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ORIGINAL ARTICLE

Aspirin but not statins is inversely related to gastric cancer with a duration–risk effect: Results from the Stomach Cancer Pooling Project Consortium

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Abstract

Background: Aspirin and statins have been suggested to have potential chemopreventive effects against gastric cancer (GC), although the results of previous studies have been inconsistent. This study therefore aimed to investigate the association between the use of aspirin and statins and GC.

Methods: A pooled analysis of seven case-control studies within the Stomach Cancer Pooling Project, including 3220 cases and 9752 controls, was conducted. Two-stage modeling analyses were used to estimate the association between aspirin and statin use and GC after adjusting for potential confounders.

Results: The pooled odds ratio (OR) of GC for aspirin users versus nonusers was 0.72 (95% confidence interval [CI], 0.54–0.95). The protective effect of aspirin appeared stronger in individuals without a GC family history (OR, 0.60; 95% CI, 0.37–0.95), albeit with borderline heterogeneity between those with and without a family history ($p = .064$). The OR of GC decreased with increasing duration of aspirin use, with an OR of 0.41 (95% CI, 0.18–0.95) for durations of ≥15 years. An inverse, nonsignificant association with the risk of GC was observed for the use of statins alone (OR, 0.79; 95% CI, 0.52–1.18).

Conclusions: These findings suggest that aspirin use, particularly long-term use, is associated with a reduced risk of GC, whereas a similar association was not observed with statins, possibly because of the low frequency of use.

KEYWORDS
aspirin, epidemiological study, gastric cancer, statins

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide and the fourth leading cause of cancer deaths, despite long-term trends of decreasing incidence and mortality.[1,2] Gastric carcinogenesis involves *Helicobacter pylori* infection as well as other risk cofactors, including tobacco smoking, dietary factors, alcohol consumption, and genetic predisposition.[3,4]

There is some evidence on GC that suggests a protective effect of commonly prescribed cardiovascular drugs, such as aspirin and statins.[5,6] Aspirin, via prostaglandin-dependent and -independent pathways, inhibits the production of cyclooxygenases 1 and 2 (COX-1 and COX-2),[7] which have been implicated in the development of several neoplasias. Although aspirin's chemopreventive role has been recognized for many types of cancer,[8,9] evidence of its role in GC prevention remains inconsistent. Previous studies have reported an inverse association between aspirin use and GC risk.[10–12] However, the optimal dosage and duration of aspirin use, as well as its association with GC risk in specific subgroups, remain unclear, particularly in non-Asian populations.[13]

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, an enzyme involved in cholesterol synthesis. Besides their lipid-lowering effect, statins have shown potential chemopreventive effects on various neoplasms, which are mediated by arresting cell-cycle progression, inducing apoptosis, inhibiting angiogenesis, and immunomodulation.[14] A meta-analysis of statin use, including 11 studies (seven case-control, one cohort, and three post hoc analyses of 26 clinical trials), reported a significant 16% reduction in GC risk in Asian and Western populations.[15] However, a recent large cohort study confirmed a beneficial effect of statins only on GC mortality.[16]

Statins and aspirin are often coprescribed, especially for the prevention of cardiovascular diseases,[17] but there are few studies examining the potential combined effect of the two drugs on the risk of GC.[16] The aim of our study was to evaluate the association between the use of aspirin and statins and GC risk by conducting a pooled analysis within the Stomach Cancer Pooling (StoP) Project.[18]

MATERIALS AND METHODS

Study population

The StoP Project is an epidemiological consortium, initiated in 2012, that aims to examine the role of lifestyle and genetic factors in the etiology of GC via pooled analyses of individual-level data from previously conducted observational studies after central collection, validation, and harmonization of the original data. Detailed information on the consortium has been provided elsewhere.[18]

This analysis is based on the third release (version 3.1) of the StoP Project data set, which included 33 case-control studies, or case-control analyses nested within cohort studies, for a total of 12,753 GC cases and 30,682 controls. GC cases were incidents histologically confirmed at the time of diagnosis, whereas controls were population- or hospital-based individuals without cancer or nested in cohorts. Hospital-based controls were cancer-free individuals admitted to the hospital in the same time period as cases, whereas population-based controls were cancer-free individuals randomly selected by geographic location. Questionnaires used for data collection and any further information useful for data handling (e.g., codebooks and labels) were also obtained from the participating studies. All data sets were harmonized at the coordinating center (University of Milan) according to a prespecified format. The University of Milan Institutional Review Board provided ethical approval for the StoP Project (reference 19/15, April 1, 2015). This study was performed in line with the principles of the Declaration of Helsinki. Each study contributing data to the present analysis was approved by the local ethical committee, and written informed consent was obtained from all study participants.

For the current analysis, a total of 12,972 subjects (3220 cases; 9752 controls) enrolled in seven study centers from six countries (Italy [Italy 1, Milan[19]; Italy 2, Rome[20]], Russia,[21] Portugal,[22] Spain,[23] Mexico,[24] and the United States[25]) were included, on the basis of the availability of data on aspirin or statin medications (Table S1). A total of 11,531 subjects (2861 cases; 8670 controls) were included in the aspirin analysis, whereas 9345 (1788 cases; 7557 controls) were included in the statin analysis. The analysis of the combined use of aspirin and statins was performed on 7904 subjects (1429 cases; 6475 controls) (Figure S1; Table S2).

