Non-steroidal Anti-inflammatory Drug Use and the Risk of Gastric Cancer: A Systematic Review and Meta-analysis

Wei Hong Wang, Jia Qing Huang, Ge Fan Zheng, Shiu Kum Lam, Johan Karlberg, Benjamin Chun-Yu Wong

Background: The relationship between the use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, and the risk of gastric cancer has not been well studied. We performed a systematic review and meta-analysis of published studies to evaluate the association between use of this class of drugs and the risk of gastric cancer. Methods: A fully recursive literature search to January 2003 was conducted in MEDLINE, PubMed, and CANCERLIT to identify potentially relevant case-control or cohort studies. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated under a random-effects model. Results: Nine studies (eight case-control and one cohort) with a total of 2831 gastric cancer case patients were identified. NSAID use was associated with a reduced risk of gastric cancer, with a summary odds ratio of 0.78 (95% CI = 0.69 to 0.87). Users of aspirin (OR = 0.73, 95% CI = 0.63 to 0.86) and non-aspirin NSAIDs (OR = 0.74, 95% CI = 0.55 to 1.00) experienced similar magnitudes of risk reduction. Regular users of NSAIDs (OR = 0.57, 95% CI = 0.44 to 0.74) experienced a lower risk of gastric cancer relative to nonusers than did irregular users (OR = 0.76, 95% CI = 0.62 to 0.94; P = .09 versus regular users). A stratified analysis showed that NSAID use was associated with a statistically significant reduction in risk of noncardia gastric cancer (OR = 0.72, 95% CI = 0.58 to 0.89), but not of gastric cancer at the cardia (OR = 0.80, 95% CI = 0.53 to 1.20). There was no evidence that study design or type of control subject substantially influenced the estimate of effects. Conclusion: NSAID use was associated with a decreased risk of gastric cancer in a dose-dependent manner. This finding warrants proper clinical trials in populations with high risk of gastric cancer. [J Natl Cancer Inst 2003;95:1784–91]

Gastric cancer is the fourth most common cancer and the second leading cause of cancer deaths worldwide (1). Although early diagnosis and treatment of gastric cancer statistically significantly improves prognosis (2,3), the 5-year survival rate is only 10%–15% in individuals with advanced disease (4). Therefore, the primary prevention of gastric cancer is of particular importance.

Gastric carcinogenesis is a multistep and multifactorial process (5), although the etiology of gastric cancer is not fully understood. Several studies (6–10) have shown that the cyclooxygenase 2 (COX-2) gene is overexpressed in several gastrointestinal malignancies, including gastric cancer, suggesting a possible role of COX-2 in gastrointestinal carcinogenesis. COX-2 participates in several key cellular activities, such as cell proliferation (11,12), apoptosis (11–14), and angiogenesis (15,16). Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, are known to inhibit production of COX-1 and COX-2 through both prostaglandin-dependent and -independent pathways (17,18). Therefore, NSAIDs, including COX-2-selective inhibitors, are potential agents for the chemoprevention of gastric cancer.

In several epidemiologic studies (19–23), long-term use of NSAIDs has been associated with a decreased incidence of several types of gastrointestinal malignancies. However, the current literature focuses primarily on the chemoprevention of colorectal cancer with NSAIDs (24–29); fewer studies have examined the association between chronic NSAID use and the development of gastric cancer, and these studies have had inconsistent results (30–37). Thus, the effect of NSAID use on the risk of gastric cancer remains to be determined.

Several recent review articles (18,19,21,22) have summarized the association between NSAID use and the risk of gastrointestinal malignancies. However, none of these articles has been a quantitative systematic review, and none focused on gastric cancer. Therefore, we systematically identified case-control and cohort studies of the association between use of NSAIDs and risk of gastric cancer. We then carried out a meta-analysis of these studies to evaluate the association, to compare the magnitude of any associations between aspirin and gastric cancer with that between non-aspirin NSAIDs and gastric cancer, and to examine associations with dose and with the location of gastric cancer.

Materials and Methods

Search Strategy

A computerized literature search was conducted in the MEDLINE, PubMed, and CANCERLIT databases for relevant articles published in any language to January 2003. We used the following Medical Subject Heading (MeSH) terms and/or text words: “stomach neoplasm,” “stomach cancer,” “gastric carcinoma,” “gastric cancer,” or “gastric carcinoma” combined with “aspirin,” “NSAIDs,” or “non-steroidal anti-inflammatory agents.” Meeting abstracts were searched in the ISI Proceedings database (1990–2002) and CD-ROMs of major gastrointestinal meetings held from 1998 through 2002 (American Digestive

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See “Notes” following “References.”

