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ORIGINAL ARTICLE

Effect of aspirin use on gastric cancer incidence and survival: A systematic review and meta-analysis

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Key words
aspirin, gastric cancer death, gastric cancer incidence.

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Abstract

Background and Aim: A number of recent studies have been published evaluating the chemopreventive effect of aspirin against gastric cancer, and an updated meta-analysis is required to evaluate this relationship further. This study presents a meta-analysis of studies examining the effect of aspirin on gastric cancer incidence and death.

Methods: The PUBMED and Cochrane Central Registration of Controlled Trials databases were searched for eligible studies published up to December 2018. Pooled risk ratios for gastric cancer incidence and death in aspirin users *versus* nonusers were determined using fixed- and random-effects models. The influence of the frequency of aspirin use, duration of aspirin use, and geographic location on gastric cancer incidence was evaluated.

Results: The meta-analysis comprised 33 studies with a total of 1 927 971 patients. The pooled risk ratios for gastric cancer incidence in the fixed- and random-effects models were 0.890 (95% confidence interval, 0.871–0.909) and 0.826 (0.740–0.922), respectively. In Asia and North America, the maximum preventive benefit of aspirin use was observed with weekly or daily use. Aspirin use was most effective for noncardiac gastric cancer. The pooled risk ratios for gastric cancer death in the fixed- and random-effects models were 0.798 (0.749–0.850) and 0.894 (0.780–1.024), respectively. Significant heterogeneity was observed among studies of gastric cancer incidence but not gastric cancer death.

Conclusion: Aspirin use may reduce the risk of gastric cancer incidence and death; however, the relationship may be limited to a specific frequency and duration of aspirin use and geographic location.

Introduction

Gastric cancer, primarily associated with *Helicobacter pylori* infectious inflammation, is one of the most common fatal cancers worldwide.[1,2] Aspirin exhibits a protective effect in gastrointestinal cancer,[3] including gastric cancer development, due to its anti-inflammatory and antiplatelet functions, including induction of apoptosis[4] and inhibition of angiogenesis.[5] Previous meta-analyses have reported a potential relationship between aspirin use and prevention of gastric cancer.[6–14]

Previous studies, including a randomized controlled trial (RCT) and our propensity scores-matched analysis,[15–28] did not find a significant association between aspirin use and gastric cancer development.[29] The effect of aspirin use on gastric carcinogenesis remains undetermined. There are limited data on whether aspirin use is associated with decreased gastric cancer incidence and death. More than 40 studies on this topic have been published since 2016.[7] Further systematic review and meta-analysis are required to evaluate the protective effects of aspirin use on gastric cancer.

This study provides a comprehensive systematic review and updated meta-analysis to estimate risk reduction associated with aspirin use on gastric cancer incidence and death.

Methods

Search strategy and eligibility criteria. A search of the PUBMED and Cochrane Central Registration of Controlled Trials database was performed to identify all English-language studies published that evaluated the association between aspirin use and the risk of gastric cancer incidence or death up to December 2018. Search terms used were "aspirin," "non-steroidal anti-inflammatory agents," "non-steroidal anti-inflammatory drug," "stomach carcinoma," "stomach neoplasms," "stomach cancer," "stomach tumor," "stomach adenocarcinoma," "gastric carcinoma," "gastric neoplasms," "gastric cancer," "gastric tumor," "gastric adenocarcinoma," "epidemiology,"

"incidence," and "mortality." Detailed search queries are provided in Table S1, Supporting information. A manual scan of the bibliographies of relevant articles for additional studies was performed.

Observational and RCT studies of cohorts or case–control studies that met the following criteria were included: written in English, reported on gastric cancer incidence or death, outcomes of aspirin users were compared with nonusers, and studies provided adequate data to enable risk ratio estimation. Aspirin use was defined as nonsteroidal anti-inflammatory drug (NSAIDs) aspirin use only.