Exposure definition

In all studies, the use of aspirin/statins was assessed via structured questionnaires that asked participants to report their consumption before diagnosis (for cases), hospital admission (for controls in hospital-based case-control studies), or recruitment (for controls in population-based case-control studies). Study participants were defined as "users" (exposed) if they reported regular use (at least

once a week) of aspirin or statins in the last year (the studies from Russia, Mexico, and the United States) or if they reported aspirin or statin intake for a duration of at least 6 months (the studies from Italy 1, Italy 2, and Spain), or at least 12 months (the study from Portugal).

Statistical analysis

We used two two-stage modeling analyses to estimate the association between aspirin and statin use and GC. In the first stage, for each study, we estimated the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of GC comparing users to nonusers via multivariable logistic regression models. The models were adjusted for age at diagnosis/interview (continuous), sex, body mass index (BMI) categories, smoking status, alcohol intake, and socioeconomic status. These adjustment variables were selected on the basis of their significance in univariate analysis ($p < .15$) and a missing data percentage of less than 10%.

In the second stage, the summary (pooled) ORs and corresponding 95% CIs were estimated with a random-effects model.[26] Heterogeneity between studies was assessed with the I^2 statistic and χ^2 p value.[27]

Moreover, we used a two-stage modeling analysis to estimate the association between the combined use of the two drugs and GC.

Stratified analyses were conducted to evaluate whether the effect of each drug on GC varied across subgroups, defined by age at diagnosis/interview (<65 and ≥65 years), sex (male and female), socioeconomic status (low, intermediate, and high), smoking status (never, former, and current), alcohol intake (never, low [≤12 g/day], intermediate [>12 and ≤47 g/day], and high consumption [>47 g/day]), *H. pylori* infection (no and yes as defined by immunoglobulin serum antibody titers [the studies from Russia, Portugal, and Mexico] or multiplex serology [the study from Spain]), family history of GC (in first-degree relatives, yes and no), GC anatomical site (cardia and noncardia), histological type (intestinal, diffuse, and undifferentiated), metformin intake (users and nonusers),[28] proton-pump inhibitors (users and nonusers),[29] and type of control (hospital and population).

For each stratifying variable, the Q statistic was computed to test the heterogeneity across strata.[30] The interaction between administration of the drug and the above reported potential effect modifiers was tested via a meta-regression model.

Missing data were handled by applying multiple imputation procedures. We applied multiple imputations (10 imputations) with the mi impute syntax in Stata statistical software[31] for smoking status, alcohol intake, and socioeconomic status that were missing for <10% of the total subjects (2.3%, 8.3%, and 4.0%, respectively). We assumed that these data were missing at random. We used the logistic regression model to predict the association of smoking status, alcohol intake, and socioeconomic status with age at diagnosis/interview (continuous), sex, and the presence/absence of GC within each study center separately.

A sensitivity analysis was conducted on the summary (pooled) ORs for GC comparing users to nonusers of aspirin/statins. This analysis used the one-stage approach with a generalized linear mixed model (GLMM) that featured random intercept and slope effects, which were estimated by restricted maximum likelihood with Laplace approximation. The 95% CI was determined with the Wald method.

Furthermore, we investigated the dose–response relationship between the duration of aspirin and statin intake and GC via a one-stage logistic model. The analysis encompassed two studies providing information on aspirin intake[19,23] and three studies on statin intake.[20,23,25] To assess linearity, the variable for the duration of intake was included as a continuous variable in the model. Nonlinearity was evaluated via first- and second-order fractional polynomials. The analysis was adjusted for age at diagnosis/interview, sex, socioeconomic status, smoking status, and alcohol intake. The model that minimized the deviance difference compared to the linear model was selected as the best fitting model.[32] Furthermore, a secondary analysis was conducted that focused specifically on whether the therapy had been administered for at least 12 months.

All statistical analyses were performed with Stata software, version 16 (StataCorp, College Station, Texas) and R, version 4.2.0 (2022-04-22) for Windows.

RESULTS

Table 1 presents the main characteristics of the 3220 GC cases and 9752 controls included in the analysis for the overall study population; detailed information for each study is reported in Table S3. The proportion of cases regularly taking aspirin, statins, or both drugs was 30.6%, 25.9%, and 14.5%, respectively, whereas for controls these percentages were 28.6%, 28.3%, and 13.6%. Compared to controls, cases had higher proportions of individuals with low socioeconomic status (37.2% vs. 33.8%), a history of peptic ulcer (19.5% vs. 8.4%), and high alcohol consumption (19.1% vs. 10.9%).