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Disease Weeks, American College of Gastroenterology annual meetings, the United European Gastroenterology Weeks, and the World Congresses of Gastroenterology). Finally, to find any additional published studies not found by our computer search, we manually searched the reference lists of the computer-retrieved review articles (17–22) and of all original studies.

The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. All searches were conducted independently by three reviewers (W. H. Wang, J. Q. Huang, G. F. Zheng), and the results were combined.

Inclusion Criteria

The following criteria were used to include published studies. First, they had to be case–control or cohort studies examining exposure to NSAIDs (including aspirin) and the incidence or mortality of gastric cancer in adults, with age- and/or sex-matched controls. Second, they had to contain an explicit description of NSAID use, with raw data on either number of users or on duration of exposure, or details of the methods used to detect cases. Studies without raw data available for retrieval and duplicate publications were excluded.

Data Extraction

Data were extracted from each study by three reviewers (W. H. Wang, J. Q. Huang, G. F. Zheng) independently by using a predefined review spreadsheet. Any differences were resolved by discussion to reach consensus among the investigators.

### Table 1. Characteristics of studies included in the meta-analysis*

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Study design</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>Diagnosis method</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akre et al. (39)</td>
<td>C-C</td>
<td>480 GC patients from tumor registry</td>
<td>1055 population controls, matched on age and sex</td>
<td>Tumor registry, pathology</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Farrow et al. (40)</td>
<td>C-C</td>
<td>612 GC patients from tumor registry</td>
<td>687 randomly selected population controls, matched on age and sex</td>
<td>Pathology</td>
<td>Aspirin and non-aspirin NSAIDs</td>
</tr>
<tr>
<td>Schreinemachers and Everson (37)</td>
<td>C-C</td>
<td>39 GC patients in NHANES I, NHEFS</td>
<td>11 411 subjects without cancer in the same cohort</td>
<td>Hospital record, interview, death certificate</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Coogan et al. (41)</td>
<td>C-C</td>
<td>250 GC patients from multiple hospitals</td>
<td>5833 hospital patients without cancer, matched on age and sex</td>
<td>Pathology</td>
<td>Aspirin and non-aspirin NSAIDs</td>
</tr>
<tr>
<td>Langman et al. (34)</td>
<td>C-C</td>
<td>613 GC patients in general practice database</td>
<td>1837 patients without GC in the same database, matched on age and sex</td>
<td>Database record</td>
<td>Aspirin and non-aspirin NSAIDs</td>
</tr>
<tr>
<td>Zaridze et al. (36)</td>
<td>C-C</td>
<td>448 GC patients from two hospitals</td>
<td>610 patients without cancer or GI disease in the same hospital</td>
<td>Pathology</td>
<td>Aspirin and non-aspirin NSAIDs</td>
</tr>
<tr>
<td>Gillies and Skyring (42)</td>
<td>C-C</td>
<td>25 GC patients from one hospital</td>
<td>25 hospital patients without GI symptoms or history of GI diseases, matched on age and sex</td>
<td>Pathology</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Suleiman et al. (43)</td>
<td>C-C</td>
<td>56 COA patients, death certificate in general practitioner and hospital records</td>
<td>56 myocardial infarction patients matched by age and sex, death certificate in the same records</td>
<td>Pathology</td>
<td>Aspirin and non-aspirin NSAIDs</td>
</tr>
<tr>
<td>Thun et al. (35)</td>
<td>Cohort</td>
<td>152 aspirin-using patients in Cancer Prevention Study II cohort, died of GC</td>
<td>156 non-aspirin using patients in the same cohort who died of GC</td>
<td>Death certificate</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

*Studies were ranked according to their relative validity. NHANES I: National Health and Examination Survey I; NHEFS: NHANES I Epidemiologic Follow-up Studies; GC: gastric cancer; COA: cardiosophageal adenocarcinoma; C-C: case–control; GI: gastrointestinal. Detailed information on validity assessment for each study is available from the authors upon request.

