in the general population. Fourth, due to the limitations of the KNHI claim database, the safety of long-term use of low-dose aspirin within this population was not evaluated. Aspirin use, even low dosages, is associated with gastrointestinal complications, including esophagitis, peptic ulcers, small and large bowel mucosa damage, and bleeding [6]. Therefore, despite the CV and cancer-protective benefits of aspirin use, the risk of adverse events must also be evaluated.

Conclusion

In conclusion, among Korean patients with hypertension or type 2 diabetes, long-term, low-dose aspirin use was associated with a reduced risk of gastric cancer. Administration of low-dose aspirin may be a candidate regimen for prevention of gastric cancer in areas where its incidence is high. However, regarding its use as a chemopreventive agent, further studies evaluating the risk of adverse events may be needed.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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