Figure 1 shows the study-specific and pooled adjusted OR of GC and corresponding 95% CIs for aspirin and statin users compared with nonusers. The pooled OR of GC for aspirin users versus nonusers was 0.72 (95% CI, 0.54–0.95), with substantial between-study heterogeneity (I^2 = 73.6%; p = .002). These findings remained consistent when using a one-stage GLMM (aspirin users vs. nonusers: OR, 0.65; 95% CI, 0.45–0.94). The Galbraith plot (Figure S2) identified the study conducted in Portugal[22] as a potential source of heterogeneity. However, although after removing the Portugal study the between-study heterogeneity decreased (I^2 = 0.0%; p = .69), the association remained (OR, 0.83; 95% CI, 0.73–0.96). The pattern of findings was similar for the analysis without imputed data (data not shown).

The results from the stratified analysis of aspirin use are presented in Table 2. The stratified analysis showed a similar effect of aspirin use among strata of age group, sex, GC anatomical and histological sites, *H. pylori* infection status, socioeconomic status, smoking status, alcohol intake, statin use, and type of control. A reduced odds of GC for aspirin

TABLE 1 Distribution of Stomach Cancer Pooling Project Consortium gastric cancer cases and controls included in the analysis by selected characteristics.

	Cases N = 3220	Controls N = 9752	p
Aspirin, No. (%)	N = 2861	N = 8670	.045
User	875 (30.6)	2481 (28.6)	
Nonuser	1986 (69.4)	6189 (71.4)	
Missing	359 (11.2)	1082 (11.1)	
Statins, No. (%)	N = 1788	N = 7557	.044
User	464 (25.9)	2141 (28.3)	
Nonuser	1324 (74.1)	5416 (71.7)	
Missing	1432 (44.5)	2195 (22.5)	
Both aspirin and statins, No. (%)	N = 1429	N = 6475	.41
User	207 (14.5)	884 (13.6)	
Nonuser	1222 (85.5)	5591 (86.4)	
Missing	1791 (55.6)	3277 (33.6)	
Age at diagnosis/interview, median (IQR), years	68 (59–74)	66 (56–73)	<.0001
Age group, No. (%), years			<.0001
<65	1188 (36.9)	4375 (44.9)	
≥65	2032 (63.1)	5377 (55.1)	
<40	93 (2.9)	394 (4.0)	
40–44	100 (3.1)	466 (4.8)	
45–49	146 (4.5)	602 (6.2)	
50–54	190 (5.9)	696 (7.1)	
55–59	301 (9.4)	917 (9.4)	
60–64	358 (11.1)	1300 (13.3)	
65–69	631 (19.6)	1760 (18.1)	
70–74	680 (21.1)	1804 (18.5)	
≥75	721 (22.4)	1813 (18.6)	
Sex, No. (%)			<.0001
Male	2099 (65.2)	5756 (59.0)	
Female	1121 (34.8)	3996 (41.0)	
Ethnic group, No. (%)			<.0001
White	2034 (94.4)	6910 (97.1)	
Black/African American	55 (2.6)	69 (1.0)	
Asian	21 (1.0)	39 (0.6)	
Hispanic/Latino	42 (1.9)	88 (1.2)	
Other	2 (0.1)	8 (0.1)	
Missing	1066 (33.1)	2638 (27.1)	
BMI category, No. (%), kg/m^2			.025
Underweight, <18.5	44 (1.6)	102 (1.2)	
Normal, 18.5–24.9	996 (36.9)	2951 (35.1)	
Overweight, 25–29.9	1091 (40.4)	3649 (43.3)	

TABLE 1 (Continued)

	Cases N = 3220	Controls N = 9752	p
Obese, ≥30	570 (21.1)	1715 (20.4)	
Missing	519 (16.1)	1335 (13.7)	
GC anatomical site, No. (%)			—
Cardia	743 (25.3)		
Noncardia	1605 (54.6)		
Unspecified	593 (20.1)		
Missing	279 (8.7)		
GC histological type, No. (%)			—
Intestinal	772 (27.9)		
Diffuse	608 (22.0)		
Undifferentiated	1387 (50.1)		
Missing	453 (14.1)		
Helicobacter pylori infection status, No. (%)			<.0001
Negative	364 (25.6)	732 (16.7)	
Positive	1058 (74.4)	3655 (83.3)	
Missing	1798 (55.8)	5365 (55.0)	
GC family history, No. (%)			<.0001
No	1487 (82.7)	5182 (92.9)	
Yes	311 (17.3)	399 (7.1)	
Missing	1422 (44.2)	4171 (42.8)	
History of peptic ulcer, No. (%)			<.0001
No	1189 (80.5)	5010 (91.6)	
Yes, at least 1 year	288 (19.5)	460 (8.4)	
Missing	1743 (54.1)	4282 (43.9)	
Socioeconomic status, No. (%)			<.0001
Low	1147 (37.2)	3172 (33.8)	
Intermediate	1317 (42.7)	3577 (38.2)	
High	621 (20.1)	2626 (28.0)	
Missing	135 (4.2)	377 (3.9)	
Smoking status, No. (%)			.10
Never	1361 (43.6)	4370 (45.8)	
Former	1180 (37.8)	3452 (36.1)	
Current	583 (18.6)	1726 (18.1)	
Missing	96 (3.0)	204 (2.1)	
Alcohol intake, No. (%), g/day			<.0001
Never, 0	723 (23.9)	2057 (23.2)	
Low, ≤12	951 (31.4)	3598 (40.5)	
Intermediate, >12 and ≤47	774 (25.6)	2255 (25.4)	
High, >47	579 (19.1)	964 (10.9)	

(Continues)

TABLE 1 (Continued)

	Cases N = 3220	Controls N = 9752	p
Missing	193 (6.0)	878 (9.0)	
Type of control, No. (%)			—
Hospital	—	2057 (21.1)	
Population	—	7695 (78.9)	

Abbreviations: BMI, body mass index; GC, gastric cancer; IQR, interquartile range.

