Cumulative Dose Threshold for the Chemopreventive Effect of Aspirin Against Gastric Cancer

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OBJECTIVES: **Many studies have found evidence that aspirin has protective effects against certain cancers, but quantitative dose–response data have been available only on a limited basis. This study aimed to confirm the dose–response relationship of aspirin usage and gastric cancer and to estimate the cumulative dose threshold of aspirin to achieve protective effects against gastric cancer in the general population.**

METHODS: **A total of 461,489 individuals in a population-based longitudinal cohort provided by the National Health Insurance Services (NHIS) in the Republic of Korea were observed from 2007 to 2012 to identify gastric cancer incident cases. The pharmacy claims data of these individuals from 2002 to 2006 were reviewed to assess cumulative medication exposure using the defined daily dose (DDD) system. Hazard ratios (HRs) of aspirin use for gastric cancer were estimated using multivariate Cox Proportional Hazard regression. Sensitivity analyses, including propensity-score matching and a nested case–control design, were performed to evaluate the variability caused by study design.**

RESULTS: **A total of 5674 incident gastric cancers were identified from 2,965,500 person-years of follow-up observation, giving an overall incidence rate of 191.00 gastric cancers per 100,000 person-years. Compared to non-users, those with aspirin use of $\geq$3 DDD-years showed a statistically significant protective effect of aspirin use against gastric cancer; the adjusted HR (95% confidence intervals) were 0.79 (0.63–0.98) and 0.63 (0.48–0.83) for those with aspirin use of 3–4 DDD-years and 4–5 DDD-years, respectively (P for trend $<$ 0.001). Sensitivity analyses using propensity-score matching and a nested case–control design consistently showed a chemopreventive effect of aspirin.**

CONCLUSION: **Long-term aspirin use was associated with reduced gastric cancer incidence in the general population of South Korea when the cumulative dose was $>$3 DDD-years.**

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INTRODUCTION

Gastric cancer is a major public health burden with high incidence, and it is one of the leading causes of cancer-related deaths worldwide. Stomach cancer was the third leading cause of cancer deaths in both sexes worldwide with 723,000 deaths in 2012 [1], and the estimated years lived with disability was 290,400 with a prevalence of 2,532,100 in 2013 [2]. In the Republic of Korea, although the incidence of gastric cancer is decreasing, it still has one of the highest incidences, with an age-standardized incidence rate of 39.9 per 100,000 and an age-standardized mortality rate of 11.2 per 100,000 in 2012 [3].

Gastric cancer is known to have several associated risk factors, including host, environmental, and microbiological factors [4, 5]. *Helicobacter pylori* is associated with >60% of gastric cancer worldwide [6]. Socioeconomic factors, unhealthy diet, obesity, harmful use of alcohol, tobacco use, and genomic factors also contribute to an increased risk of gastric cancer [4, 5, 7].

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Notably, there is evidence that aspirin and related non-steroidal anti-inflammatory drugs (NSAIDs) have protective effects against certain cancers, including colorectal, esophageal, gastric, biliary, and breast cancer [8, 9]. In the context of gastric cancer, the potential interaction between *H. pylori* and NSAIDs may also play a complex role in ulcerogenesis and carcinogenesis, because of either *H. pylori*'s augmentation of NSAID-associated mucosal damage, or conversely, its attenuation of aspirin's inhibition of cyclo-oxygenase-2/prostaglandin-E_2-induced ulcer healing [10].

Although the role of aspirin in preventing cardiovascular events is well established, the role of aspirin in preventing cancers may require more evidence to improve our understanding. For certain cancers, randomized controlled trials (RCTs) and cohort studies have produced strong evidence of the long-term chemopreventive effects of aspirin and other NSAIDs [11–16]. However, specific evidence regarding gastric cancer is limited. Some evidence in the literature has been based on specific disease cohorts [17, 18], which limits their ability to represent the general population. Other evidence based on population-based cohorts could not precisely assess the frequency and duration of medication use because the information was obtained through surveys [19, 20].

In the literature, meta-analyses on the chemopreventive effect of aspirin against gastric cancer concluded that the effect is dose-dependently maximized when aspirin is taken five times per week [21] and taken for at least 4 years [22]. However, the authors of the meta-analyses noted that their adjustment for confounding factors was limited due to a lack of individual-level data.

Recently, a nested case–control study in the Republic of Korea, based on a cohort of 100,000 hypertension patients and 100,000 type 2 diabetes patients, analyzed 117 observed gastric cancer incident cases and reported that those who continuously took aspirin for >3 years had a lower rate of gastric cancer (hazard ratio (HR) 0.40; 95% confidence interval (CI) 0.16–0.98) [18]. The authors, however, noted that this finding was based on a patient cohort of specific diseases; thus the study population may not represent the general population. In addition, the study did not use the recently available Health Examination Database within the National Health Information Database (NHID), which includes vital signs, laboratory tests, and survey questionnaires regarding past medical history and lifestyles (e.g., physical activity, tobacco, and alcohol usage), all of which may be potential confounding factors for gastric cancer.

In the current study, we attempted to evaluate the long-term effect of aspirin on gastric cancer based on the defined daily dose (DDD) using longitudinal data samples covering the whole population of the Republic of Korea. We employed a study design distinguishing the exposure ascertainment period from the outcome ascertainment period to avoid immortal time bias. In addition, we performed sensitivity analyses with variation of the index date between the exposure ascertainment period and outcome ascertainment period, as well as overlapping exposure and outcome ascertainment periods. We also conducted additional analyses with propensity-score-matched design and nested case–control design to evaluate the variability caused by study design. This study aimed to confirm the cumulative dose threshold for the protective effect of aspirin against gastric cancer in a retrospective cohort of South Korea.

