Association Between Aspirin Use and Gastric Adenocarcinoma: A Prospective Cohort Study

Sohee Kwon[1,2], Wenjie Ma[1,2], David A. Drew[1,2], Samuel J. Klempner[3], Brianna M. Leonardo[1,2], Jacqueline J. Flynn[1,2], Yin Cao[4], Edward L. Giovannucci[5,6,7], Ying Bao[8], Charles S. Fuchs[9], Mingyang Song[1,2,5,6], and Andrew T. Chan[1,2,7,10]

ABSTRACT

Prospective data examining the association of aspirin use, according to dose and duration, with long-term risk of gastric adenocarcinoma in non-Asian cohorts are lacking. We evaluated the association between aspirin use and risk of gastric adenocarcinoma in two large prospective U.S. cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study. Cox proportional hazards regression models were used to calculate multivariable adjusted HRs and 95% confidence intervals (CI). Among the 159,116 participants, we documented 316 gastric adenocarcinoma cases (176 women, 140 men) over 34 years encompassing 4.5 million person-years. Among women, regular aspirin use (at least two times or more per week) was significantly associated with lower risk of gastric adenocarcinoma (multivariable HR, 0.52; 95% CI, 0.37–0.73) compared with nonregular use. However, regular aspirin use was not associated with gastric adenocarcinoma risk among men (multivariable HR, 1.08; 95% CI, 0.77–1.52; $P_{heterogeneity}$ for sex = 0.003). Among women, the lower risk of gastric adenocarcinoma was more apparent with increasing duration of aspirin use ($P_{trend} < 0.001$) and more than five tablets per week (multivariable HR, 0.51; 95% CI, 0.31–0.84). Regular, long-term aspirin use was associated with lower risk of gastric adenocarcinoma among women, but not men. The benefit appeared after at least 10 years of use and was maximized at higher doses among women. The heterogeneity by sex in the association of aspirin use with risk of gastric adenocarcinoma requires further investigation.

Prevention Relevance: Novel prevention is urgently needed to reduce incidence and mortality of gastric cancer. We found that regular aspirin use was associated with lower risk of gastric adenocarcinoma among women, but not men. The benefit appeared after at least 10 years of use and was maximized at higher doses among women.

See related Spotlight, p. 213

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death worldwide (1). Despite a decline in incidence and mortality and advances in therapeutic strategies, the burden remains high (2). Almost 1 million new diagnoses of gastric cancer are made annually and the 5-year survival rate is 31% (1, 3). Therefore, preventive options are urgently needed to reduce the incidence and mortality of gastric cancer.

Previous studies reported overexpression of prostaglandin synthase-2 (PTGS-2), also known as COX-2, in metaplastic and adenomatous cells as well as cancer cells in gastric adenocarcinoma, suggesting prostaglandin synthesis may play an important role in gastric carcinogenesis (4, 5). Helicobacter pylori (H. pylori) infection which is established to cause gastric cancer, has been reported to be significantly related to COX-2 expression (6–8). H. pylori infection can cause inflammation, promote cell proliferation, and inhibit apoptosis (9). Therefore, aspirin, which inhibits prostaglandin synthesis and reduces risk of colorectal neoplasia (10), has been considered as a potential chemopreventive agent for gastric cancer. In recent systematic reviews, an inverse association between aspirin use and gastric cancer risk has been shown (11–13). However, the optimal dosage and duration of aspirin use, including its association in specific subgroups, remain unclear. Thus, a more thorough investigation and clear understanding about the potential role of aspirin as a chemopreventive agent for gastric cancer, particularly in non-Asian populations, remain urgently needed.

[1]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [2]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [3]Mass General Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St. Louis, St. Louis, Missouri. [5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [6]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [7]Channing Division of Network Medicine, Department of Medicine Research, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. [8]Center for Observational Research & Data Science, Bristol-Myers Squibb, Princeton, New Jersey. [9]Yale University Cancer Center, New Haven, Connecticut. [10]Broad Institute of MIT and Harvard, Cambridge, Massachusetts.

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Corresponding Author: Andrew T. Chan, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114. Phone: 617-726-7802; Fax: 617-726-3673; E-mail: achan@mgh.harvard.edu

Cancer Prev Res 2022;15:265–72

doi: 10.1158/1940-6207.CAPR-21-0413

Thus, we prospectively examined the associations between aspirin use and the risk of gastric adenocarcinoma with dose and duration dependent manner in two large prospective U.S. cohort studies that provided detailed information on aspirin use over three decades. These two large cohorts provided an in-depth assessment of long-term aspirin use at a wide range of doses and durations for risk of gastric adenocarcinoma.

Materials and Methods

Study participants

We included two large prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The NHS enrolled 121,700 U.S. female nurses aged 30 to 55 at enrollment in 1976 and the HPFS enrolled 51,529 male health professional aged 40 to 75 in 1986 (14, 15). Participants have completed a mailed questionnaire at enrollment and every 2 years thereafter to provide data on lifestyle factors, medical history, and disease outcomes. Dietary intake has been updated every 4 years using a validated semiquantitative food frequency questionnaire (SFFQ) (15). The follow-up rates for both cohorts have exceeded 90% (16). We excluded participants with a cancer diagnosis at baseline except nonmelanoma skin cancer and participants with missing aspirin use information at baseline. The study protocol was approved by the institutional review boards (IRB) of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA), and the IRBs allowed participants' completion of questionnaires to be considered as implied consent. The study was done with ethical standards consistent with the Belmont Report.