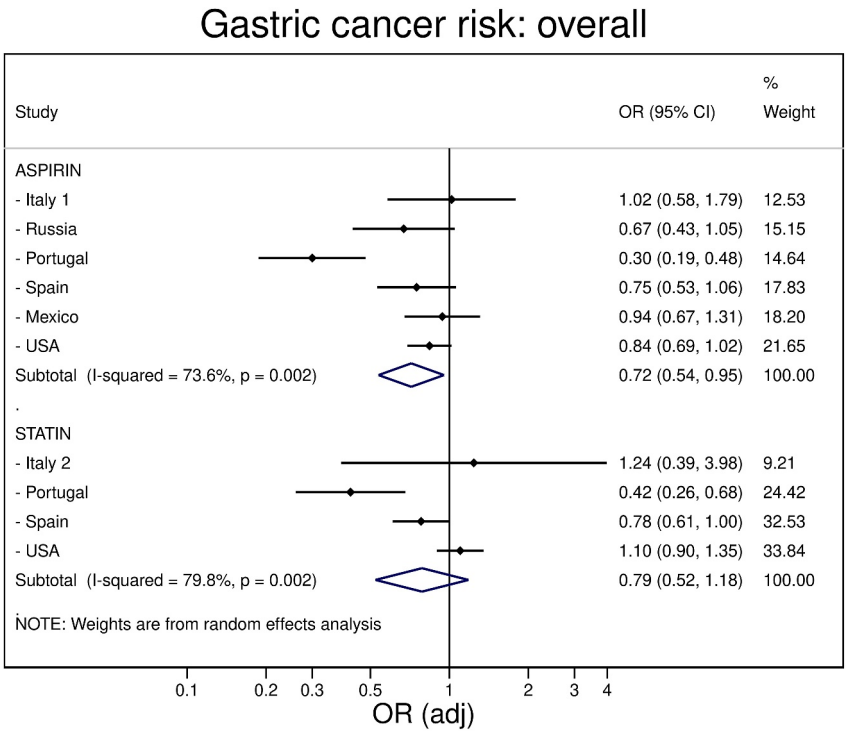


FIGURE 1 Study-specific and adjusted pooled ORs and corresponding 95% CIs of gastric cancer risk for aspirin and statin users compared with nonusers. ORs were adjusted for age at diagnosis/interview (continuous), sex, socioeconomic status, smoking status, alcohol intake, and body mass index category. CI indicates confidence interval; OR, odds ratio.

users was observed for individuals without a GC family history (OR, 0.60; 95% CI, 0.37–0.95; $Q = 3.44$; $p = .064$).

In the overall analysis, the use of statins was inversely, but nonsignificantly, associated with the risk of GC (OR, 0.79; 95% CI, 0.52–1.18; $I^2 = 79.8\%$; $p = .002$) (Figure 1), with the result being consistent across all strata considered (Table S4). These findings remained consistent when using a one-stage GLMM (statin users vs. nonusers; OR, 0.61; 95% CI, 0.32–1.17).

Finally, in the only three studies with information on the combined use of aspirin and statins, there was no significant association between the two drugs and GC in the overall analysis (OR, 0.84; 95% CI, 0.51–1.39) and in the stratified analysis (Figure S3; Table S5).

The duration–risk relationships between aspirin and statin use and GC are depicted in Figure 2 and Figure S4, respectively. The result of the duration–response analysis shows that the risk of GC decreases with increasing duration of aspirin use from a near-null effect with short duration (e.g., 1 year: OR, 1.02; 95% CI, 0.94–1.12; 7 years: OR, 1.02; 95% CI, 0.65–1.62) to an OR of 0.41 (95% CI, 0.18–0.95) for a use of ≥15 years. Further analysis, which considered only aspirin therapy durations of at least 12 months, yielded similar results (data not shown). The relationship with statins, on the other hand, did not vary over different lengths of intake.

DISCUSSION

Our pooled analysis of seven case-control studies from the international StoP Consortium, which involved a total of 3220 cases and 9752 controls, identified that aspirin use decreases the risk of GC, whereas a similar association was not observed with statins.

Two-stage modeling analyses were used to estimate the association between aspirin and statin use and GC after adjusting for

TABLE 2 Pooled adjusted[a] odds ratios with 95% confidence intervals for gastric cancer associated with aspirin in the Stomach Cancer Pooling Project overall and stratified by participants' characteristics.