Study selection and data extraction, outcome and variables measured, and study quality assessment. Two researchers (Ryota Niikura and Yoshihiro Hirata) independently reviewed the included studies. Uncertainty about the inclusion of a study was resolved by discussing issues to achieve consensus. Data, including the number of participants, events, or risk ratios for gastric cancer incidence or death; first author's surname; year of publication; type of outcome; study design; patient inclusion criteria; aspirin use frequency, duration, and dose; and age and gender of participants, were independently extracted from the included studies by both researchers and verified for accuracy.

Outcomes included gastric cancer incidence, cardiac gastric cancer incidence, noncardiac gastric cancer incidence, and gastric cancer death.

Aspirin use duration was categorized as <5 years, >5 years, or >10 years. Aspirin use frequency and dose were categorized as occasionally, monthly, weekly, or daily use. Geographic location was categorized as Asia, Europe, or North America.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of observational studies (range: 0–9), which consisted of each category of selection of the study groups, the comparability of the groups, and the ascertainment of the exposure (case–control studies) or outcome of interest (cohort studies) (Tables S2 and S3).

Statistics. The pooled risk ratios were calculated using both fixed-effect and random-effects models. Heterogeneity among studies was evaluated using the Q-statistic, and the inconsistency I^2 was quantified.[30]

Subgroup analyses were performed to assess the potential impact of aspirin use duration and frequency, geography, cardiac gastric cancer, and noncardiac gastric cancer on the pooled effects. Publication bias was assessed using funnel plots and the Egger regression test of funnel plot asymmetry.[31] In each funnel plot, the standard errors of the estimates were plotted on a vertical reversed scale against the effect estimates on the horizontal scale. The triangle was centered on the pooled estimate and extended to 1.96 times the standard errors on either side. The statistical analyses were performed using the Comprehensive Meta-Analysis version 3 and SAS version 9.4 (SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant.

Results

A total of 463 studies were identified in the systematic search. After screening the titles and abstracts, 86 studies were considered eligible for analysis. Of these, 53 failed to satisfy inclusion criteria and were excluded. A total of 33 studies were included in the final analysis (Fig. 1).[12,16–29,32–46] Characteristics of the included studies, outcomes, characteristics of the drug exposure, and study quality are provided in Table 1. A total of 1 927 971 patients were analyzed.

Aspirin use and risk of gastric cancer incidence. A total of 30 studies on the effect of aspirin use and gastric cancer incidence were included in the analysis. The directions of the estimated risk ratios and 95% confidence intervals (CIs) were not

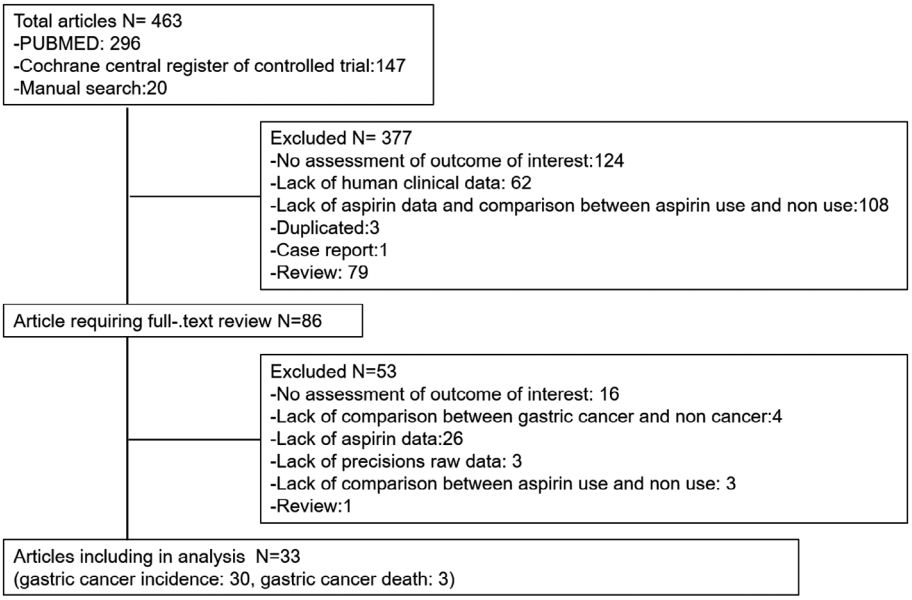

Figure 1 Flow chart for study selection.