**Assessment of Study Quality**

Study quality was assessed independently by three reviewers (W. H. Wang, J. Q. Huang, G. F. Zheng) according to criteria modified from the guidelines for reading case–control studies proposed by Lichtenstein et al. (38). These criteria include an explicit statement of the research question, a description of how case patients and control subjects were selected, definition of aspirin or NSAID exposure, and information on data collection, analytic methods, and sample size. To avoid subjective assessments, we did not generate an overall quality score; instead, we used these validity criteria to rank the studies (Table 1). For example, a study with a clearly defined population control group matched for age and sex, a large sample size, and an explicit description of NSAID use would be ranked higher than a study without this information.

**Statistical Methods and Assessment of Homogeneity**

Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the raw data of the selected studies, using the DerSimonian and Laird method under a random-effects model (44). Statistical homogeneity between studies was assessed using the Cochrane Q value calculated from the Mantel–Haenszel method (44). When statistical heterogeneity was detected, the sources of heterogeneity were explored and sensitivity analyses were performed. For analysis of potential interactions, studies were grouped by the type of control subjects (population- or hospital-based), the site of gastric cancer (cardia or noncardia cancer), the type of medicine (aspirin or non-aspirin NSAIDs), and the frequency and duration of NSAID use.
Publication bias, a phenomenon in which studies with positive results are more likely to be published than studies with negative results, was assessed by plotting the odds ratios of the individual study against their standard errors (44) and then calculating correlation coefficients between the odds ratios and their standard errors by the rank correlation method (45).

Data reporting conforms to the guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (46). All analyses were carried out using Comprehensive Meta Analysis software (version 1.0.25; Biostat, Englewood, NJ).

RESULTS

Study Characteristics

We identified a total of 271 citations and 30 meeting abstracts with the computerized search. Our manual search (i.e., of references cited sections) identified three more articles. However, after screening of the titles and abstracts of all 304 citations, 291 were excluded because they were either animal studies or in vitro cell line experiments, review articles, or irrelevant to the current study. Of the 13 potentially relevant studies identified for full article retrieval, nine (34–37,39–43) met the inclusion criteria (Table 1). The other four studies were excluded because they evaluated the risk of malignancies in patients with rheumatoid arthritis and did not provide an explicit description of NSAID exposure (30–32) or because they analyzed gastric cancer only in combination with other cancers (47).

Overall Analysis

Of the nine studies analyzed, eight (34,36,37,39–43) were case–control studies and one (35) was a cohort study. The case–control studies included a total of 2523 case patients and 21 514 control subjects, and the cohort study included 308 case patients, for a total of 2831 case patients. The overall prevalence of NSAID use was 28.5% (720/2523) and 53.7% (11 559/21 514) in case patients and control subjects, respectively, giving a summary odds ratio of 0.78 (95% CI = 0.69 to 0.87) (Fig. 1 and Table 2), that is, a 22% reduction in the odds of developing gastric cancer for NSAID users as compared with nonusers. The test for homogeneity among studies was not statistically significant (Cochrane Q value = 7.83, \( P = .35 \)) (Table 2). However, we did obtain evidence of publication bias as shown by a statistically significant \( P \) value of .03 from the rank correlation test (45) (Table 2).

Population-Based Versus Hospital-Based Control Subjects

Of the eight case–control studies, population-based control subjects were used in three (37,39,40) and hospital-based control subjects in five (34,36,41–43). In the studies with population-based control subjects, 30.9% (349/1131) of the case patients and 56.5% (7436/13 153) of the control subjects were NSAID users, giving a summary odds ratio of 0.79 (95% CI = 0.67 to 0.92). The test for homogeneity was not statistically significant (Cochrane Q value = 0.24, \( P = .89 \)) (Table 2). In the studies with hospital-based control subjects, the prevalence of NSAID use was 25.9% (360/1392) in case patients and 49.1% (4104/8361) in control subjects, giving a summary odds ratio of 0.73 (95% CI = 0.57 to 0.93). The test for homogeneity was also not statistically significant (Cochrane Q value = 7.54, \( P = .11 \)) (Table 2). Moreover, no statistically significant difference in odds ratios was observed between studies using different control groups (Table 2). Therefore, the choice of control group did not substantially affect the magnitude of the odds ratios.