	Cases, exposed/ unexposed[b]	Controls, exposed/ unexposed[b]	Study, No.	Adjusted OR (95% CI)	I^2, %	Heterogeneity χ^2, p
Overall	875/1986	2481/6189	6	0.72 (0.54–0.95)	73.6	.002
Age at diagnosis/interview, years						
≥65	697/1066	1819/2830	6	0.77 (0.59–1.00)	49.2	.080
<65	178/920	662/3359	6	0.62 (0.40–0.97)	62.7	.020
Sex						
Male	656/1218	1802/3195	6	0.71 (0.55–0.92)	49.0	.081
Female	219/768	679/2994	6	0.81 (0.53–1.23)	64.7	.015
GC anatomical site						
Cardia	315/345	2481/6189	5/5	0.76 (0.45–1.29)	58.0	.049
Noncardia	318/1120	2481/6189	5/5	0.75 (0.50–1.13)	74.8	.003
GC histological type						
Intestinal	116/579	2481/6189	6	0.76 (0.59–0.98)	0.0	.48
Diffuse	90/464	2481/6189	6	0.75 (0.49–1.15)	39.6	.14
Undifferentiated	634/582	2481/6189	4/6	0.79 (0.55–1.14)	39.7	.17
Helicobacter pylori infection status						
Positive	132/819	618/3037	4/4	0.67 (0.36–1.23)	82.1	.001
Negative	40/269	113/619	3/4	0.99 (0.60–1.62)	0.0	.41
GC family history[c]						
Yes	32/263	50/333	4/4	1.39 (0.65–2.97)	25.3	.26
No	108/1224	643/4144	4/4	0.60 (0.37–0.95)	71.0	.016
History of peptic ulcer						
Yes	56/228	81/377	4/4	0.93 (0.57–1.51)	0.0	.55
No	138/896	713/3866	4/4	0.75 (0.60–0.95)	0.0	.42
Socioeconomic status						
Low	147/910	570/2512	5/6	0.73 (0.46–1.15)	65.4	.021
Intermediate	417/788	1054/2154	6	0.81 (0.63–1.04)	22.7	.26
High	282/269	817/1492	6	0.75 (0.50–1.12)	25.4	.24
Smoking status						
Never	277/940	928/2984	6	0.79 (0.59–1.07)	48.0	.087
Former	457/582	1189/1803	6	0.69 (0.48–0.98)	48.6	.083
Current	107/419	296/1293	6	0.78 (0.47–1.31)	42.7	.12
Alcohol intake						
Never	217/418	487/1229	6	0.65 (0.40–1.04)	51.9	.065
Low	364/439	1080/2086	5/6	0.82 (0.60–1.13)	41.3	.15
Intermediate	173/528	530/1482	6	0.73 (0.47–1.11)	43.9	.11
High	104/440	204/701	4/6	0.89 (0.42–1.88)	70.4	.018
Statins						
Users	207/143	884/869	3/3	0.98 (0.72–1.33)	1.0	.36

(Continues)

TABLE 2 (Continued)

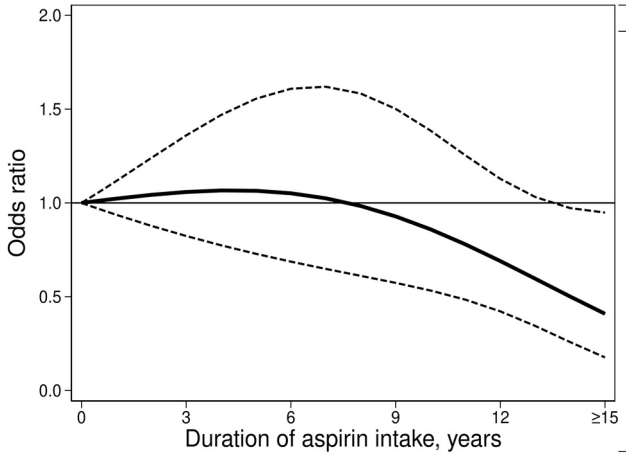
	Cases, exposed/ unexposed[b]	Controls, exposed/ unexposed[b]	Study, No.	Adjusted OR (95% CI)	I^2, %	Heterogeneity χ^2, p
Nonusers	163/916	853/3869	3/3	0.78 (0.41–1.46)	90.1	<.0001
Metformin						
Users	12/48	101/206	2/2	0.71 (0.33–1.55)	0.0	.39
Nonusers	61/903	563/4132	2/2	0.50 (0.17–1.44)	91.4	.001
PPIs						
Users	27/177	194/915	2/2	0.65 (0.41–1.04)	0.0	.35
Nonusers	46/794	492/3506	2/2	0.47 (0.18–1.19)	86.9	.006
Type of control						
Hospital	158/746	319/1297	3/4	0.87 (0.68–1.10)	0.0	.40
Population	717/1240	2162/4892	3/3	0.60 (0.35–1.01)	87.3	<.0001

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; PPI, proton-pump inhibitor.

[a]ORs were adjusted for age at diagnosis/interview (continuous), sex (male and female), socioeconomic status (low, intermediate, and high), smoking status (never, former, and current), alcohol intake (never, low, intermediate, and high), and body mass index category (underweight, normal weight, overweight, and obese).

[b]Exposed indicates aspirin user; unexposed indicates aspirin nonuser.

[c]Q statistic to test the heterogeneity across strata: 3.44; $p = .064$.