Table 1 Characteristics of studies evaluating aspirin use and gastric cancer incidence and death

Study. no	Author, year	Geographic area	Outcome, cancer location	Study design	*Helicobacter pylori* infection rate	Event in aspirin users/nonevents in aspirin users	Event in nonaspirin user/nonevent in nonaspirin user	Aspirin use, frequency and duration	Study quality
1	Abnet *et al.*, 2009[12]	North America	Incidence Cardia Noncardia	Cohort	Not reported	245/227198	115/83917	Not reported	8
2	Bertuccio *et al.*, 2010[19]	Europe	Incidence	CC	Not reported	21/229	46/543	<60 months, ≥60 months	6
3	Cheung *et al.*, 2018[20]	Europe	Incidence Cardia Noncardia	CC	High	25/9045	144/54560	<Monthly, monthly to weekly, weekly to daily, daily <2 years, 2–5 years, ≥5 years	6
4	Coogan *et al.*, 2000[32]	North America	Incidence	CC	Not reported	127/3621	123/2339	Regular, nonregular <5 years, >5 years	6
5	Cook *et al.*, 2005[29]	North America	Incidence	RCT	Not reported	10/19934	10/19942	Not reported	
6	Duan *et al.*, 2008[33]	North America	Incidence Cardia Noncardia	CC	Not reported	139/457	575/1612	2–7 pills, ≥7 pills/week, <5 years, ≥5 years	7
7	Akre *et al.*, 2001[34]	Europe	Incidence Cardia Noncardia	CC	High	170/594	310/941	<1 tab, 1–29 tab, ≥30 tab/month	8
8	Farrow *et al.*, 1998[35]	North America	Incidence Cardia Noncardia	CC	Not reported	159/375	453/924	<1 tab, 1 tab, >1 tab/day <5 years, 5–9 years, ≥10 years	6
9	Figueroa *et al.*, 2009[22]	North America	Incidence Cardia Noncardia	CC	Not reported	58/282	86/410	Not reported	6
10	Fortuny *et al.*, 2007[36]	North America	Incidence Cardia Noncardia	CC	Not reported	314/1902	296/1044	<2 tab, 2–11 tab, >11 tab/week	6
11	Gillies and Skyring, 1968[28]	Asia	Incidence	CC	Not reported	2/6	23/44	Not reported	5
12	Gong *et al.*, 2014[37]	Asia	Incidence	CC	High	21/81	306/573	Not reported	8
13	Hoyo *et al.*, 2009[24]	North America	Incidence Cardia Noncardia	CC	Not reported	33/97	75/203	Not reported	5
14	Iqbal *et al.*, 2016[38]	Asia	Incidence	CC	Not reported	4158/18416	17096/73200	Not reported	4
15	Kim *et al.*, 2018[17]	Asia	Incidence	Cohort	Low	1207/86446	4466/375043	1–29 days, 30–364 days, 1–2 years 2–3 years, 3–4 years, 4–5 years	8

(*Continues*)

Table 1 (Continued)