Assessment of aspirin use

Detailed information about the assessment of aspirin use in both the NHS and the HPFS has been published previously (14). NHS participants were asked in 1980 whether they used aspirin, the number of pills taken each week, and the number of years of use and they have updated the aspirin use every 2 years since then except in 1986. Similarly, HPFS participants were asked whether they used aspirin two or more times per week in 1986 questionnaire and in questionnaires every 2 years thereafter. Beginning in 1992, the average number of tablets taken per week was assessed. In both cohorts, we specifically inquired about standard-dose (325-mg) aspirin tablets. Beginning in 1994, we also asked participants to convert intake of four baby (81 mg) aspirin to one standard aspirin tablet. Since 2000, we inquired about regular use of baby aspirin separately from standard aspirin. Consistent with prior analyses (17, 18), participants who reported using aspirin two or more times per week were defined as regular users, whereas those who reported less aspirin use were defined as nonregular users. In a substudy of 4,238 women in the NHS who reported using aspirin more than 15 days per month, the major reasons for aspirin use were cardiovascular disease prevention (48%), musculoskeletal or back pain (32%), headache (12%), and other reasons (8%; refs. 19, 20). In a separate substudy of 47,363 men in the HPFS, 211 men reported that the major reasons for use were to decrease risk for cardiovascular disease (58.4%), joint or musculoskeletal pain (33.0%), cardiovascular disease (25.4%), headaches (25.4%), and other reasons (7.0%) in HPFS (17).

Ascertainment of gastric adenocarcinoma

Diagnoses of gastric cancer cases were identified by self-report from biennial questionnaire and the National Death Index. For 90% of cases, we obtained permission from participants or next-of-kin to review their medical records. For cases without records, we accessed cancer registries to confirm the diagnosis of cancer. Study physicians who were blinded to the aspirin use information reviewed medical records including pathology and imaging reports and death certificates to confirm gastric cancer and to classify histology and tumor location (proximal, distal, or entire). Proximal lesions included the gastroesophageal junction, cardia, or fundus, and distal lesions included the body, antrum, or pylorus. Furthermore, presence of concurrent H. pylori infection and Lauren classification (intestinal- or diffuse-type) were also abstracted from tumor pathology reports. For this analysis, we included gastric cancer cases diagnosed between the baseline questionnaire and the end of the analysis (June 30, 2014 for the NHS; January 31, 2014 for the HPFS). We excluded cases with nonadenocarcinoma due to the histologic and etiologic distinction from gastric adenocarcinoma.

Ascertainment of H. pylori infection status

We used extant data to examine the association of aspirin use and H. pylori infection. A subgroup of participants, 32,826 women and 18,159 men, in each cohort provided blood samples between 1989 and 1990 in the NHS and between 1993 and 1995 in the HPFS. We previously conducted nested case-control studies of pancreatic and colon cancer among men and women in each cohort. For the pancreatic cancer case control study, archived blood samples from 384 women and 280 men were assayed for H. pylori IgG in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA) using ELISA (21). Positive results for H. pylori infection was defined as a level of blood antibody to H. pylori was more than 7 units/mL based on manufacturer's instructions. For the colorectal cancer case control study, blood samples from 616 women and 324 men were analyzed in the German Cancer Research Center (Heidelberg, Germany). These blood samples assayed by multiplex serology, a fluorescent bead-based suspension array (22). Antigen-specific cutoffs were applied as defined in the prior study and positive results for H. pylori infection was defined as being positive to any four or more of the included thirteen H. pylori antigens (22, 23). For this analysis, we combined controls from the pancreatic and colorectal cancer case-control studies.

Statistical analysis

We analyzed the association between regular aspirin use and the risk for gastric adenocarcinoma in the main analysis.

Person-years accrued from the date of return of the baseline questionnaire (1980 in the NHS and 1986 in the HPFS) to the date of gastric adenocarcinoma diagnosis, death, or the end of follow-up (June 30, 2014 for the NHS; and January 31, 2014 for the HPFS), whichever came first. Once a participant was diagnosed with gastric adenocarcinoma, the participant was censored in all later follow-up cycles. Cox proportional hazards regression models were used to calculate age adjusted and multivariable adjusted HR and 95% confidence intervals (CI) of the association between regular aspirin use and gastric adenocarcinoma risk. No significant violation of proportionality was found ($P > 0.05$). Test for trend was examined using the median of each category as a continuous variable.

We applied time-varying aspirin exposure and covariates. We updated aspirin exposure and all covariates biennially. The covariates included in the multivariable models were established or potential risk factors for gastric adenocarcinoma. In our age-adjusted model, we controlled for age (years) and questionnaire cycle. In the multivariate models, we additionally adjusted for the following potential confounders: race (White or non-White), body mass index (BMI; <25.0, 25.0–29.9, or ≥30.0 kg/m^2), alcohol intake (0, <5.0, 5.0–14.9, or ≥15.0 g/day), smoking status (never, past, or current), physical activity (<3.0, 3.0 to 8.9, or ≥9.0 metabolic equivalent hours/week), current multivitamin use (yes or no), intake of red and processed meat, fruits and vegetables (quartiles), and current acid suppression medication use (yes or no). In women, we also adjusted for menopausal hormone therapy (never, ever, or premenopausal). To control for potential confounding by nonaspirin nonsteroidal anti-inflammatory drug, we further adjusted for regular use of nonaspirin nonsteroidal anti-inflammatory drug (yes or no) in the multivariate model 3. For missing data on each covariate, we carried forward from the previous questionnaire and used indicator variable to present the missing category for remained missing values after the carrying forward. For dose analyses, we calculated cumulative average intake of aspirin from all available questionnaires before each 2-year follow-up interval for better estimation of long-term intake (17, 19). For duration analyses, we estimate the number of years of aspirin use according to all biennial questionnaires before each 2-year follow-up interval (17, 19).