MATERIALS AND METHODS

Study population and data

The Republic of Korea has a single-payer health insurance system, managed by the National Health Insurance Services (NHIS). All health-care providers need to submit medical claims to NHIS for review and reimbursement. NHIS also provides national health examinations for those who are aged >40 years, biannually for office workers and annually for non-office workers. All of this data including demographic profile, health insurance claims data, death registry, disability registry, and national health check-up data, are centrally collected at the NHID.

Representative data from NHIS's longitudinal cohort is provided to public health researchers and policy makers for research purposes [23]. The Sample Research Cohort Database [23–26] and the Health Examination Cohort Database was established in 2002 with statistical sampling from the NHID, which consists of Eligibility Database (DB), Medical Treatment DB, Health Examination DB, and Medical Care Institution DB.

In this study, 12-year longitudinal data from 2002 to 2013 were divided into two periods using January 1, 2007 as the index date (for the main analysis); the 5 years before the index date (2002 – 2006) is the "exposure ascertainment period" and the 7 years following the index date (2007–2013) is the "outcome ascertainment period". During the exposure ascertainment period, individual demographic features, medical history, and cumulative medication usage information were captured. During the follow-up outcome ascertainment period, qualifying events for gastric cancer incidents were captured. Inclusion and exclusion criteria for the eligible population for the analysis were determined at the point of the index date. A sensitivity analysis was conducted by shifting the index date to January 1, 2005 and January 1, 2009. Eligible population was re-assessed according to the shifted index date, and the aspirin exposure, as well as other medication exposures, disability registry, medical conditions, Charlson Comorbidity Index, and behavioral factors (cigarette smoking, alcohol consumption, and physical activity) were re-measured from the time-stamped database, so that the predictors are always measured prior to the outcome ascertainment period.

In the Health Examination Cohort Database, there were a total of 514,866 individuals who were aged ≥40 years in 2002 and also attended the national health examination at least once between January 1, 2002 and December 31, 2003. We excluded individuals ($n = 53{,}377$) who fit in the following criteria during the exposure ascertainment period; (i) diagnosed of any kind of cancer represented by the International Classification of Diseases code–Tenth Revision (ICD-10) "C" diagnosis code, (ii) had a medical history of cancer according to the health check-up survey data within the Health Examination DB, or (iii) recorded in the death registry. Among the 53,377 excluded individuals, 48,457 people had past history of cancer and 4920 people had a death record without cancer history. Finally, a total of 461,489 individuals were included in the main analysis.

The primary outcome of this study was a newly diagnosed gastric cancer during the follow-up outcome ascertainment period starting from the index date (from January 1, 2007 to December 31, 2013 for the main analysis). A gastric cancer case was defined as a patient who visited a health facility with the ICD-10 diagnosis code C16 at least once and met one or more of the following additional criteria: (i) at least three outpatient visits with the C16 code as one of the diagnoses, (ii) an admission of ≥3 days with the C16 code as one of the diagnoses, (iii) received any curative cancer treatments claimed via Korean Diagnosis-related Group (KDRG) code 'G60-Digestive Malignancy', or (iv) included in the death registry with the C16 code as the cause of death. The date of event was defined as the first date of the C16 code diagnosis. Cases that met the criteria but involved a diagnosis of any other cancer prior to the date of the event were not considered for the purpose of our analysis.

The primary exposure of interest was cumulative use of aspirin. Medication codes, dosage, duration, and the date of pharmacy claims data for aspirin, other NSAIDs, H2 receptor antagonists, and proton-pump inhibitors (PPIs) were collected according to the Anatomic Therapeutic Chemical (ATC) classification system [27] of drugs by World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. Cumulative exposure to medication was calculated using the DDD system [27] recommended by WHO for drug utilization studies, which provides a reference maintenance dose of each medication according to its main indication in adults. As acetylsalicylic acid for anti-platelet indication is independent of strength, any given acetylsalicylic acid at any dose at any frequency in a single day is calculated as 1 DDD (ATC code B01AC06). In Korea, usual dose of acetylsalicylic acid for anti-platelet indication is 100 mg once daily and usual dose of acetylsalicylic acid for analgesic and antipyretic indication is 500 mg three times per day or higher. DDDs for NSAIDs except acetylsalicylic acid were calculated with the WHO ATC/DDD for ATC codes M01AA01-M01AA05, M01AB01-M01AB55, M01AC01-M01AC06, M01AE01-M01AE52, M01AG01-M01AG03, M01AH01-M01AH06, and M01AX01-M01AX17. DDDs for H2 antagonists were calculated with the WHO ATC/DDD for ATC codes A02BA01-A02BA08. DDDs for PPIs were calculated with the WHO ATC/DDD for ATC codes A02BC01-A02BC06. Cumulative DDDs are the total sum of the DDD for each individual medication representing total exposure for each individual. *H. pylori* eradication therapy was defined when an ICD code in the Medical Treatment Database for *H. pylori* infection was recorded with prescription that meets following criteria: (i) PPI or H2 receptor antagonists, (ii) clarithromycin or metronidazole, and (iii) amoxicillin or tetracyclin. Charlson Comorbidity Score [28] was calculated based on the ICD-10 codes in the Medical Treatment Database, using the sum of the weighted scores of the comorbidities, including cardiovascular disease, pulmonary disease, renal disease, liver disease, and others [29].