Study. no	Author, year	Geographic area	Outcome, cancer location	Study design	*Helicobacter pylori* infection rate	Event in aspirin users/nonevents in aspirin users	Event in nonaspirin user/nonevent in nonaspirin user	Aspirin use, frequency and duration	Study quality
16	Langman *et al.*, 2000[23]	Europe	Incidence	CC	Not reported	148/620	465/1830	1 tab, 2–6 tab, ≥30 tab/13–24 months 1 tab, 2–6 tab, ≥30 tab/25–36 months 1 tab,2–6 tab, ≥30 tab/13–36 months	5
17	Lee *et al.*, 2012[39]	Asia	Incidence	CC	Low	184/799	347/636	Not reported	7
18	Meade, 1998[55]	Europe	Incidence	CC	Not reported	5/1268	1/1272	Not reported	5
19	Niikura *et al.*, 2018[41]	Asia	Incidence	CC	Low	17/2082	8/2082	Not reported	6
20	Nomura *et al.*, 2003[42]	North America	Incidence	CC	Not reported	63/193	237/553	<3 years, >3 years	5
21	Pandeya *et al.*, 2010[25]	Asia	Incidence Cardia	CC	Not reported	305/1523	100/427	<weekly, ≥weekly	5
22	Sadeghi *et al.*, 2008[21]	Asia	Incidence Cardia	CC	Not reported	255/1197	171/809	Occasionally, less than weekly, at least weekly	6
23	Schreinemachers *et al.*,1994[26]	North America	Incidence	CC	Not reported	20/6716	19/4634	Not reported	5
24	Suleiman *et al.*, 2000[43]	Europe	Incidence Cardia	CC	Not reported	35/82	24/33	<1 year, >1 year	5
25	Tsoi *et al.*, 2019[44]	Asia	Incidence	CC	Not reported	1385/204170	4442/408339	<7 years, <10 years, <14 years	4
26	Wang *et al.*, 2015[16]	Asia	Incidence	CC	High	31/86	47/160	1–6 tab, ≥7 tab/week <5 years, ≥5 years	6
27	Wu *et al.*, 2010[45]	Asia	Incidence	CC	Low	69/25145	103/27016	Not reported	5
28	Kim *et al.*, 2016[27]	Asia	Incidence	CC	Low	31/3907	86/7808	0.5–1 year, 1.1–2 years, 2.1–3 years, >3 years	4
29	Epplein *et al.*, 2009[18]	North America	Incidence Cardia Noncardia	CC	Not reported	349/86695	294/82597	≤1 year, 2–5 years, ≥6 years	4
30	Zaridze *et al.*, 1999[46]	Europe	Incidence Noncardia	Cohort	High	48/135	400/923	Not reported	9
31	Spence *et al.*, 2018[53]	Europe	Death	Cohort	Not reported	412/808	1980/3025	<365, ≥365, 1–182, 183–364, 365–547, 548–729, ≥730 tab	8
32	Ratnasinghe *et al.*, 1999[51]	North America	Death	Cohort	Not reported	23/14815	25/7971	Not reported	8
33	Thrift *et al.*, 2012[54]	Asia	Death	Cohort	Not reported	129/204	150/212	Not reported	8

Helicobacter pylori infection was categorized as high (>40%), low (<40%), or not reported. Study quality was evaluated using the Newcastle-Ottawa Scale detailed in Tables S2 and S3.
CC, case control study; RCT, randomized controlled trial.