We performed stratified analysis by risk factors including age, BMI, physical activity, smoking, and alcohol intake. We tested the interactions by likelihood ratio tests. Furthermore, to explore potential heterogeneity in the association between regular aspirin use and gastric adenocarcinoma in different location, we performed stratified analysis of gastric adenocarcinoma by cancer location (proximal, distal, or entire). Proximal gastric adenocarcinoma was defined as tumors located in gastroesophageal junction, cardia, or fundus, and distal gastric adenocarcinoma was defined as tumors located in body of the stomach, antrum, or pylorus. Gastric adenocarcinoma with an extent that encompassed both proximal and distal regions of the stomach was defined as entire. We also examined stratified analysis of gastric adenocarcinoma by Lauren classification (Intestinal-type or diffuse-type) to explore potential heterogeneity in the association between regular aspirin use and gastric adenocarcinoma in different histopathology. Additionally, we investigated potential heterogeneity in the association between regular aspirin use and gastric adenocarcinoma by presence of locally advanced disease or metastasis (positive lymph nodes and/or distant metastases, or negative lymph nodes and no metastases). As a sensitivity analysis, we evaluated the latency of aspirin use and gastric adenocarcinoma risk using a lag of 4 years. To evaluate the association between regular aspirin use and H. pylori infection, we applied logistic regression models to calculate ORs and their 95% CI. This model included the regular aspirin use and covariables that were defined for Cox proportional hazards regression models.

We performed all analyses in the NHS and the HPFS separately. To test for heterogeneity between cohorts, we calculated the Cochrane Q statistic and the I2 statistic in a random effects model. All the statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) with two-sided and P value < 0.05 indicating statistically significant.

Data availability

Data, the statistical code, questionnaires, and technical process are available from the corresponding author at achan@mgh.harvard.edu.

Results

Over the 34 years of follow-up, we documented 316 incident cases of gastric adenocarcinoma (176 women, 140 men) among 159,116 participants (109,684 women, 49,432 men) encompassing 4,506,058 person-years. In 1996, the midpoint of study follow-up, regular aspirin users were more likely to be older, previously smoke, consume more alcohol, and use multivitamins, compared with nonregular users. Among women, aspirin users were more likely to be postmenopausal (**Table 1**).

Compared with nonregular use, regular aspirin use was significantly associated with a lower risk of gastric adenocarcinoma among women (multivariable HR, 0.52; 95% CI, 0.37–0.73; **Table 2**). However, regular aspirin use was not associated with gastric adenocarcinoma risk among men (multivariable HR, 1.08; 95% CI, 0.77–1.52). A statistical test for the heterogeneity of the association of aspirin use with gastric adenocarcinoma according to sex was significant ($P_{\text{heterogeneity}} = 0.003$). The results remained unchanged after additional adjustment for regular use of nonaspirin NSAIDs.

We identified Lauren classification (intestinal- or diffuse-type) based on the tumor pathology reports, and the data was available in 49% of gastric adenocarcinoma cases in NHS and 42% of gastric adenocarcinoma cases in HPFS. The association between regular aspirin use and risk of adenocarcinoma among women appeared consistent for intestinal-type adenocarcinoma (multivariable HR, 0.55; 95% CI, 0.27–1.11) and diffuse-type adenocarcinoma (multivariable HR, 0.39; 95% CI,

Table 1. Age-standardized characteristics of study participants[a].

Characteristic[b]	Women		Men	
	Aspirin use		Aspirin use	
	Nonregular ($n = 62,669$)	Regular[c] ($n = 40,529$)	Nonregular ($n = 23,558$)	Regular[c] ($n = 22,299$)
Age, years	61.4 (7.0)	63.1 (7.0)	62.0 (9.5)	64.4 (9.4)
White, %	96.1	98	94.6	96.5
BMI, kg/m^2	26.5 (5.4)	26.7 (5.3)	25.9 (3.9)	26.2 (3.9)
Physical activity, MET hours/week	16.3 (20.7)	17.8 (22.1)	28 (29.6)	28.8 (29)
Smoking status, %				
Never	45.2	42.6	50.5	46.1
Past smokers	40.7	43.3	42	47.4
Current smokers	14.1	14.1	7.5	6.5
Alcohol intake, grams/day	4.1 (7.6)	4.8 (8.3)	10.2 (14.5)	11.5 (15.1)
Multivitamin use, %	43	55.8	37.3	51.3
Acid suppression medication use, %	9.2	10.1	3.7	4.6
Nonaspirin NSAID use, %	23.9	23.4	12.1	13.1
Red or processed meat intake, servings/day	0.9 (0.4)	0.8 (0.4)	1.1 (0.6)	1.0 (0.6)
Fruits intake, servings/day	1.9 (1.0)	1.9 (1.0)	1.8 (1.1)	1.8 (1.2)
Vegetables intake, servings/day	3.4 (1.6)	3.5 (1.8)	3.2 (1.6)	3.2 (1.7)
Postmenopausal, %	73.9	83.4		
Menopausal hormone, ever user, %	69.7	72.1		

Abbreviation: MET, metabolic equivalent task.
[a]Data were obtained from NHS (women) and HPFS (men) in 1996 at the midpoint of follow-up.
[b]All data reported as percentage (%) or mean with SD. Except for mean of age, all data were age standardized.
[c]Regular aspirin use was defined as consumption of at least two times or more per week (vs. nonregular use).