For sociodemographic profiles, we included age, sex, income, and disability registry status. Age was in integer and sex was of dichotomous data type. Income was in decile based on the nationwide income distribution, which determines monthly premium payment for the individuals. For financially dependent individuals, the income deciles reflect that of the supporting individuals (family member). Higher decile reflects higher income. Disability registry is a part of Korean national social security services, and subsidy level is determined in six grades in the disability grade determination committee, where both physician's diagnosis and a separate evaluation are considered.

For the features from the laboratory tests and the health checkup data within the Health Examination Database, the latest data (ones nearest to the index date) were selected; these include height, weight, blood pressure, self-reported health-related habits (tobacco use, alcohol consumption, and physical activity), and laboratory test results. Numerical variables of the Health Examination DB were categorized as follows: body mass index [30] (BMI, kg/m^2) (BMI < 18.5, 18.5 ≤ BMI < 23, 23 ≤ BMI < 25, 25 ≤ BMI < 30, or BMI ≥ 30 kg/m^2); blood pressure [31] (normal: systolic blood pressure (SBP) < 120 mm Hg and diastolic blood pressure (DBP) < 80 mm Hg, prehypertension: neither SBP or DBP meets the hypertension criteria but 120 mm Hg ≤ SBP < 140 mm Hg or 80 mm Hg ≤ DBP < 90 mm Hg, hypertension, SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg); fasting glucose level [32] (<100 mg/dL, ≥100 mg/dL but <126 mg/dL, or ≥126 mg/dL); frequency of physical activity (none, 1–2 times/week, or ≥3 times/week); smoking status (never, former, or current smoker); and frequency of alcohol drinking (none, <1, 1–2 times/week, or ≥3 times/week).

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: E-1509-004-699). The need for participant consent was waived by the ethics committee because this study involved routinely collected medical data that were anonymously managed at all stages, including data cleaning and statistical analyses.

Analytical methods

Incidence rates were calculated per 100,000 person-years by dividing the number of gastric cancer events by the total number of person-years at risk and multiplying the result by 100,000. Cox Proportional Hazard regression for the gastric cancer incidence was used for estimating the HRs and 95% CIs. Accumulated person-years of risk were calculated starting on the index date until either the date of diagnosis of a gastric cancer, death, or December 31, 2013, whichever came first.

To investigate the independent effect of aspirin on gastric cancer risk and determine the cumulative dose threshold, we analyzed cumulative exposure of aspirin and NSAIDs with Cox Proportional Hazard regression adjusting for potential confounders as our main analysis. Covariates in the multivariable Cox regression are aspirin, NSAIDs, sociodemographic characteristics (age, sex, income), behavioral factors (cigarette smoking, alcohol consumption, and physical activity), medical conditions (body mass index, disability registry, Charlson Comorbidity Index, history of gastric ulcer, history of gastrointestinal bleeding), gastrointestinal medication use (H2 blockers, PPIs, *H. pylori* eradication therapy), gastrointestinal test for gastric cancer (esophagogastroduodenoscopy (EGD) or gastrofluoroscopy), and active user status of aspirin in the year before the index date. For the proportional hazard assumption, we performed a statistical test of correlation between the Schoenfeld residuals and ranked survival time. Cumulative exposure of

aspirin and NSAIDs was treated as continuous numerical variables for evaluating a trend of effect per unit cumulative dose of DDD-year. Cumulative exposure of aspirin was further investigated in seven categories (non-user, 1–29 DDD-days, 30–364 DDD-days, 1–2 DDD-years, 2–3 DDD-years, 3–4 DDD-years, and 4–5 DDD-years) to further examine dose–response relationship and cumulative dose threshold. Adjusted curve for cumulative hazards (1−survival rates) was estimated with the multivariate Cox Proportional Hazard model for gastric cancer with cumulative dose of aspirin in seven categories, where adjusting variables were used with mean for continuous variables and mode for categorical variables. Effect modification for the aspirin was evaluated by adding respective interaction terms with aspirin for the statistically significant covariates in the multivariate Cox regression model without interaction terms.

For the subpopulation with hypertension and diabetes patients, we investigated additional measures of quality of management and patients' adherence, by including test results of blood pressure and fasting plasma glucose and annual number of physician visits with the respective diagnosis codes in the multivariate Cox regression model.

Sensitivity analysis for the index date between the exposure ascertainment period and the follow-up outcome ascertainment period was performed by multivariable Cox regression after shifting the index date forward and backward to check possible confounding caused by medication consumption after the index date, as well as by the length of the exposure ascertainment period. Eligible study population is re-assessed based on the shifted index date. In addition, the cumulative dose of medication, disability registry, medical diagnoses, Charlson Comorbidity Index, and the latest health examination results from the index date (including the behavioral factors for cigarette smoking, alcohol consumption, and physical activity) are re-captured from the time-stamped database, so that our predictors are always measured prior to the outcome ascertainment period.