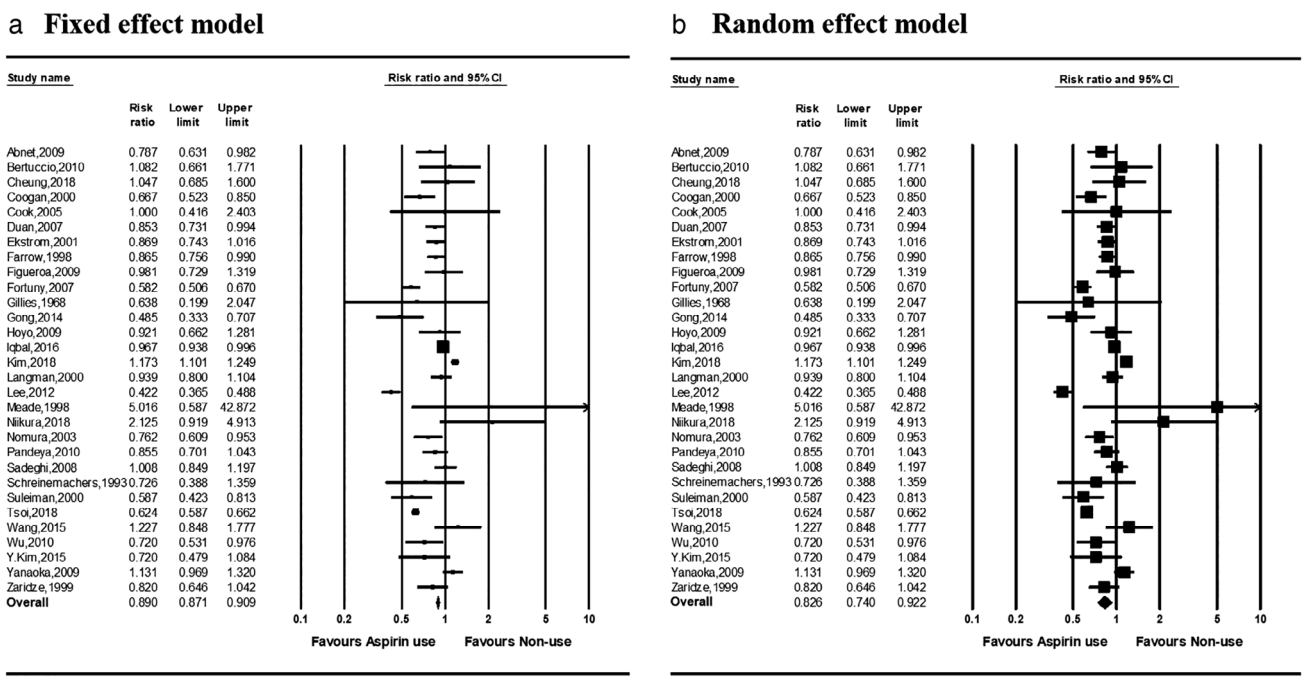

Figure 2 Forest plots of risk ratios for gastric cancer incidence in aspirin users *versus* nonusers in (a) fixed- and (b) random-effects models. CI, confidence interval.

consistent among the studies (Fig. 2). The pooled risk ratios (95% CI) of aspirin users compared with nonusers in the fixed- and random-effects models were 0.890 (0.871–0.909) and 0.826 (0.740–0.922), respectively. Significant heterogeneity was observed among studies in the fixed-effects model ($P < 0.001$; I^2 93.2%).