0.22–0.71). In addition, we also observed an inverse association but limited power among women when we performed subgroup analyses according to anatomic location of gastric adenocarcinoma as well as for disease that presented with lymph node involvement or metastases at diagnosis (multivariable HR, 0.63; 95% CI, 0.40–0.97) or without lymph node involvement or metastases (multivariable HR, 0.34; 95% CI, 0.14–0.83; Supplementary Table S1).

Table 2. Regular aspirin use and risk of gastric adenocarcinoma[a].

Characteristic	Aspirin use	
	Nonregular	Regular[b]
Women		
Cases per person-years	125/2,097,414	51/1,258,158
Age-adjusted HR (95% CI)	1 [Reference]	0.52 (0.37–0.73)
Model 2 HR (95% CI)[c]	1 [Reference]	0.52 (0.37–0.73)
Model 3 HR (95% CI)[d]	1 [Reference]	0.52 (0.37–0.73)
Men		
Cases per person-years	65/601,125	75/549,361
Age-adjusted HR (95% CI)	1 [Reference]	1.07 (0.77–1.50)
Model 2 HR (95% CI)[c]	1 [Reference]	1.08 (0.77–1.52)
Model 3 HR (95% CI)[d]	1 [Reference]	1.08 (0.77–1.52)

[a]Data were obtained from the 1980 to 2014 NHS (women) and the 1986 to 2014 HPFS (men).
[b]Regular aspirin use was defined as consumption of at least two times or more per week (vs. nonregular use) and modeled as a time-varying covariate.
[c]Model 2 was adjusted for race (White or non-White), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), alcohol intake (0, <5.0, 5.0–14.9, or ≥15.0 g/day), smoking status (never, past, or current), physical activity (<3.0, 3.0 to 8.9, or ≥9.0 metabolic equivalent hours per week), current multivitamin use (yes or no), intake of red and processed meat, fruits and vegetables (quartiles), and current acid suppression medication use (yes or no). For women, we also adjusted for menopausal hormone therapy (never, ever, or premenopausal). The model was also conditioned on age (continuous years), and year of questionnaire return. All covariates were updated over time.
[d]Model 3 was additionally adjusted for regular use of nonaspirin nonsteroidal anti-inflammatory drug (yes or no) modeled as a time-varying covariate.

In women, the apparent benefit of aspirin use for gastric adenocarcinoma was substantially greater with increasing dose ($P_{trend} = 0.01$; **Table 3**). Compared with nonusers, the multivariable HRs (Model 3) were 0.72 (95% CI, 0.47–1.09) for 0.5 to 1.5 standard tablets per week, 0.71 (95% CI, 0.48–1.05) for 1.5 to less than 5 tablets per week, and 0.51 (95% CI, 0.31–0.84) for ≥5 tablets per week. In men, compared with nonusers, increasing dose was not significantly associated with reduced risk of gastric adenocarcinoma ($P_{trend} = 0.27$), although aspirin use at ≥5 tablets per week was associated with a nonsignificant inverse association (HR = 0.85; 95% CI, 0.47–1.51).

We assessed the association of duration of regular aspirin use with gastric adenocarcinoma risk (**Table 4**). In women, the apparent beneficial association of aspirin use for gastric adenocarcinoma was stronger with longer duration, without observed departures from linearity ($P_{trend} < 0.001$). Compared with nonusers, the multivariable HRs (Model 3) were 0.77 (95% CI, 0.50–1.18) for less than 5 years, 0.99 (95% CI, 0.63–1.56) for 5 to less than 10 years, and 0.45 (95% CI, 0.29–0.69) for ≥10 years. In men, compared with nonusers, aspirin use for ≥10 years was associated with nonsignificant reduced risk of gastric adenocarcinoma (HR, 0.77; 95% CI, 0.46–1.28).

In stratified analyses, the inverse association between regular aspirin use and gastric adenocarcinoma risk were consistent within subgroups defined by cancer risk factors among women. No significant interactions were observed between regular aspirin use and age, BMI, physical activity, intake of alcohol,

Table 3. Dose of standard aspirin and risk of gastric adenocarcinoma[a].

Characteristic	Number of weekly aspirin tablets (cumulative average)				P_{trend}[b]
	<0.5 tabs	0.5 to <1.5 tabs	1.5 to <5 tabs	≥5 tabs	
Women					
Cases per person-years	77/1,304,616	34/691,971	44/811,338	21/547,647	
Age-adjusted HR (95% CI)	1 [Reference]	0.70 (0.47–1.06)	0.69 (0.47–1.01)	0.51 (0.31–0.82)	0.01
Model 2 HR (95% CI)[c]	1 [Reference]	0.71 (0.46–1.07)	0.69 (0.47–1.02)	0.49 (0.30–0.80)	0.01
Model 3 HR (95% CI)[d]	1 [Reference]	0.72 (0.47–1.09)	0.71 (0.48–1.05)	0.51 (0.31–0.84)	0.01
Men					
Cases per person-years	28/289,893	20/198,754	72/445,153	20/216,686	
Age-adjusted HR (95% CI)	1 [Reference]	1.14 (0.64–2.02)	1.60 (1.03–2.47)	0.85 (0.48–1.51)	0.29
Model 2 HR (95% CI)[c]	1 [Reference]	1.16 (0.65–2.07)	1.64 (1.05–2.55)	0.84 (0.47–1.50)	0.26
Model 3 HR (95% CI)[d]	1 [Reference]	1.17 (0.65–2.07)	1.64 (1.06–2.55)	0.85 (0.47–1.51)	0.27

[a]Data were obtained from the 1980to 2014 NHS (women) and the 1986 to 2014 HPFS (men).
[b]Calculated using the median value of each category as a continuous variable.
[c]Model 2 was adjusted for race (White or non-White), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), alcohol intake (0, <5.0, 5.0–14.9, or ≥15.0 g/day), smoking status (never, past, or current), physical activity (<3.0, 3.0–8.9, or ≥ 9.0 metabolic equivalent hours per week), current multivitamin use (yes or no), intake of red and processed meat, fruits and vegetables (quartiles), and current acid suppression medication use (yes or no). For women, we also adjusted for menopausal hormone therapy (never, ever, or premenopausal). The model also conditioned on age (continuous years), and year of questionnaire return. All covariates were updated over time.
[d]Model 3 was additionally adjusted for regular use of non-aspirin nonsteroidal anti-inflammatory drug (yes or no) modeled as a time-varying covariate.

and multivitamin use (all $P_{interaction} > 0.05$; Supplementary Table S2).