Exposure to Aspirin or Non-aspirin NSAIDs

Of the eight case–control studies, five (36,37,39,40,42) provided raw data on aspirin use and the rest did not differentiate between aspirin and non-aspirin NSAID use. The prevalence of aspirin use was 21.7% (332/1533) in case patients and 54.2% (7397/13 651) in control subjects, giving a summary odds ratio of 0.73 (95% CI = 0.63 to 0.86). This is equivalent to a 27% reduction in the odds of developing gastric cancer in chronic aspirin users. The test for homogeneity was not statistically significant (Table 2).

Two case–control studies (36,40) provided raw data on non-aspirin NSAID use, with 8.2% (83/1015) of the case patients and 10.4% (127/1225) of the control subjects reporting the use of non-aspirin NSAIDs. The summary OR was 0.74 (95% CI = 0.55 to 1.00), that is, a 26% reduction in the odds of developing gastric cancer in NSAID users with a marginally statistical significance. The test for homogeneity was not statistically significant (Table 2). In addition, no statistically significant difference in the magnitude of odds ratios was observed for people who used aspirin or non-aspirin NSAIDs (Table 2).

Dose Effect

To analyze any association between dose of NSAIDs and the risk of gastric cancer, drug exposure was grouped as “irregular use” and “regular use,” according to the definitions given by the individual studies (Table 3) (34,35,39–41,43). The prevalence of regular NSAID users was 11.8% (183/1551) in case patients and 15.6% (889/5697) in control subjects, giving a summary odds ratio of 0.57 (95% CI = 0.44 to 0.74), that is, a 43% reduction in the odds of developing gastric cancer for regular NSAID users as compared with nonusers. However, the prevalence of irregular users was 22.1% (389/1757) in case patients and 43.0% (3634/8442) in control subjects, respectively, giving a summary odds ratio of 0.84 (95% CI = 0.66 to 1.07) for irregular users as compared with nonusers. Thus, there was no...
probably because NSAID exposure was loosely defined in the group of irregular users (Cochrane Q value = 9.74, \( P = .045 \), Table 2). Further scrutiny identified the study by Langman et al. (34) as contributing most to the heterogeneity, probably because NSAID exposure was loosely defined in this study and the exclusion criteria for hospital control subjects were unclear. A sensitivity analysis excluding this study (Table 2) showed a summary odds ratio of 0.76 (95% CI = 0.62 to 0.94), that is, a 24% reduction in the odds of developing gastric cancer in irregular users as compared with nonusers. When this study was excluded, the test of homogeneity was not statistically significant (Table 2). Furthermore, there was no statistically significant difference in the odds ratios for gastric cancer among regular NSAID users (compared with nonusers) (\( P = .09 \)).

**Duration of Exposure**

Two case–control studies (40,41) provided raw data on the duration of NSAID exposure, which allowed us to dichotomize duration to less than 5 years and 5 or more years. The studies showed that use of NSAIDs for 5 or more years was associated with a reduced risk of developing gastric cancer (Table 4).

**Prospective Cohort Study**

In the single prospective cohort study (35) that we identified, 635 031 people were followed for 6 years. Aspirin use was defined as any use in the month preceding study entry. A total of 308 patients died of gastric cancer, of whom 152 were aspirin users and 156 were nonusers (information on the use of other NSAIDs was not provided). The death rate from gastric cancer was 7.8 per 100,000 person-years among the aspirin users and 12.3 per 100,000 person-years in the nonusers, respectively, giving a relative risk (RR) of 0.64 (95% CI = 0.51 to 0.80), that is, a 36% relative reduction in the risk of death from gastric cancer in aspirin users. In addition, a dose-dependent trend in risk reduction was observed, with relative risks of 0.73 (95% CI = 0.56 to 0.96) for occasional use (1–15 times per month) and 0.49 (95% CI = 0.33 to 0.74) for use 16 or more times per month. Although raw data were not provided for analysis of the