In addition to the sensitivity analysis with varying index date, we performed an additional sensitivity analysis with overlapping exposure and outcome ascertainment period. In this additional sensitivity analysis, eligible study population was defined at the time point of an index date of January 1, 2005, and a total of 481,536 individuals were included after applying the same exclusion criteria. However, in this additional sensitivity analysis, exposure was captured beyond the index date to assess the cumulative exposure more closely with the time of the event.

In addition to the sensitivity analyses, we performed additional analyses using propensity-score matching and a nested case–control design to evaluate the variability caused by study design. In the propensity-score matched design, respective pairs were created for each of the propensity-score model for thresholds of 1, 2, 3, and 4 DDD-years of cumulative dose, using sociodemographic characteristics (age, sex, income), behavioral factors (cigarette smoking, alcohol consumption, and physical activity), medical conditions (body mass index, disability registry, Charlson Comorbidity Index, history of gastric ulcer, history of gastrointestinal bleeding), gastrointestinal medication use (H2 blockers, PPIs, *H. pylori* eradication therapy), and gastrointestinal test for gastric cancer (EGD or gastrofluoroscopy). With a caliper of 0.2 times the standard deviation of the logit propensity score, matching ratio of 1:5 resulted in sample sizes of 126,306; 96,822; 61,218; and 26,514 for 1, 2, 3, and 4 DDD-years of aspirin use, respectively.

In the nested case–control design, incidence density sampling stratified by sex, age decade, income quartile, and disability registry status was performed to match three controls at the time of diagnosis for each case. Five thousand five hundred and three cases were matched to 16,509 individuals in 1:3 matching ratio. With the matched sample, conditional logistic regression estimated the rate ratios (RRs) and 95% CIs.

All analyses were performed using the STATA statistical software (version 11.0 for Windows; STATA Corp., Inc.,) and R statistical software (version 3.4.1 for Windows; R Foundation for Statistical Computing) with libraries tidyverse [33], tidystat [34], tableone [35], Matching [36], survminer [37], and survival [38].

RESULTS

A total of 5673 new gastric cancer cases were identified from 2,965,500 person-years of observation in the main analysis, giving an overall incidence rate of 191.00 gastric cancers per 100,000 person-years. Table **1** shows the baseline sociodemographic characteristics, behavioral factors, medical conditions, medication use, and claims of gastrointestinal tests of study population in the main analysis, comparing those with gastric cancer events from those who are censored without the event. Average (standard deviation) time to censor was 6.47 (1.47) years in those censored without event, and 3.57 years in those with gastric cancer. On average, those with gastric cancer had higher age, more males, more tobacco users, and more alcohol consumption, with standardized mean difference >0.1. Test for the violation of proportional hazard assumption was performed using Schoenfeld residuals and was non-significant for the multivariate model and all of the individual variables tested.

Table **2** shows trend estimates as a function of cumulative dose (per DDD-year) of aspirin and NSAIDs (per DDD-year) from Cox Proportional Hazard regression models. Cumulative exposure of aspirin showed statistically significant protective effect in both age- and sex-adjusted regression model and multivariate-adjusted regression model. Cumulative exposure of NSAIDs did not show any statistically significant effect in the regression models. In the multivariate regression model, statistically significant variables were age (HR 1.06, 95% CI 1.06–1.06), sex (female HR 0.45, 95% CI 0.42–0.48), tobacco use (former smoker HR 1.13, 95% CI 1.03–1.23; current smoker HR 1.22, 95% CI 1.14–1.31), alcohol consumption ($\geq$3 times/week HR 1.24, 95% CI 1.15–1.34), and *H. pylori* treatment (HR 0.70, 95% CI 0.53–0.91). Income, disability registry, body mass index, physical activity, Charlson Comorbidity Index, history of gastric ulcer, history of gastrointestinal bleeding, H2 antagonist use, PPI use, claims of EGD or gastrofluoroscopy test, and the active user status of aspirin in the year before the index date were not statistically significant. Full model estimates from the regression models are shown in Supplementary Table **1**.

Table 1 Baseline sociodemographic characteristics, behavioral factors, medical conditions, medication use, and reception of gastrointestinal tests of study population in the main analysis, comparing those with gastric cancer events from those who are censored without the event

	Censored without event	Gastric cancer cases	SMD
N	455,816	5673	
Time to censor (year)	6.47 (1.47)	3.52 (2.00)	1.679
Aspirin (DDD-year)	0.22 (0.78)	0.25 (0.82)	0.039
NSAIDs (DDD-year)	0.10 (0.35)	0.11 (0.31)	0.047
Age	52.00 (9.37)	56.78 (9.58)	0.504
Sex (female vs. male)	212,413 (46.6)	1678 (29.6)	0.356
Income (decile)[c]	6.34 (3.00)	6.15 (3.01)	0.061
Disability Registry			0.049
No disability	453,558 (99.5)	5623 (99.1)	
Levels 1–2	877 (0.2)	15 (0.3)	
Levels 3–6	1381 (0.3)	35 (0.6)	
Body Mass Index	24.02 (2.94)	23.92 (2.99)	0.035
Tobacco			0.206
Never smoker	317,167 (70.4)	3400 (60.7)	
Former smoker	39,409 (8.7)	635 (11.3)	
Current smoker	93,935 (20.9)	1569 (28.0)	
Alcohol consumption			0.202
<1 times/week	331,866 (73.2)	3717 (66.0)	
1–2 times/week	73,788 (16.3)	951 (16.9)	
≥3 times/week	47,450 (10.5)	967 (17.2)	
Physical activity			0.052
No exercise	239,145 (52.9)	3098 (55.1)	
1–2 exercise/week	115,778 (25.6)	1320 (23.5)	
≥3 exercise/week	96,945 (21.5)	1204 (21.4)	
Charlson Comorbidity Index[b]	1.55 (1.47)	1.68 (1.54)	0.087
History of gastric ulcer	1.75 (4.24)	1.89 (4.86)	0.031
History of gastrointestinal bleeding	0.01 (0.15)	0.01 (0.15)	0.017
H. pylori treatment	6572 (1.4)	57 (1.0)	0.040
H2 antagonist (DDD-year)	0.10 (0.26)	0.10 (0.28)	0.035
Proton-pump inhibitor (DDD-year)	0.01 (0.05)	0.01 (0.05)	0.004
EGD or gastrofluoroscopy tested	0.53 (0.99)	0.54 (1.07)	0.014
Not active user in the year before the index date	397,531 (87.2)	4811 (84.8)	0.069