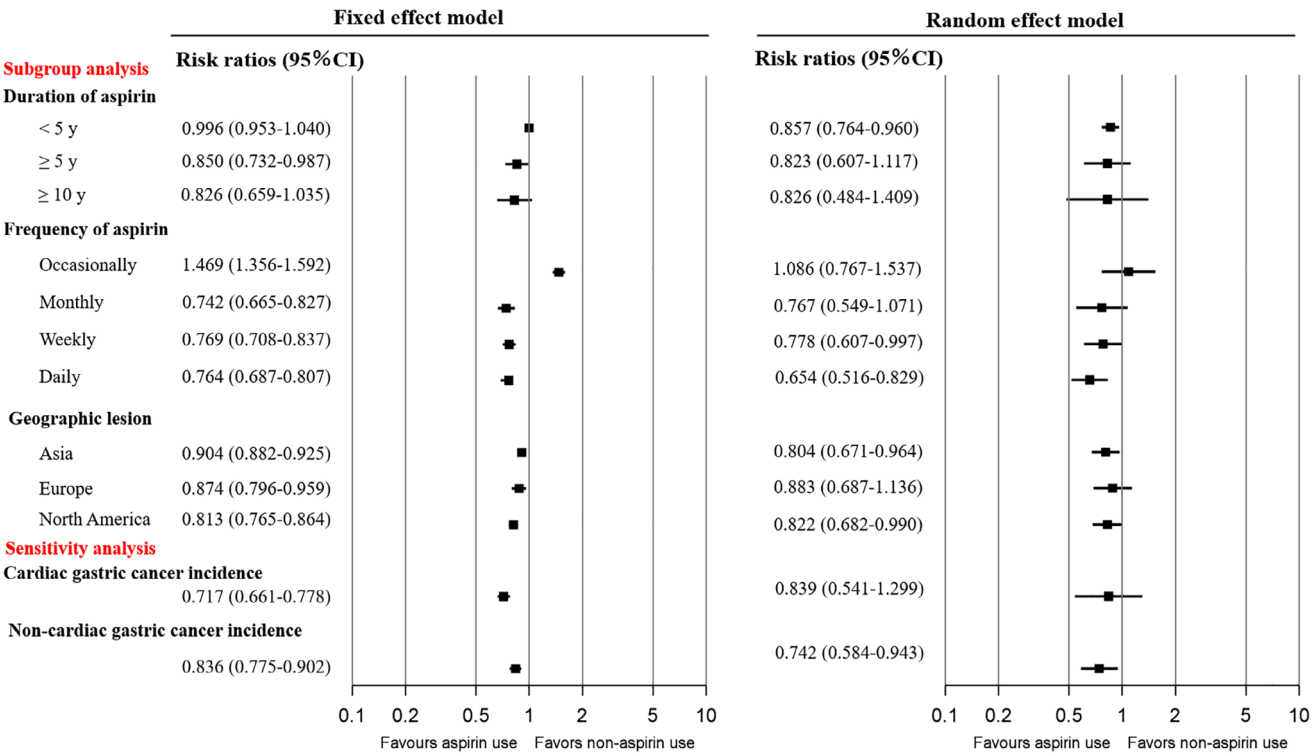

Figure 3 Relative risks for the subgroup analyses. CI, confidence interval.

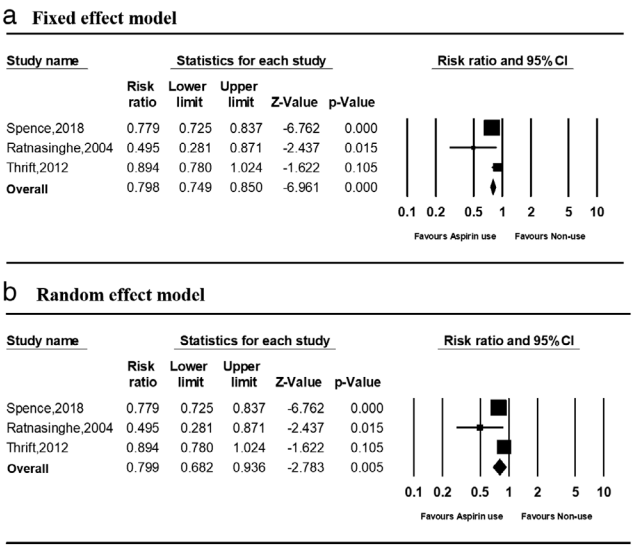

Figure 4 Forest plots of risk ratios for gastric cancer death in aspirin users *versus* nonusers in (a) fixed- and (b) random-effect models. CI, confidence interval.

The pooled risk ratios of the groups of patients with aspirin use duration <5 years, >5 years, and >10 years were 0.996 (0.953–1.040), 0.850 (0.732–0.987), and 0.826 (0.659–1.035), respectively, in the fixed-effects model and 0.857 (0.764–0.960), 0.823 (0.607–1.117), and 0.826 (0.484–1.409), respectively, in the random-effects model (Fig. 3).

With regard to the frequency of aspirin use, the pooled risk ratios for the occasional, monthly, weekly, and daily users were 1.469 (1.356–1.592), 0.742 (0.665–0.827), 0.769 (0.708–0.837), and 0.744 (0.687–0.807), respectively, in the fixed-effects model. The random-effects model had similar results, with the exception of the pooled risk ratios in the occasional and monthly use subgroups of 1.086 (0.767–1.537) and 0.767 (0.549–1.071), respectively (Fig. 3).

The pooled risk ratios in Asia, Europe, and North America were 0.904 (0.882–0.925), 0.874 (0.796–0.959), and 0.813 (0.765–0.864), respectively, in the fixed-effects model and 0.804 (0.671–0.964), 0.883 (0.687–1.136), and 0.822 (0.682–0.990), respectively, in the random-effects model (Fig. 3).