We considered the possibility that the association of regular aspirin use with lower risk of gastric adenocarcinoma in women was due to avoidance of aspirin related to symptoms of gastric cancer. First, after excluding cases of gastric adenocarcinoma diagnosed within 4 years of follow-up, we observed similar results in women (multivariable HR, 0.61; 95% CI, 0.43–0.86; Supplementary Table S3).

In an exploratory analysis, we examined the association between regular aspirin use and risk of H. pylori infection among the 1,516 individuals for whom H. pylori status was assessed through participation as controls in prior nested case-control studies (**Table 5**). The H. pylori infection rate was 30% among women and 32% among men. Compared with non-regular users, regular use of aspirin was significantly associated with reduced risk of H. pylori infection in women (multivariable OR = 0.62; 95% CI, 0.44–0.87). This association was also observed in men but not significant (multivariable OR, 0.87; 95% CI, 0.60–1.26).

Discussion

Long-term, regular aspirin use (≥2 times per week) was associated with a significantly reduced risk of gastric adenocarcinoma in women. Notably, the apparent benefit of aspirin

Table 4. Duration of regular aspirin use and risk of gastric adenocarcinoma[a].

Characteristic	Duration of aspirin use, years				P_{trend}[b]
	Never-use	<5 years	5 to <10 years	≥10 years	
Women					
Cases per person-years	78/1,417,686	30/569,374	29/362,696	39/1,005,816	
Age-adjusted HR (95% CI)	1 [Reference]	0.76 (0.50–1.17)	0.98 (0.63–1.52)	0.45 (0.30–0.68)	<0.001
Model 2 HR (95% CI)[c]	1 [Reference]	0.75 (0.49–1.16)	0.96 (0.62–1.51)	0.43 (0.28–0.66)	<0.001
Model 3 HR (95% CI)[d]	1 [Reference]	0.77 (0.50–1.18)	0.99 (0.63–1.56)	0.45 (0.29–0.69)	<0.001
Men					
Cases per person-years	37/392,863	29/230,476	36/199,212	38/327,935	
Age-adjusted HR (95% CI)	1 [Reference]	1.13 (0.69–1.85)	1.41 (0.88–2.26)	0.78 (0.48–1.28)	0.33
Model 2 HR (95% CI)[c]	1 [Reference]	1.12 (0.68–1.84)	1.40 (0.87–2.25)	0.76 (0.45–1.26)	0.27
Model 3 HR (95% CI)[d]	1 [Reference]	1.13 (0.68–1.85)	1.41 (0.88–2.27)	0.77 (0.46–1.28)	0.29

[a]Data were obtained from the 1980 to 2014 NHS (women) and the 1986 to 2014 HPFS (men).
[b]Calculated using the median value of each category as a continuous variable.
[c]Model 2 was adjusted for race (White or non-White), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), alcohol intake (0, <5.0, 5.0–14.9, or ≥15.0 g/day), smoking status (never, past, or current), physical activity (<3.0, 3.0– 8.9, or ≥ 9.0 metabolic equivalent hours per week), current multivitamin use (yes or no), intake of red and processed meat, fruits and vegetables (quartiles), and current acid suppression medication use (yes or no). For women, we also adjusted for menopausal hormone therapy (never, ever, or premenopausal). The model also conditioned on age (continuous years), and year of questionnaire return. All covariates were updated over time.
[d]Model 3 was additionally adjusted for regular use of nonaspirin nonsteroidal anti-inflammatory drug (yes or no), assessed as a time-varying covariate.

Table 5. Regular aspirin use and risk of H. pylori infection[a].

Characteristic	Aspirin use	
	Nonregular	Regular
Women		
No. of H. pylori infection	213	67
No. of participants	650	282
Age-adjusted OR (95% CI)	1 [Reference]	0.59 (0.42–0.81)
Model 2 OR (95% CI)	1 [Reference]	0.62 (0.45–0.88)
Model 3 OR (95% CI)	1 [Reference]	0.62 (0.44–0.87)
Men		
No. of H. pylori infection	101	87
No. of participants	306	278
Age-adjusted OR (95% CI)	1 [Reference]	0.87 (0.61–1.24)
Model 2 OR (95% CI)	1 [Reference]	0.87 (0.60–1.26)
Model 3 OR (95% CI)	1 [Reference]	0.87 (0.60–1.26)

[a]For 1,516 men and women with measurements of H. pylori who participated as controls in a nested case-control study, aspirin use was assessed on the questionnaire prior to blood collection (1990 in NHS and 1994 in HPFS).
[b]Regular aspirin use was defined as consumption of at least two times or more per week (vs. nonregular use).
[c]Model 2 was adjusted for age (continuous years), race (White or non-White), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), alcohol intake (0, <5.0, 5.0–14.9, or ≥15.0 g/day), smoking status (never, past, or current), physical activity (<3.0, 3.0–8.9, or ≥ 9.0 metabolic equivalent hours per week), current multivitamin use (yes or no), intake of red and processed meat, fruits and vegetables (quartiles), and current acid suppression medication use (yes or no). For women, we also adjusted for menopausal hormone therapy (never, ever, or premenopausal).
[d]Model 3 was additionally adjusted for regular use of nonaspirin nonsteroidal anti-inflammatory drug (yes or no) modeled as a time-varying covariate.

use appeared after at least 10 years of use and was particularly pronounced with a dose of more than five tablets per week. In contrast, we did not observe an association among men.