For numerical variables, arithmetic means are presented with standard deviation in parenthesis. For categorical variables, frequencies are presented with percentage within the subpopulation in parenthesis

DDD defined daily dose, *NSAID* non-steroidal anti-inflammatory drug, *EGD* esophagogastroduodenoscopy, *SMD* standardized mean difference

[b]Charlson Comorbidity Index is calculated from acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, renal disease, severe liver disease, and HIV based on ICD-10 codes of hospital visits during years 2003–2006

[c]Income decile is based on the nationwide income distribution, which determines monthly premium payment for the individuals. For financially dependent individuals, the income deciles reflect that of the supporting individuals (family member). Higher decile reflects higher income

Incidence rates for gastric cancer stratified by age, sex, and categorized cumulative dose of aspirin and the adjusted HRs (95% CIs) of each factor from a multivariate Cox Proportional Hazard regression model with categorized variables are shown in Table 3. People in their 70s show an incident rate of 413.79 and adjusted HR of 4.60 (95% CI 4.13–5.12) in reference to the 40s. Incident

Table 2 Trend estimates as a function of cumulative dose (per DDD-year) of aspirin and NSAIDs (per DDD-year) from Cox Proportional Hazard regression models ($N=461,489$)

	Age- and sex-adjusted HRs (95% CI)	Multivariate-adjusted HRs (95% CI)
Aspirin (DDD-year)	0.93 (0.90–0.96)	0.93 (0.89–0.97)
NSAIDs (DDD-year)	1.03 (0.99–1.07)	1.03 (0.99–1.07)

Multi-dimensional Cox Proportional Hazard regression model included continuous variables of aspirin and NSAIDs, sociodemographic characteristics (age, sex, socioeconomic status), behavioral factors (cigarette smoking, alcohol consumption, and physical activity), medical conditions (body mass index, disability registry, Charlson Comorbidity Index, history of gastric ulcer, history of gastrointestinal bleeding), gastrointestinal medication use (H2 blockers, proton pump inhibitors, *H. pylori* eradication therapy), gastrointestinal screening history (esophagogastroduodenoscopy or gastrofluoroscopy), and active user status in the year before the index date. Full model estimates are shown in Supplementary Table **1**.
CI confidence interval, *DDD* defined daily dose, *NSAID* non-steroidal anti-inflammatory drug

rates and adjusted HR were higher in male than in female (HR of female compared to male = 0.46, 95% CI 0.43–0.49). Compared to aspirin non-users, those with aspirin use of ≥3 DDD-years showed a statistically significant protective effect of aspirin against gastric cancer: the adjusted HR (95% CIs) were 0.79 (0.63-0.98) and 0.63 (0.48–0.83) for those with aspirin use of 3–4 DDD-years and 4–5 DDD-years, respectively (P for trend <0.001). Figure 1 shows Kaplan–Meier curve with cumulative hazard (1−survival rate) adjusted with Cox Proportional Hazard regression presented in Table 3.

Supplementary Table **2** shows HRs and P-values for the interaction term in the Cox Proportional Hazard regression models with the respective interaction terms between aspirin and the covariates with the multivariate-model P-value < 0.05 in Supplementary Table **1**. None of the covariates showed statistically significant interaction with cumulative exposure of aspirin.

Supplementary Table **3** shows the estimates from the Cox regression models for the risk of gastric cancer with measures of quality of management and treatment adherence in the subpopulations of hypertension and diabetes patients. Fasting plasma glucose of ≥126 mg/dL was statistically significant in the subpopulation of hypertension patients (HR 1.23, 95% CI 1.05–1.43). Blood pressure and number of outpatient visits per year were not statistically significant.

Supplementary Table **4** shows the estimates from the sensitivity analysis for HRs (95% CIs) of aspirin against gastric cancer with shifting the index date from January 1, 2005 to January 1, 2009. The protective effect of aspirin against gastric cancer was statistically significant in index dates evaluated. Estimates for the protective effect of aspirin against gastric cancer was changed not >0.1 in HR scale when the index date was January 1, 2007 or later. Estimates for the protective effect of aspirin against gastric cancer was exaggerated when the index date was January 1, 2006 or earlier.

Supplementary Table **5** shows estimates from Cox Proportional Hazard regression models against gastric cancer with a study design with overlapping exposure ascertainment period and outcome ascertainment period. The protective effect of aspirin against gastric cancer was exaggerated in this study design. NSAIDs also showed statistically significant protective effect against gastric cancer in this study design.