Duration of intake	OR (95% CI)
6 months	1.01 (0.97-1.06)
1 year	1.02 (0.94-1.12)
2 years	1.04 (0.88-1.24)
3 years	1.06 (0.82-1.36)
4 years	1.07 (0.77-1.47)
5 years	1.06 (0.73-1.56)
6 years	1.05 (0.69-1.61)
7 years	1.02 (0.65-1.62)
8 years	0.98 (0.61-1.58)
9 years	0.93 (0.57-1.50)
10 years	0.86 (0.53-1.39)
11 years	0.78 (0.48-1.25)
12 years	0.69 (0.42-1.13)
13 years	0.60 (0.34-1.03)
14 years	0.50 (0.26-0.97)
≥15 years	0.41 (0.18-0.95)

FIGURE 2 Results of the dose–response analysis of the duration of aspirin intake and gastric cancer fitted by using a one-stage logistic mixed-effects model with fractional polynomials (adjusted for age at diagnosis/interview [continuous], sex, socioeconomic status, smoking status, alcohol intake, and body mass index category). The analysis was based on 4194 subjects (637 cases; 3557 controls) from studies Italy 1 and Spain. Bold line represents the odds ratio (OR); dashed lines: upper and lower limits of the 95% confidence interval (CI).

potential confounders such as age at diagnosis/interview, sex, BMI category, smoking status, alcohol intake, and socioeconomic status.

Aspirin use was associated with a reduction in the odds of GC, with a duration–risk relationship. Our results are biologically plausible and support the previous findings of observational studies and meta-analyses that have suggested a protective effect of aspirin against GC.[8,11,13,33–35]

COX-2 is excessively produced in metaplastic and adenomatous cells, as well as in cancer cells in gastric adenocarcinoma. This suggests that prostaglandin synthesis might play a crucial part in the development of GC.[13] Additionally, *H. pylori* infection, which is known to cause GC, has been linked to COX-2 expression. *H. pylori* infection can lead to inflammation, cell proliferation, and reduced apoptosis. Therefore, aspirin can be suggested as a possible chemopreventive agent for GC because it inhibits prostaglandin synthesis.[13,36,37]

Aspirin has a similar effect among strata of age group, sex, GC anatomical and histological sites, *H. pylori* infection status, socioeconomic status, smoking status, alcohol intake, and history of peptic ulcer and among users of statins, metformin, and proton-pump inhibitors, whereas the protective effect against GC appears greater in

individuals without a family history of GC. However, our analysis did not reveal any interactions between this factor and the effect of aspirin.

Because aspirin may cause gastrointestinal bleeding, it is possible that at least part of the inverse association observed is a result of the avoidance of aspirin use in patients with early symptoms of GC. However, we conducted a duration–risk analysis to assess the relationship between the duration of aspirin use and GC. The analysis showed that the OR of GC decreased with increasing duration of aspirin use, with a protective effect observed for durations of ≥15 years. These findings are consistent with a previous analysis by Kwon et al.,[13] which reported an apparent benefit of aspirin after at least 10 years of use.

We did not find any association between the use of statins and GC risk, nor did we find any association between the combined use of statins and aspirin and GC risk, despite the limited number of studies providing information on the combined use of aspirin and statins. The lack of association between statin use and GC is consistent with some but not all previous research.[16,38,39] Some studies have suggested that statins may have anticancer properties by inducing apoptosis, inhibiting tumor growth, and reducing inflammation.[40]

However, a recent meta-analysis suggested that the association between statin use and GC varied among study designs, and no association was observed in randomized clinical trials.[38] In addition, a stronger protective effect was observed in Asian populations compared to Western individuals.[38] Moreover, the incidence of GC is influenced by the type of statins used. In fact, the risk of GC was reduced in those exposed to lipophilic statins, yet not in those exposed to hydrophilic statins.[41]

Our study has several strengths, including the large sample size, the pooling of data from multiple studies, and the availability of data on different medications for cardiovascular prevention, diabetes, and gastrointestinal condition management. Furthermore, the inverse association between aspirin and GC observed in the present study was similar in case-control studies and in the large cohort study from the United States (included in the analysis via a nested case-control approach). However, there are some limitations. First, our analysis was based mostly on retrospective studies, which relied on self-reported data on drug use, which may be subject to recall bias. Potential recall bias in case-control studies due to possible more careful reporting of aspirin use in cases than controls should bias risk estimates toward the null. Although cohort studies are less susceptible to recall bias than case-control studies, they usually collect data at baseline and lack information on exposure changes over time, and thus may cause possible misclassification of aspirin exposure and its duration. In addition, record-linkage cohort studies do not cover over-the-counter drug use, which may represent a considerable proportion of aspirin use.

Second, the use of hospital controls may have introduced selection bias in each study because of the possibility that some controls suffered from conditions that made them either more likely or less likely to use aspirin or statins.

Third, we did not have information on dosages, adherence to drug use, and type of statin (lipophilic/hydrophilic statins), which may affect the association with GC risk. For many of the pooled estimates, there is a between-study heterogeneity, which does not seem to be explained by the covariates considered. Different study populations, baseline cancer risks, and drug doses and variability in the duration of aspirin/statin intake may be responsible for such heterogeneity. Additionally, duodenal and gastric ulcers could not be evaluated separately because of over 90% missing data.