Our results are supported by prior studies primarily conducted in Asian participants (24–30). Specifically, several studies reported that aspirin use was associated with a reduced noncardia gastric cancer risk but not cardia gastric cancer risk (31–35). In our analyses, we observed that aspirin use, particularly at longer durations, was associated with reduced risk of both of proximal and distal gastric adenocarcinoma in women. Although longer duration of use of aspirin has been shown to be associated with a lower risk of gastric cancer (24, 28, 36, 37), the majority of previous studies evaluated aspirin used for durations less than 10 years or had an insufficient sample size of participants using for longer durations (28, 36, 38). Thus, our results significantly expand upon prior studies by prospectively examining aspirin use at a wider range of doses and durations in non-Asian participants.

Our findings are biologically plausible. Specifically, PTGS-2, or COX-2, plays an important role in inflammatory processes and carcinogenesis in many cancers (18, 39–41) including gastric cancer (4, 5, 42–44). Inflammation may promote gastric carcinogenesis by inhibiting apoptosis, inducing angiogenesis and lymphatic metastasis, and assisting tumor invasion and immunosuppression (5, 42–44). Moreover, previous studies demonstrated that H. pylori infection, an established risk factor for gastric cancer (45–48) was significantly associated with COX-2 expression (6–8). The p38MAPK/ATF-2-mediated signaling pathway induced by H. pylori is a key mechanism in COX-2 expression (49). In addition, hypergastrinemia induced by H. pylori infection may promote the expression of COX-2 at the transcriptional and posttranscriptional levels by PI3K pathways (50). Aspirin inhibits the growth of H. pylori in a dose-dependent manner *in vitro* (51). We also observed that regular aspirin use was significantly associated with reduced risk of H. pylori infection among women in our cross-sectional analysis. Our results suggest a possible mechanism underlying the association between aspirin use and gastric cancer may be mediated by an effect of aspirin use on H. pylori. However, further studies are needed to confirm these findings and determine if there is a causal association between aspirin use and H. pylori infection.

Notably, the apparent association between aspirin use and reduced risk of gastric adenocarcinoma was observed in women but not men. A potential heterogeneity of the association between aspirin use and gastric adenocarcinoma according to sex has not been previously reported. There are several potential reasons causing the heterogeneity according to sex. First, the size of the baseline cohort and length of follow-up was shorter for the men than women, which may have limited our ability to detect an association in men. In fact, there was evidence of a nonsignificant inverse association between aspirin use and gastric cancer among men who used for more than 10 years or used at the highest doses (>5 tablets/week). Second, a greater proportion of men compared with women aspirin users reported using low dose aspirin use for cardiovascular disease prevention (52), which may be less effective in preventing cancer than standard doses. In support of this possibility, we observed a borderline nonsignificant association among men who used aspirin in the highest dose category. Finally, our results may be due to a biological difference between men and women in the effect of aspirin on risk of gastric cancer, such as the potential heterogeneity in the association of aspirin with H. pylori infection that we observed here.

This study has several strengths. First, aspirin assessments have been updated over 34 years of follow-up, permitting us to evaluate long-term use of aspirin. Moreover, since the aspirin data has been collected prospectively prior to diagnosis with gastric adenocarcinoma, we were effectively able to exclude the possibility of recall bias. Second, we had detailed information for aspirin use including dose, duration, and consistency of use. Third, we were able to adjust for a wide range of lifestyle and dietary factors relevant to the association between aspirin use and gastric adenocarcinoma.

Our study has limitations. First, although H. pylori is well established risk factor for risk of gastric cancer, we were not able to fully account for H. pylori infection within the entire cohort. However, because H. pylori infection is not routinely assessed in clinical practice, it would have been infeasible to capture such information comprehensively within a large, prospective cohort. Second, although we had information on a wide range

of risk factors, since our study is observational, we cannot rule out the potential for residual confounding. However, definitive results through a randomized controlled trial would not be feasible given the need for a large number of participants and long-term follow-up. Finally, more than 90% of participants in our study are White, our results thus cannot be generalized to other races and ethnicities. However, a potential preventive effect of aspirin for gastric adenocarcinoma has also been reported in cohort studies conducted in Asian countries (24, 25, 27, 30).

In summary, we found that regular, long-term aspirin use is associated with a reduced risk of gastric adenocarcinoma among women, but not men. Further studies are needed to confirm these results and elucidate a potential mechanistic basis for a sex difference in the effect of aspirin on gastric neoplasia.

Authors' Disclosures

D.A. Drew reports grants from NIH during the conduct of the study. S.J. Klempner reports personal fees from Merck, BMS, Astellas, Foundation Medicine, Natera, Daiichi Sankyo, Sanofi-Aventis, Eli Lilly and Company; and other support from Turning Point Therapeutics outside the submitted work. C.S. Fuchs reports personal fees from Amylin Pharma, AstraZeneca, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly and Company, Entrinsic Health, Evolveimmune Therapeutics, Genentech, Merck, Taiho; and personal fees from Unum Therapeutics outside the submitted work; in addition, C.S. Fuchs is a co-Founder of Evolveimmune Therapeutics and has equity in this private company; and had provided expert testimony for Amylin Pharmaceuticals and Eli Lilly and Company. C.S. Fuchs is now an employee of Genentech and Roche. No disclosures were reported by the other authors.