Supplementary Table **6** shows HRs and 95% CIs for the effect of aspirin exposure estimated with Cox Proportional Hazard regression models with propensity-score matched design. In this design, those with cumulative aspirin use of >1 DDD-year ($N=21,051$) showed statistically significant protective effect against gastric cancer (HR 0.85, 95% CI 0.75–0.96), when compared to the propensity-score matched sample ($N=105,255$). The effect estimates for those with cumulative aspirin use 2, 3, and 4 DDD-years were also statistically significant with lower point estimates for HRs.

Supplementary Table **7** shows RRs and 95% CIs of aspirin (DDD-year) and NSAIDs (DDD-year) estimated with conditional logistic regression model in the nested case–control design ($N=22,012$). Cumulative exposure of aspirin showed statistically significant protective effect against gastric cancer (RR 0.95, 95% CI 0.91–0.98). Cumulative exposure of NSAIDs did not show statistically significant effect (RR 1.06, 95% CI 0.96–1.17).

DISCUSSION

Based on a population-based longitudinal cohort, we demonstrated that long-term aspirin use was associated with reduced gastric cancer incidence in the general population of South Korea when the cumulative dose is >3 DDD-years. Although some studies have suggested that aspirin has protective effects against certain cancers [8, 9, 11, 12], further evidence from RCTs may be limited because the cardiovascular effects of aspirin are already well established; thus only subjects without cardiovascular risks may be ethically eligible for long-term RCTs. Generating unbiased results regarding the chemopreventive effects of aspirin is also challenging; therefore, well-designed population-based cohort studies could be the best alternative to demonstrate its chemopreventive effects.

Multiple observational studies have investigated the chemopreventive effect of aspirin against various types of cancers, but cohort studies with evidence specific for gastric cancer are limited. In the most recent meta-analysis [21], only eight studies could be included [17–20,39–42]. Among the eight studies, two were based on specific disease cohorts (hospitalized gastric ulcer [17], hypertension [18], or type 2 diabetes [18]), limiting the generalizability of their results. In addition, four cohort studies were focused on multiple type of cancers, where the incident cases of gastric cancer were limited (24 [39], 48 [41], 91 [42], and 131 cases [40], respectively). Although two population-based cohort studies observed larger numbers of gastric cancer cases (360 [19] and 643 cases [20], respectively), information on the frequency and duration of medication use was obtained through surveys, and cumulative dose could not be assessed precisely.

Meta-analyses on the chemopreventive effect of aspirin against gastric cancer concluded that there is a dose-dependent effect that is maximized when aspirin is taken 5 times per week [21] and taken for at least 4 years [22]. However, the quantitative analysis

Table 3 Incidence rates for gastric cancer stratified by age, sex, and categorized cumulative dose of aspirin and the adjusted HRs (95% CIs) of each factor from a multivariate Cox Proportional Hazard regression model with categorized variables

	No. of subjects	Person-years	No. of events	Incident rate	Adjusted HR (95% CI)[a]
All subjects	461,489	2,970,232	5673	191.00	
Age group					
40s	222,744	1,483,311	1533	103.35	1
50s	130,069	838,209	1792	213.79	2.17 (2.03–2.33)
60s	84,655	517,002	1803	348.74	3.73 (3.46–4.01)
70s	24,021	131,710	545	413.79	4.60 (4.13–5.12)
Sex					
Male	247,398	1,572,984	3995	253.98	1
Female	214,091	1,397,248	1678	120.09	0.46 (0.43–0.49)
Aspirin					
Non-user	375,043	2,432,961	4466	183.56	1
1–29 DDD-days	21,562	136,230	278	204.07	0.97 (0.86–1.10)
30–364 DDD-days	31,243	193,229	449	232.37	0.96 (0.86–1.06)
1–2 DDD-years	13,800	85,274	211	247.44	0.96 (0.83–1.10)
2–3 DDD-years	9143	56,508	129	228.28	0.85 (0.71–1.01)
3–4 DDD-years	6182	38,272	86	224.71	0.79 (0.63–0.98)
4–5 DDD-years	4516	27,757	54	194.54	0.63 (0.48–0.83)
					P for trend[b]<0.001

HR hazard ratio, *CI* confidence interval, *DDD* defined daily dose, *NSAID* non-steroidal anti-inflammatory drug

[a]Adjusted hazard ratios and 95% confidence intervals are calculated with a multivariate Cox Proportional Hazard Model for gastric cancer with cumulative dose of aspirin in seven categories, sociodemographic characteristics (age category in decades, sex, socioeconomic status), behavioral factors (cigarette smoking, alcohol consumption, and physical activity), medical conditions (body mass index, disability registry, Charlson Comorbidity Index), and medication use (non-aspirin NSAIDs, H2 blockers, proton pump inhibitors, *H. pylori* eradication therapy)

[b]*P* for trend for aspirin was calculated by fitting a multivariate Cox proportional hazard regression with continuous aspirin dose data in individual level

was solely based on summary estimates from previous literature without individual data; therefore, the result may be confounded by multiple factors. Furthermore, most publications did not provide information with the level of detail necessary for quantitative dose–response analysis. For example, some studies only reported the frequency of aspirin binned with a single threshold [43–45] and this may be insufficient information for quantitative analysis. In this study, we confirmed a dose–response relationship using individual data with reliable dose information from the prescription database cohort of 461,489 people. Because the prescription records are time-stamped and include the total dose prescribed, cumulative dose time may be a better way of representing both frequency and duration of aspirin use.