In conclusion, our study provides evidence that long-term aspirin use is associated with a reduced risk of GC, whereas statin use was not significantly associated with GC risk in the populations studied, possibly because of the low frequency of use, which resulted in limited statistical power. These findings may have implications for the use of aspirin as a chemopreventive agent against GC in high-risk populations, but further research with a trial design is needed to confirm and extend these findings and to identify the optimal doses and durations of aspirin use for cancer prevention.

AUTHOR CONTRIBUTIONS

Roberta Pastorino: Conceptualization, data curation, formal analysis, writing–original draft, and writing–review and editing. **Denise Pires Marafon**: Formal analysis and writing–review and editing. **Michele Sassano**: Conceptualization, formal analysis, and writing–review and editing. **Ilda Hoxhaj**: Formal analysis and writing–review and editing. **Claudio Pelucchi**: Writing–review and editing. **Linda M. Liao**: Writing–review and editing. **Charles S. Rabkin**: Writing–review and editing. **Rashmi Sinha**: Writing–review and editing. **Nuno Lunet**: Writing–review and editing. **Samantha Morais**: Writing–review and editing. **David Zaridze**: Writing–review and editing. **Dmitry Maximovich**: Writing–review and editing. **Nuria Aragonés**: Writing–review and editing. **Gemma Castaño-Vinyals**: Writing–review and editing. **Inés Gómez-Acebo**: Writing–review and editing. **Lizbeth López-Carrillo**: Writing–review and editing. **Malaquias López-Cervantes**: Writing–review and editing. **Rossella Bonzi**: Writing–review and editing. **Federica Turati**: Writing–review and editing. **Paolo Boffetta**: Writing–review and editing. **Maria Constanza Camargo**: Writing–review and editing. **Maria Paula Curado**: Writing–review and editing. **Jesus Vioque**: Writing–review and editing. **Zuo-Feng Zhang**: Writing–review and editing. **Eva Negri**: Writing–review and editing. **Carlo La Vecchia**: Funding acquisition, supervision, and writing–review and editing. **Stefania Boccia**: Conceptualization, funding acquisition, supervision, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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REFERENCES

1. Clinton SK, Giovannucci EL, Hursting SD. The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: impact and future directions. *J Nutr*. 2020;150(4):663-671. doi:10.1093/jn/nxz268
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer*. 2021;149(4):778-789. doi:10.1002/ijc.33588
3. Toh JWT, Wilson RB. Pathways of gastric carcinogenesis, *Helicobacter pylori* virulence and interactions with antioxidant systems, vitamin C and phytochemicals. *Int J Mol Sci*. 2020;21(17):6451. doi:10.3390/ijms21176451
4. Boccia S, La Vecchia C. Dissecting causal components in gastric carcinogenesis. *Eur J Cancer Prev*. 2013;22(6):489-491. doi:10.1097/CEJ.0b013e3283603480
5. Sierra MS, Cueva P, Bravo LE, Forman D. Stomach cancer burden in Central and South America. *Cancer Epidemiol*. 2016;44(suppl 1):S62-S73. doi:10.1016/j.canep.2016.03.008
6. Su CH, Islam MM, Jia G, Wu CC. Statins and the risk of gastric cancer: a systematic review and meta-analysis. *J Clin Med*. 2022;11(23):7180. doi:10.3390/jcm11237180
7. Ornelas A, Zacharias-Millward N, Menter DG, et al. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention. *Cancer Metastasis Rev*. 2017;36(2):289-303. doi:10.1007/s10555-017-9675-z
8. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol*. 2012;23(6):1403-1415. doi:10.1093/annonc/mds113
9. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol*. 2020;31(5):558-568. doi:10.1016/j.annonc.2020.02.012
10. Yang P, Zhou Y, Chen B, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. *Dig Dis Sci*. 2010;55(6):1533-1539. doi:10.1007/s10620-009-0915-0
11. Huang XZ, Chen Y, Wu J, et al. Aspirin and non-steroidal anti-inflammatory drugs use reduce gastric cancer risk: a dose-response