Authors' Contributions

S. Kwon: Conceptualization, data curation, formal analysis, validation, visualization, methodology, writing–original draft, writing–review and editing. **W. Ma:** Methodology, writing–review and editing. **D.A. Drew:** Resources, project administration. **S.J. Klempner:** Writing–review and editing. **B.M. Leonardo:** Data curation. **J.J. Flynn:** Data curation. **Y. Cao:** Writing–review and editing. **E.L. Giovannucci:** Writing–review and editing. **Y. Bao:** Writing–review and editing. **C.S. Fuchs:** Writing–review and editing. **M. Song:** Writing–review and editing. **A.T. Chan:** Conceptualization, resources, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, project administration, writing–review and editing.

Acknowledgments

We thank the participants and staff of the NHS and the HPFS for their valuable contributions as well as the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, Wyoming. The authors assume full responsibility for analyses and interpretation of these data. This work was supported by a Stand Up to Cancer Gastric Cancer Interception Research Team Grant (grant no. SU2C-AACR-DT-30-20). Stand Up To Cancer is a division of the Entertainment Industry Foundation. Research grants are administered by the American Association for Cancer Research, the Scientific Partner of SU2C. The NHS and HPFS were supported by grants UM1 CA186107, P01 CA87969, and U01 CA167552. A.T. Chan was supported by NIH R35 CA253185 and the abovementioned Stand Up to Cancer Gastric Cancer Interception Grant. Y. Cao was supported by NIH K07 CA218377.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 28, 2021; revised November 18, 2021; accepted December 29, 2021; published first January 3, 2022.

Reference

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. The Lancet. 2016;388:2654–64.
3. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019.
4. Lim HY, Joo HJ, Choi JH, Yi JW, Yang MS, Cho DY, et al. Increased expression of cyclooxygenase-2 protein in human gastric carcinoma. Clin Cancer Res 2000;6:519–25.
5. Cheng J, Fan X-M. Role of cyclooxygenase-2 in gastric cancer development and progression. World J Gastroenterol 2013;19:7361–8.
6. Zhang L-J, Wang S-Y, Huo X-H, Zhu Z-L, Chu J-K, Ma J-C, et al. Anti-Helicobacter pylori therapy followed by celecoxib on progression of gastric precancerous lesions. World J Gastroenterol 2009;15:2731–8.
7. Pero R, Peluso S, Angrisano T, Tuccillo C, Sacchetti S, Keller S, et al. Chromatin and DNA methylation dynamics of Helicobacter pylori-induced COX-2 activation. Int J Med Microbiol 2011;301:140–9.
8. Targosz A, Brzozowski T, Pierzchalski P, Szczyrk U, Ptak-Belowska A, Konturek SJ, et al. Helicobacter pylori promotes apoptosis, activates cyclooxygenase (COX)-2 and inhibits heat shock protein HSP70 in gastric cancer epithelial cells. Inflamm Res 2012;61:955–66.
9. Asaka M. Helicobacter pylori infection and gastric cancer. Intern Med 2002;41:1–6.
10. Drew DA, Cao Y, Chan AT. Aspirin and colorectal cancer: the promise of precision chemoprevention. Nat Rev Cancer 2016;16:173–86.
11. Huang X, Chen Y, Wu J, Zhang X, Wu C, Zhang C, et al. Aspirin and non-steroidal anti-inflammatory drugs use reduce gastric cancer risk: a dose-response meta-analysis. Oncotarget 2017;8;4781–95.
12. Niikura R, Hirata Y, Hayakawa Y, Kawahara T, Yamada A, Koike K. Effect of aspirin use on gastric cancer incidence and survival: a systematic review and meta-analysis. JGH Open 2020;4:117–25.
13. Win TT, Aye SN, Lau Chui Fern J, Ong Fei C. Aspirin and reducing risk of gastric cancer: systematic review and meta-analysis of the observational studies. J Gastrointest Liver Dis 2020;29:191–8.
14. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol 1986;123:894–900.
15. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.