**Table 2.** Statistical results of case–control studies analyzed under a random effects model*

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of studies</th>
<th>No. of cases</th>
<th>OR (95% CI)</th>
<th>Test of homogeneity†</th>
<th>Publication bias‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cochrane Q value</td>
<td>( P ) value</td>
</tr>
<tr>
<td>Any exposure</td>
<td>8</td>
<td>2523</td>
<td>0.78 (0.69 to 0.87)</td>
<td>7.83</td>
<td>.35</td>
</tr>
<tr>
<td>Type of control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population-based</td>
<td>3</td>
<td>1131</td>
<td>0.79 (0.67 to 0.92)</td>
<td>0.24</td>
<td>.89</td>
</tr>
<tr>
<td>Hospital-based</td>
<td>5</td>
<td>1392</td>
<td>0.73 (0.57 to 0.93)</td>
<td>7.54</td>
<td>.11</td>
</tr>
<tr>
<td>Type of exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>5</td>
<td>1533</td>
<td>0.73 (0.63 to 0.86)</td>
<td>0.44</td>
<td>.98</td>
</tr>
<tr>
<td>NSAID</td>
<td>2</td>
<td>1015</td>
<td>0.74 (0.55 to 1.00)</td>
<td>0.52</td>
<td>.47</td>
</tr>
<tr>
<td>Dose of exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>5</td>
<td>1757</td>
<td>0.84 (0.66 to 1.07)</td>
<td>9.74</td>
<td>.045</td>
</tr>
<tr>
<td>Irregular†</td>
<td>4</td>
<td>1175</td>
<td>0.76 (0.62 to 0.94)</td>
<td>3.84</td>
<td>.28</td>
</tr>
<tr>
<td>Regular</td>
<td>5</td>
<td>1551</td>
<td>0.57 (0.44 to 0.74)</td>
<td>5.64</td>
<td>.23</td>
</tr>
<tr>
<td>Site of cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardia</td>
<td>4</td>
<td>481</td>
<td>0.80 (0.53 to 1.20)</td>
<td>7.41</td>
<td>.06</td>
</tr>
<tr>
<td>Cardia†</td>
<td>3</td>
<td>425</td>
<td>0.92 (0.71 to 1.21)</td>
<td>2.33</td>
<td>.31</td>
</tr>
<tr>
<td>Noncardia</td>
<td>3</td>
<td>1111</td>
<td>0.72 (0.58 to 0.89)</td>
<td>3.17</td>
<td>.20</td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval; NSAID = non-steroidal anti-inflammatory drug.
†Test of homogeneity between studies was assessed using the Mantel–Haenszel method (44).
‡Publication bias was measured by calculating correlation coefficients between the odds ratios and their standard errors by using the rank correlation method (45).
§Excluding one heterogeneous study (34).
<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>Definition of use</th>
<th>Definition of irregular use</th>
<th>Definition of regular use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akre et al. (39)</td>
<td>More than once per month until 2 years before interview</td>
<td>1–20 tablets per month</td>
<td>More than 30 tablets per month</td>
</tr>
<tr>
<td>Farrow et al. (40)</td>
<td>More than once per week for 6 months beginning 1 year before interview</td>
<td>Former use</td>
<td>Current use</td>
</tr>
<tr>
<td>Schreinemachers and Everson (37)</td>
<td>Within 30 days of the baseline interview</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Coogan et al. (41)</td>
<td>More than 4 days per week for at least 3 months, initiated at least 1 year before hospital admission</td>
<td>No clear definition was given</td>
<td>At least 4 days per week for at least 3 months</td>
</tr>
<tr>
<td>Langman et al. (34)</td>
<td>More than 2 days per week for more than 6 months</td>
<td>Two to six prescriptions†</td>
<td>More than seven prescriptions</td>
</tr>
<tr>
<td>Zaridze et al. (36)</td>
<td>More than 2 days per week for more than 6 months</td>
<td>NA</td>
<td>More than 2 days per week for more than 6 months</td>
</tr>
<tr>
<td>Gillies and Skyring (42)</td>
<td>Any use in prior 13–36 months</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Suleiman et al. (43)</td>
<td>More than once a day for at least 1 year</td>
<td>Any use</td>
<td>Total use for 1 year or less</td>
</tr>
<tr>
<td>Thun et al. (35)</td>
<td>Occasional use</td>
<td>1–15 times per month</td>
<td>Total use for more than 1 year</td>
</tr>
</tbody>
</table>

*NA = not available.
†No definition of prescription was provided.
than those who had used aspirin for 10 years or more experienced greater risk reduction. The authors reported that those who had used aspirin for 10 years or more experienced greater risk reduction. The test of homogeneity was statistically significant (P = .06; Table 2). The study by Suleiman et al. (43) was probably responsible for the heterogeneity because it included patients with cardioesophageal adenocarcinoma and control subjects who had died of myocardial infarction. However, sensitivity analysis without this study did not yield statistically significant odds ratios for cardio gastric cancer (Table 2). In the analyses of noncardia gastric cancer, the prevalence of NSAID use was 24.0% (267/1111) in case patients and 31.7% (746/2352) in control subjects, respectively, yielding a summary OR of 0.72 (95% CI = 0.53 to 1.20, Table 2). The test of homogeneity was statistically significant (P = .06; Table 2).