meta-analysis. *Oncotarget*. 2017;8(3):4781-4795. doi:10.18632/oncotarget.13591
12. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol*. 2012;13(5):518-527. doi:10.1016/S1470-2045(12)70112-2
13. Kwon S, Ma W, Drew DA, et al. Association between aspirin use and gastric adenocarcinoma: a prospective cohort study. *Cancer Prev Res (Phila)*. 2022;15(4):265-272. doi:10.1158/1940-6207.CAPR-21-0413
14. Morofuji Y, Nakagawa S, Ujifuku K, et al. Beyond lipid-lowering: effects of statins on cardiovascular and cerebrovascular diseases and cancer. *Pharmaceuticals (Basel)*. 2022;15(2):151. doi:10.3390/ph15020151
15. Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Ann Oncol*. 2013;24(7):1721-1730. doi:10.1093/annonc/mdt150
16. Cho MH, Yoo TG, Jeong SM, Shin DW. Association of aspirin, metformin, and statin use with gastric cancer incidence and mortality: a nationwide cohort study. *Cancer Prev Res (Phila)*. 2021;14(1):95-104. doi:10.1158/1940-6207.CAPR-20-0123
17. Lafeber M, Spiering W, van der Graaf Y, et al. The combined use of aspirin, a statin, and blood pressure-lowering agents (polypill components) and the risk of vascular morbidity and mortality in patients with coronary artery disease. *Am Heart J*. 2013;166(2):282-289.e1. doi:10.1016/j.ahj.2013.04.011
18. Pelucchi C, Lunet N, Boccia S, et al. The Stomach Cancer Pooling (StoP) Project: study design and presentation. *Eur J Cancer Prev*. 2015;24(1):16-23. doi:10.1097/CEJ.0000000000000017
19. Lucenteforte E, Scita V, Bosetti C, Bertuccio P, Negri E, La Vecchia C. Food groups and alcoholic beverages and the risk of stomach cancer: a case-control study in Italy. *Nutr Cancer*. 2008;60(5):577-584. doi:10.1080/01635580802054512
20. De Feo E, Simone B, Persiani R, et al. A case-control study on the effect of apolipoprotein E genotypes on gastric cancer risk and progression. *BMC Cancer*. 2012;12(1):494. doi:10.1186/1471-2407-12-494
21. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control*. 2000;11(4):363-371. doi:10.1023/a:1008907924938
22. Lunet N, Valbuena C, Vieira AL, et al. Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. *Eur J Cancer Prev*. 2007;16(4):312-327. doi:10.1097/01.cej.0000236255.95769.22
23. Castaño-Vinyals G, Aragonés N, Pérez-Gómez B, et al. Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. *Gac Sanit*. 2015;29(4):308-315. doi:10.1016/j.gaceta.2014.12.003
24. López-Carrillo L, López-Cervantes M, Robles-Díaz G, et al. Capsaicin consumption, *Helicobacter pylori* positivity and gastric cancer in Mexico. *Int J Cancer*. 2003;106(2):277-282. doi:10.1002/ijc.11195
25. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health–American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001;154(12):1119-1125. doi:10.1093/aje/154.12.1119
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2
27. Ruppar T. Meta-analysis: how to quantify and explain heterogeneity? *Eur J Cardiovasc Nurs*. 2020;19(7):646-652. doi:10.1177/1474515120944014
28. Sassano M, Mariani M, Pelucchi C, et al. Chronic metformin intake and gastric cancer: a pooled analysis within the Stomach Cancer Pooling (StoP) Project. *Cancer Epidemiol*. 2022;81:102286. doi:10.1016/j.canep.2022.102286
29. Sassano M, Mariani M, Pelucchi C, et al. Intake of proton-pump inhibitors and gastric cancer within the Stomach Cancer Pooling (StoP) Project. *Cancer Epidemiol Biomarkers Prev*. 2023;32(9):1174-1181. doi:10.1158/1055-9965.EPI-23-0241
30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
31. De Silva AP, De Livera AM, Lee KJ, Moreno-Betancur M, Simpson JA. Multiple imputation methods for handling missing values in longitudinal studies with sampling weights: comparison of methods implemented in Stata. *Biom J*. 2021;63(2):354-371. doi:10.1002/bimj.201900360
32. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol*. 1999;28(5):964-974. doi:10.1093/ije/28.5.964
33. 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*. 2019;4(2):117-125. doi:10.1002/jgh3.12226
34. Win TT, Aye SN, Fern JLC, Fei CO. Aspirin and reducing risk of gastric cancer: systematic review and meta-analysis of the observational studies. *J Gastrointestin Liver Dis*. 2020;29(2):191-198. doi:10.15403/jgld-818
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(4):473-476. doi:10.1002/(sici)1097-0215(19990812)82:4<473:aid-ijc1>3.0.co;2-k
36. 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(21):2131-2142. doi:10.1056/NEJMoa067208
37. Wang WH, Wong WM, Dailidiene D, et al. Aspirin inhibits the growth of *Helicobacter pylori* and enhances its susceptibility to antimicrobial agents. *Gut*. 2003;52(4):490-495. doi:10.1136/gut.52.4.490
38. Su CH, Islam MM, Jia G, Wu CC. Statins and the risk of gastric cancer: a systematic review and meta-analysis. *J Clin Med*. 2022;11(23):7180. doi:10.3390/jcm11237180
39. Cheung KS, Chan EW, Wong AYS, et al. Statins were associated with a reduced gastric cancer risk in patients with eradicated *Helicobacter pylori* infection: a territory-wide propensity score matched study. *Cancer Epidemiol Biomarkers Prev*. 2020;29(2):493-499. doi:10.1158/1055-9965.EPI-19-1044
40. Jiang W, Hu JW, He XR, Jin WL, He XY. Statins: a repurposed drug to fight cancer. *J Exp Clin Cancer Res*. 2021;40(1):241. doi:10.1186/s13046-021-02041-2
41. Lou D, Fu R, Gu L, Su H, Guan L. Association between statins' exposure with incidence and prognosis of gastric cancer: an updated meta-analysis. *Expert Rev Clin Pharmacol*. 2022;15(9):1127-1138. doi:10.1080/17512433.2022.2112178

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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