16. Rimm EB, Stampfer MJ, Colditz GA, Giovannucci E, Willett WC. Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. Am J Epidemiol 1990;131:1068–71.
17. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology 2008;134:21–8.
18. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007; 356:2131–42.
19. Chan AT, Manson JE, Feskanich D, Stampfer MJ, Colditz GA, Fuchs CS. Long-term aspirin use and mortality in women. Arch Intern Med 2007;167:562–72.
20. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. Arch Intern Med 2004;164:1519–24.
21. Laheij RJF, Straatman H, Jansen JBMJ, Verbeek ALM. Evaluation of commercially availablehelicobacter pylori serology kits: a review. J Clin Microbiol 1998;36:2803–9.
22. Michel A, Waterboer T, Kist M, Pawlita M. Helicobacter pylori multiplex serology. Helicobacter 2009;14:525–35.
23. Epplein M, Pawlita M, Michel A, Peek RM, Cai Q, Blot WJ. Helicobacter pylori protein–specific antibodies and risk of colorectal cancer. Cancer Epidemiol Prev Biomark 2013;22:1964–74.
24. Kim Y-I, Kim SY, Kim JH, Lee JH, Kim Y-W, Ryu KW, et al. Long-term low-dose aspirin use reduces gastric cancer incidence: a Nationwide Cohort Study. Cancer Res Treat 2016;48:798–805.
25. Wang Y, Shen C, Ge J, Duan H. Regular aspirin use and stomach cancer risk in China. Eur J Surg Oncol 2015;41:801–4.
26. Jacobs EJ, Newton CC, Gapstur SM, Thun MJ. Daily aspirin use and cancer mortality in a large US cohort. J Natl Cancer Inst 2012;104: 1208–17.
27. Wu C-Y, Wu M-S, Kuo KN, Wang C-B, Chen Y-J, Lin J-T. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in helicobacter pylori–infected patients. J Clin Oncol 2010;28:2952–7.
28. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Stolley PD, et al. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. Cancer Epidemiol Prev Biomark 2000;9:119–23.
29. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CW. Aspirin use and risk of fatal cancer. Cancer Res 1993;53:1322–7.
30. Lee J, Lee SH, Hur KY, Woo SY, Kim SW, Kang WK. Statins and the risk of gastric cancer in diabetes patients. BMC Cancer 2012;12:596.
31. Figueroa JD, Terry MB, Gammon MD, Vaughan TL, Risch HA, Zhang F-F, et al. Cigarette smoking, body mass index, gastro-esophageal reflux disease, and non-steroidal anti-inflammatory drug use and risk of subtypes of esophageal and gastric cancers by P53 overexpression. Cancer Causes Control 2009;20:361–8.
32. Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br J Cancer 2009;100:551–7.
33. Duan L, Wu AH, Sullivan-Halley J, Bernstein L. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric adenocarcinomas in Los Angeles county. Cancer Epidemiol Prev Biomark 2008; 17:126–34.
34. Fortuny J, Johnson CC, Bohlke K, Chow W, Hart G, Kucera G, et al. Use of anti-inflammatory drugs and lower esophageal sphincter–relaxing drugs and risk of esophageal and gastric cancers. Clin Gastroenterol Hepatol 2007;5:1154–9.
35. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: Results of a case-control study from Moscow, Russia. Int J Cancer 1999;82:473–6.
36. Cheung KS, Chan EW, Wong AYS, Chen L, Seto WK, Wong ICK, et al. Aspirin and risk of gastric cancer after helicobacter pylori eradication: a territory-wide study. J Natl Cancer Inst 2018;110:743–9.
37. Epplein M, Nomura AMY, Wilkens LR, Henderson BE, Kolonel LN. Nonsteroidal antiinflammatory drugs and risk of gastric adenocarcinoma. Am J Epidemiol 2009;170:507–14.
38. Farrow DC, Vaughan TL, Hansten PD, Stanford JL, Risch HA, Gammon MD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Prev Biomark 1998;7:97–102.
39. Liu Y, Sun H, Hu M, Zhang Y, Chen S, Tighe S, et al. The role of cyclooxygenase-2 in colorectal carcinogenesis. Clin Colorectal Cancer 2017;16:165–72.
40. Yip-Schneider MT, Barnard DS, Billings SD, Cheng L, Heilman DK, Lin A, et al. Cyclooxygenase-2 expression in human pancreatic adenocarcinomas. Carcinogenesis 2000;21:139–46.
41. Hussain T, Gupta S, Mukhtar H. Cyclooxygenase-2 and prostate carcinogenesis. Cancer Lett 2003;191:125–35.
42. Fu S-L, Wu Y-L, Zhang Y-P, Qiao M-M, Chen Y. Anti-cancer effects of COX-2 inhibitors and their correlation with angiogenesis and invasion in gastric cancer. World J Gastroenterol 2004;10:1971–4.
43. Tatsuguchi A, Matsui K, Shinji Y, Gudis K, Tsukui T, Kishida T, et al. Cyclooxygenase-2 expression correlates with angiogenesis and apoptosis in gastric cancer tissue. Hum Pathol 2004;35:488–95.
44. Uefuji K, Ichikura T, Mochizuki H. Cyclooxygenase-2 expression is related to prostaglandin biosynthesis and angiogenesis in human gastric cancer. Clin Cancer Res 2000;6:135–8.
45. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127–31.
46. The EUROGAST Study Group. An international association between Helicobacter pylori infection and gastric cancer. Lancet 1993;341: 1359–62.
47. Lynch DA, Axon AT. Helicobacter pylori, gastric cancer and gastric epithelial kinetics: a review. Eur J Gastroenterol Hepatol 1995;7: S17–23.
48. Loor A, Dumitraşcu DL. Helicobacter pylori infection, gastric cancer and gastropanel. Rom J Intern Med 2016;54:151–6.
49. Li Q, Liu N, Shen B, Zhou L, Wang Y, Wang Y, et al. Helicobacter pylori enhances cyclooxygenase 2 expression via p38MAPK/ ATF-2 signaling pathway in MKN45 cells. Cancer Lett 2009; 278:97–103.
50. Subramaniam D, Ramalingam S, May R, Dieckgraefe BK, Berg DE, Pothoulakis C, et al. Gastrin-mediated interleukin-8 and cyclooxygenase-2 gene expression: differential transcriptional and posttranscriptional mechanisms. Gastroenterology 2008;134:1070–82.
51. Wang WH, Wong WM, Dailidiene D, Berg DE, Gu Q, Lai KC, et al. Aspirin inhibits the growth of Helicobacter pylori and enhances its susceptibility to antimicrobial agents. Gut 2003;52:490–5.
52. Luepker RV, Steffen LM, Duval S, Zantek ND, Zhou X, Hirsch AT. Population trends in aspirin use for cardiovascular disease prevention 1980–2009: The minnesota heart survey. J Am Heart Assoc 2015;4: e002320.