Aspirin use and risk of cardiac and noncardiac gastric cancer incidence. The relationship between aspirin use and the risk of cardiac and noncardiac gastric cancer incidence was examined in 12 and 11 studies, respectively. Pooled risk ratios for cardiac gastric cancer and noncardiac gastric cancer patients were 0.717 (0.661–0.778) and 0.836 (0.775–0.902) in the fixed-effects model and 0.839 (0.541–1.299) and 0.742 (0.584–0.943) in the random-effects model (Fig. 3).

Publication bias. The funnel plot is presented in Figure 5a. Of a total of 30 data points, 9 lay outside the triangle, and 13 lay on the right side of the triangle altitude. No significant publication bias was observed by the Egger regression test ($P = 0.284$).

Aspirin use and risk of gastric cancer death. Three studies examined the effect of aspirin use on gastric cancer death. The direction of the risk ratios was not consistent between the studies (Fig. 4). The summary risk ratios in aspirin users compared with nonusers were 0.798 (0.749–0.850) and 0.894 (0.780–1.024) in the fixed- and random-effects models, respectively. No significant heterogeneity was observed among studies in the fixed-effects model ($P = 0.054$). No significant publication bias was observed based on the Egger regression test of funnel asymmetry ($P = 0.805$; Fig. 5b).

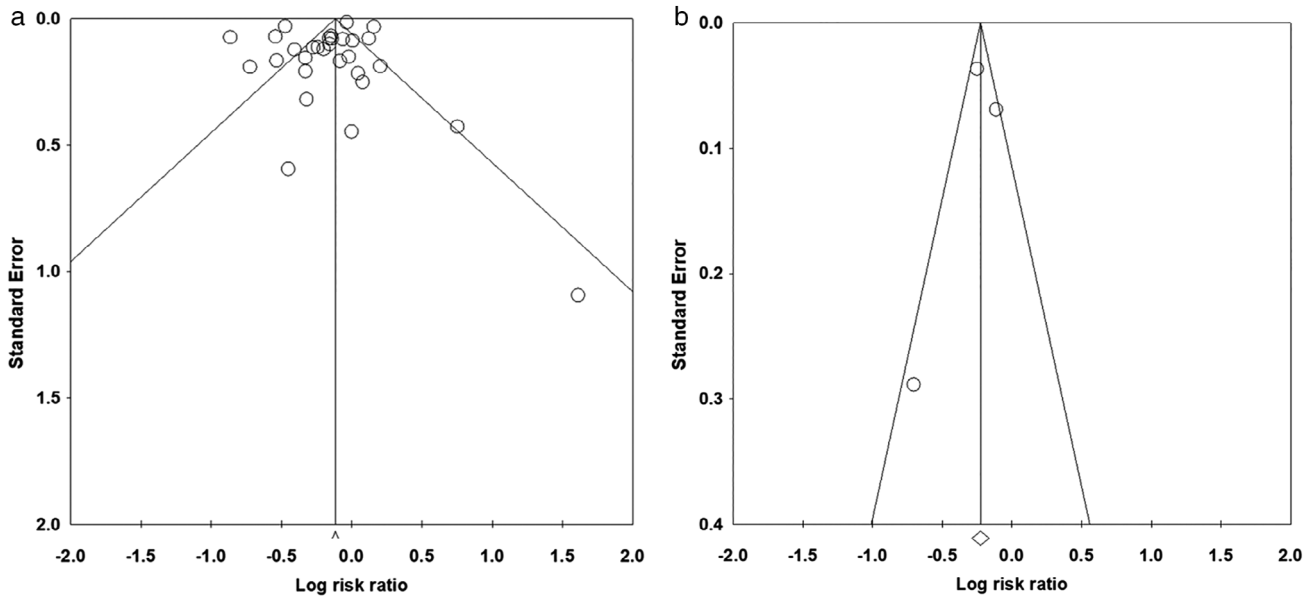

Figure 5 Funnel plot of possible publication bias of the effect of aspirin use on (a) gastric cancer incidence and (b) gastric cancer death.