**Table 4. Characteristics of the two case–control studies assessing the association of duration of NSAID use with gastric cancer* **

<table>
<thead>
<tr>
<th>Study</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>Use of NSAIDs</th>
<th>&lt;5 y</th>
<th>≥5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases†</td>
<td>Controls</td>
<td>OR (95% CI)</td>
<td>Cases†</td>
<td>Controls</td>
</tr>
<tr>
<td>Farrow et al.</td>
<td>612 patients identified from cancer case registry</td>
<td>687 population controls randomly selected, matched on age and sex</td>
<td>Aspirin 12.7% (66/519)</td>
<td>1.05 (0.73 to 1.25)</td>
<td>Aspirin 17.0% (93/546)</td>
</tr>
<tr>
<td></td>
<td>Nonaspirin NSAIDs 7.0% (41/584)</td>
<td>Nonaspirin NSAIDs 9.3% (61/655)</td>
<td>0.74 (0.49 to 1.11)</td>
<td>Nonaspirin NSAIDs 4.2% (24/567)</td>
<td>Nonaspirin NSAIDs 5.1% (32/626)</td>
</tr>
<tr>
<td>Coogan et al.</td>
<td>131 patients pathologically confirmed</td>
<td>2725 age- and sex-adjusted hospital controls</td>
<td>NSAIDs 3.9% (5/128)</td>
<td>0.48 (0.19 to 1.18)</td>
<td>NSAIDs 2.4% (3/126)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs 7.8% (198/2537)</td>
<td>NSAIDs 7.8% (198/2537)</td>
<td>0.82 (0.48 to 1.41)</td>
<td>NSAIDs 7.4% (188/2527)</td>
<td>NSAIDs 7.4% (188/2527)</td>
</tr>
</tbody>
</table>

*NSAID = non-steroidal anti-inflammatory drug (includes aspirin unless noted); OR = odds ratio; CI = confidence interval.
†Only study subjects with information on duration of NSAID use were included.

**Discussion**

A number of studies (19–23) have shown that use of NSAIDs is associated with reduction in the incidence of a variety of gastrointestinal malignancies. The association between NSAID use and development of colorectal cancer has been studied the most (23–29,48–51); esophageal cancer (52,53), gastric cancer (39–41), liver cancer (41,54,55), and pancreatic cancer (34,56,57) have been studied less extensively. A recent meta-analysis of nine observational studies (58) suggested that long-term use of NSAIDs, including aspirin, is associated with a reduced risk of esophageal cancer. However, the association between NSAID use and gastric cancer has remained unclear. The results of the meta-analysis in this article suggest that long-term use of aspirin or non-aspirin NSAIDs is associated with a statistically significant, dose-dependent reduction in the risk of gastric cancer. When the analysis was stratified by the site of gastric cancer, use of NSAIDs was associated with a statistically significantly lower risk for noncardia gastric cancer but not gastric cancer at the cardia.

It is likely that the inconsistent data from the studies of this meta-analysis may have resulted from the small number of cases, resulting in inadequate statistical power (36,37,39). When the small studies were combined in this meta-analysis, a statistically significant difference was found, suggesting that long-term use of NSAIDs is associated with a reduced risk of gastric cancer. The meta-analysis also revealed an inverse dose relationship between the frequency of NSAID use and risk of gastric cancer, although the dose relationship was not statistically significant. An inverse dose relationship was also reported by Corley et al. (58) in their study of the relationship between NSAID use and esophageal cancer. However, our results should be interpreted cautiously because of the limited number of studies and the different definitions of drug exposure. For example, most studies collected information on the frequency of NSAID use but not on the actual amount taken. The lack of information on dosing could have led to the inconsistent findings in the studies that we analyzed (34–37,40,41,43).
Treatment duration with NSAIDs has been shown to be more strongly associated than dose or frequency of use with reduction in colorectal cancer risk (28,59). However, this association was not confirmed in this systematic review according to the information from two studies (40,41) that provided data on the association between the duration of NSAID exposure and the risk of gastric cancer. However, the use of different cut-off time points, the lack of information on duration of exposure in other studies, and varying definitions of drug exposure made a meta-analysis of any duration effect impossible. Although two studies (35,41) indicated that the magnitude of gastric cancer risk reduction was greater in those with a longer duration of NSAID exposure, the minimum effective duration of NSAID use to see a reduction in gastric cancer risk remains undetermined because of the relatively small number of subjects. In the cohort study, Thun et al. (35) reported that individuals who had used aspirin for 10 years or more had a statistically significantly lower risk of death from gastric cancer compared with those who had used it for 1–9 years. This result is consistent with that of another large cohort study (50), in which the protective association of aspirin with colorectal cancer was not realized until after 20 years of regular use. However, more prospective studies are needed to clarify whether a duration effect exists in the relationship between NSAID use and gastric cancer risk.