This study contributes to the literature with many strengths. First, this study is based on a 12-year population-based prospective cohort in a region of high gastric cancer incidence. Since the Republic of Korea has a single-payer, compulsory universal health insurance system, the randomized sample for this cohort avoided selection bias. In addition, the combined claims data from all outpatient clinics, hospitals, and pharmacies allowed a complete and accurate analysis of prescription records. The national health examination data with laboratory tests and health questionnaires also provide detailed health conditions of each individual, and this allowed us to extensively investigate potential confounding factors. Furthermore, the statistical power of the 5673 gastric cancer cases observed in this cohort may outweigh those of previous studies. In addition, this study investigated multiple sensitivity analyses and study designs involving exposure and outcome ascertainment periods, propensity-score-matched sampling design, and nested case–control design.

Pharmaco-epidemiological observational study is particularly challenging due to potential biases [46–48]. To guarantee a reliable conclusion, several robust analytic strategies were employed in this study. First, our follow-up for the prospective cohort started at the same calendar date for both aspirin users and non-users to avoid survivor bias or immortal time bias. In addition, medication exposures were reliably assessed from the prescription database using the validated DDD system of the World Health Organization Collaborating Center for Drug Statistics Methodology [27]. To account for potential confounding factors that may be associated with either aspirin use or gastric cancer incidence, we adjusted for history of gastric ulcer, history of gastrointestinal bleeding,

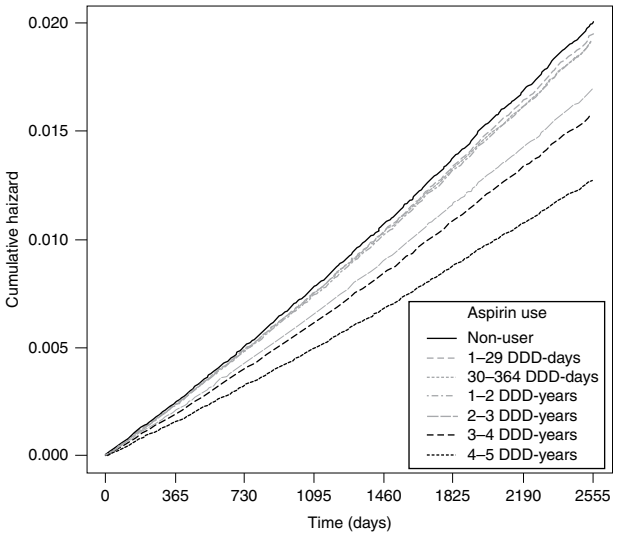

Fig. 1 Kaplan–Meier curve with cumulative hazard† (1−survival rate) adjusted with Cox Proportional Hazard regression presented in Table **3**. DDD defined daily dose. †Cumulative hazards are 1−survival rates estimated with a multivariate Cox Proportional Hazard model for gastric cancer with cumulative dose of aspirin in seven categories, sociodemographic characteristics (age, sex, socioeconomic status), behavioral factors (cigarette smoking, alcohol consumption, and physical activity), medical conditions (body mass index, disability registry, Charlson Comorbidity Index) and medication use (non-aspirin NSAIDs, H2 blockers, proton pump inhibitors, *H. pylori* eradication therapy). Adjusting variables were used with mean for continuous variables and mode for categorical variables. Black solid line indicates the baseline hazard for those who are not aspirin users with covariates with the average (means for the continuous covariates and modes for the categorical covariates). Black dashed lines indicate the hazard curves with statistical significance. Gray dashed lines indicate the hazard curves without statistical significance

H. pylori treatment, and use of H2 antagonists and PPIs. We also adjusted for claims of EGD or gastrofluoroscopy tests, which are preventive services directly related to the outcome of interest (gastric cancer) in our study. Owing to the high prevalence of gastric cancer in Korea, EGD or gastrofluoroscopy is provided by the national insurance every 2 years after the age of 40 years; therefore, these may also adjust for healthy user behaviors. We also added blood pressure, fasting plasma glucose, and number of physician visits as measures of appropriate management and patient adherence for the subpopulations of hypertension and diabetes patients. Finally, we added active user status of aspirin in the year before the index date, to account for residual effects. Supplementary Table **8** compares individuals who became non-active users to individuals who remained active users in the year before the index date among the aspirin users with cumulative dose of >1 DDD-year. However, our data did not suggest specific evidence that gastric ulcer or gastrointestinal bleeding was associated with stopping the use of aspirin.

To explore potential sources of heterogeneity in the estimates, we confirmed that there was no statistically significant variable showing an interaction with aspirin exposure (Supplementary Table **2**). The sensitivity analysis by shifting the index date confirms that the protective effect of aspirin against gastric cancer remains statistically significant in various time frames (Supplementary Table **4**). The earlier index date that makes the exposure ascertainment period shorter exaggerates the protective effect of aspirin. We chose the index date of January 1, 2007 for our main analysis, considering that the follow-up medical visits for cancer patients happen at least once in 5 years to maintain cancer patients' eligibility for the special rate of coinsurance by Korea National Health Insurance Services. On the other hand, an exposure ascertainment period >5 years would exclude the past cancer cases with less frequent follow-up medical visits. The additional sensitivity analysis confirms that overlapping exposure and outcome ascertainment periods exaggerate the protective effect of aspirin against gastric cancer (Supplementary Table **5**).