Discussion

Aspirin use was associated with the decreased risk of gastric cancer incidence and death. A chemopreventive effect was observed with high-frequency aspirin use, Asian and North American populations, and noncardiac gastric cancer. No significant chemopreventive effect was observed in long-term aspirin users or European populations.

Aspirin use contributed to a significant reduction in gastric cancer incidence, which is in agreement with previous meta-analyses.[6–14] Cancer angiogenesis inhibition and NF-kappa B activation-induced tumor apoptosis may inhibit gastric cancer incidence,[47,48] which may lead to a decrease in gastric cancer death. A dose-dependent inverse association between aspirin use and gastric cancer incidence was confirmed. The risk of gastric cancer incidence was reduced by approximately 20% with weekly or daily aspirin use.

The subgroup analysis of geographic location indicated a stronger chemoprotective effect of aspirin in Asia compared to Europe. Asian populations have a higher *H. pylori* infection rate, and the observed effect of aspirin may have been confounded by *H. pylori* infection. Several studies have adjusted for the risk of *H. pylori*; however, the influence of *H. pylori* has not been adequately studied. In addition, differences in bacterial virulence genes, such as cytotoxin-associated gene A (CagA), may have an effect. Previous meta- and sensitivity analyses (Table S4) have observed a preventive effect of aspirin on gastric cancer in *H. pylori*-infected populations. Aspirin may suppress *H. pylori*-associated inflammation, resulting in gastric cancer prevention. Other unmeasured confounding factors may also be involved; for example, aspirin users may receive more *H. pylori* eradication therapy opportunities than nonusers.

The subgroup analysis indicated that aspirin use for a duration of <5 years had a chemopreventive effect, while aspirin for >5 years did not. These nonlinear associations are consistent with previous meta-analyses. The majority of studies evaluated aspirin use durations of <10 years. The sample size of patients on long-term aspirin use may be insufficient to evaluate the association between aspirin use and risk of gastric cancer incidence. The underlying mechanisms are not well understood, and further research is required to evaluate the link between the duration of aspirin use and prevention of carcinogenesis.

The subgroup analysis demonstrated an association between aspirin use and reduced noncardiac gastric cancer incidence; however, no effects were observed on cardiac gastric cancer. This may be due to different pathology and disease progression between cardiac and noncardiac gastric cancers.[18,49,50] For example, cyclooxygenase-2 overexpression is generally lower in cardiac gastric cancer than noncardiac gastric cancer.[51] It is also possible that noncardiac gastric cancer is associated with *H. pylori*, while cardiac cancer is not.[52]

This updated meta-analysis is the first to demonstrate a preventive effect of aspirin on gastric cancer incidence and death. Several subgroup analyses reviewed the effect of frequency and duration of aspirin use, location of cancer, and geographic location. These results are useful in helping to identify the optimal aspirin use for reducing gastric cancer incidence. This study was limited by the fact that most studies were observational rather than RCTs. In addition, detailed study information from the RCTs (e.g. chemotherapy trials) was not available from the published data. Observational studies may include biased data and unmeasured confounding factors. No publication bias was observed for gastric cancer incidence and death. The placebo effect of aspirin use must also be considered. A high-quality RCT, with gastric cancer incidence or death as the primary outcome, is required to investigate the chemopreventive effect of aspirin further.

This study found aspirin use to be associated with reduced gastric cancer incidence and death. Greater chemopreventive effects were observed with weekly and daily aspirin use, <5 years duration of use, and Asian and North American populations, particularly for noncardiac gastric cancer.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 Search queries for PUBMED.
Table S2 Assessment of the case–control studies using the Newcastle-Ottawa scale.
Table S3 Assessment of the Cohort studies using the Newcastle-Ottawa scale.
Table S4 Subgroup of *H. pylori* infectious states of relative risk for gastric cancer incidence.