In a subgroup analysis stratified by anatomical site, we found that use of NSAIDs was associated with a statistically significant reduction in the risk of noncardia gastric cancer but not that of cancer of the gastric cardia, although the associations were similar. Gastric cancer at the cardia is different from noncardia gastric cancer in both clinical and pathologic features (60,61). Therefore, it would not be surprising if the effect of NSAIDs on gastric cancer differs with respect to site.

The impact of H. pylori infection on the relationship between NSAID use and gastric cancer remains unclear (36,39). H. pylori infection is known to be associated with noncardia gastric cancer (62–65); it is possible that NSAIDs may inhibit the replication and proliferation of H. pylori (66,67) and neutralize the increased COX-2 expression and prostaglandin synthesis associated with H. pylori infection (68,69), thereby reducing the risk of gastric cancer. However, because of the small number of studies (36,39) and patients in the analysis of the interaction between H. pylori infection and NSAID use on gastric cancer, we could not draw any meaningful conclusions.

There are several limitations to this meta-analysis. First, observational studies are susceptible to various biases (e.g., recall bias in case–control studies) because of their retrospective nature. Therefore, recall bias could invalidate the results from this meta-analysis. Second, the choice of control subjects in case–control studies may distort the results because hospital-based controls may not be as representative as population-based controls (70), although no evidence of the effect of control population was detected in this meta-analysis. Third, although we provided evidence for a dose-dependent relationship between NSAID use and the reduction in risk of gastric cancer, different definitions and use of different doses of drug have precluded us from making any clinically meaningful recommendations about the optimal duration and dose of treatment. Fourth, as shown in Table 2, there appears to be a strong publication bias in favor of publication of positive studies. Because of resource limitations, however, we did not attempt to search for unpublished studies of the association between NSAID use and gastric cancer. Fifth, because of the lack of individual patient data, we could not adjust prevalence of NSAID use by factors that may affect the use of these drugs, such as the motivation for NSAID use (71,72), although we excluded studies involving patients with rheumatoid arthritis. Patients with rheumatoid arthritis have a higher rate of death from cardiovascular diseases compared with age-matched control populations (73,74). Inclusion of this group of patients may lead to an inaccurate estimate of the association between NSAID use and the risk of gastric cancer. Sixth, NSAID use may cause gastrointestinal bleeding, resulting in clinical investigations that may detect an early gastric cancer that would have been undiagnosed otherwise. This early diagnosis may reduce the number of deaths from gastric cancer, leading to a lower rate of reported mortality of gastric cancer. Conversely, patients with early symptoms of undiagnosed gastric cancer may stop taking NSAIDs. This group of subjects may be classified as nonusers, therefore decreasing the risk of gastric cancer among unexposed individuals. Finally, the conclusions drawn from subgroup analyses might be limited because of the small sample size.

Although the risks (i.e., gastrointestinal complications) of regular use of conventional NSAIDs may outweigh the potential benefits in preventing gastric cancer in populations at low risk for gastric cancer, a randomized trial of NSAIDs, including aspirin, might be appropriate in populations at high risk for gastric cancer and with high rates of H. pylori infection, especially in Japan and certain areas of China. Because COX-2-selective inhibitors (e.g., rofecoxib, celecoxib, etoricoxib) have lower gastrointestinal toxicity than nonselective NSAIDs, they may be a better option for chemoprevention in both high- and low-risk populations. Nevertheless, the question of whether the epidemiologic evidence provides a firm basis for randomized clinical trials needs to be examined carefully, especially when the evidence comes from populations with different socioeconomic and environmental backgrounds, and given that gastric carcinogenesis is a multifactorial and multistep process (5).

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NOTES

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