The protective effect of aspirin against gastric cancer was also statistically significant with propensity-score-matched design (Supplementary Table **6**) and nested case–control design (Supplementary Table **7**). Propensity-score-matched design provides a great opportunity to compare exposure groups adjusting for multiple confounding factors. However, when the research goal is to establish the threshold of a numerical variable of exposure or to investigate multiple categories, propensity-score models based on the probability of exposure allocation may have limitations. Nested case–control design may also provide a great opportunity to assess the effect of exposure while minimizing potential biases. However, nested case–control design may have limited statistical power due to the imperfect utilization of censored observations. Nonetheless, the statistical significance of the protective effect of aspirin against gastric cancer in these study designs strengthens our findings.

Aspirin has been widely used as an antipyretic, analgesic, and anti-inflammatory medication since the chemist Charles Frederic Gerhardt synthesized acetylsalicylic acid in 1853 [49]. Among various NSAIDs, aspirin has a special characteristic of irreversibly inhibiting platelet cyclo-oxygenase enzyme, and it is often used for its anti-platelet effect at low dose (81–325 mg once daily) [50]. The chemopreventive effect of aspirin could be explained by restricted platelet function [51], cyclo-oxygenase inhibition [52], and apoptosis of tumor cells [53]. Animal studies also have shown tumor suppression when aspirin and other NSAIDs were applied with a carcinogen [45].

In the context of gastric cancer, the potential interaction between *H. pylori* and NSAIDs may also play a role in ulcerogenesis and carcinogenesis [6, 10]. A cohort study based on hospitalized peptic ulcer patients in Taiwan reported that the chemopreventive effect of NSAIDs against gastric cancer was significant in those who received *H. pylori* eradication therapy after hospitalization due to peptic ulcer compared to those who did not receive *H. pylori* treatment [17]. Both the Taiwan study and the current study could not specifically explore the diagnostic test results for *H. pylori*, and the comparison group may include patients who were infected by *H. pylori* but did not receive the treatment. However, the comparison group in the Taiwan study comprised patients who were hospitalized for peptic ulcer, which may have contributed to a higher incidence of gastric cancer due to prolonged periods of *H. pylori* exposure. In this study, the variable interaction between aspirin

exposure and *H. pylori* eradication was not statistically significant, and this may indicate that the chemopreventive effect of aspirin against gastric cancer may be beneficial in the general population independently.

In this study, aspirin showed a statistically significant protective effect against gastric cancer, but other NSAIDs did not show statistically significant effect. This may be due to the heterogeneity among various kinds of NSAIDs. This study included 32 different generic NSAIDs, and each individual used multiple kinds of NSAIDs in various doses (Supplementary Table **9**). The primary research aim of this study was to extensively investigate the effect of aspirin, which has already been addressed with another dataset in Korea [18]. Further research questions involving different generic NSAIDs may involve a problem of multiple comparison, and additional studies regarding the different mechanism of action is necessary.

There were several possible limitations of this study. First, potential confounders may not have been fully controlled in observational studies compared to experimental studies. In particular, non-randomized allocation of aspirin usage may be a significant limitation. Additionally, the overall participation rate of 65.3% for the national health examinations may have posed a selection bias. Specifically, those with lower income and excessive alcohol consumption were less likely to have received gastrointestinal test for gastric cancer [54]. The gastric cancer diagnosis rate and the stage at initial diagnosis may vary in certain populations due to different participation rates for gastrointestinal test for gastric cancer, and this may also be a source of heterogeneity. Particularly, the fact that Republic of Korea has a high incidence of gastric cancer may limit the generalizability to other countries [3]. In addition, the diagnosis codes for this cohort were based on insurance claims, and there may be discrepancies between claims data and actual practice. Furthermore, over-the-counter medications purchased without prescription are not captured in the database, which may result in underestimation of medication use under certain conditions [55]. Finally, further research on mechanisms and/or interventions are necessary for causal inference.

However, it should be noted that the abovementioned limitations may be unavoidable in most observational studies. Since further evidence from long-term RCTs on the chemopreventive effects of aspirin may not be available due to ethical concerns, well-designed population-based cohort studies could be the best alternative to confirm the association. This study may contribute to the literature with its large-scale cohort sample with a reliable prescription record and detailed nation-wide health examination data.

In conclusion, long-term aspirin use was associated with reduced gastric cancer incidence in the general population of South Korea when the cumulative dose was >3 DDD-years.

CONFLICT OF INTEREST

Guarantor of the article: Sang Min Park.

Specific author contributions: M-hK: contributed for study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. JC: contributed for study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. WJK: contributed for study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. SB: contributed for analysis and interpretation of data; critical revision of the manuscript for important intellectual content. SMP: contributed for study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision. All the authors approved the final draft submitted.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Aspirin may have protective effects against certain cancers.
- Large-scale population-based evidence for gastric cancer risk is limited.
- Evidence for dose–response relationship for aspirin's chemopreventive effect is limited.

WHAT IS NEW HERE

- Evidence for aspirin's chemopreventive effect is evaluated from a large-sale population-based longitudinal cohort of South Korea.
- Long-term aspirin use was associated with reduced gastric cancer incidence in the general population of South Korea.
- The effect was statistically significant when the cumulative dose is >3 DDD-years.

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