Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis

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Use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of gastric or oesophageal adenocarcinomas. We examined the association between self-reported use of aspirin or non-aspirin NSAIDs in the earlier 12 months and gastric non-cardia (N = 182), gastric cardia (N = 178), and oesophageal adenocarcinomas (N = 228) in a prospective cohort (N = 311 115) followed for 7 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) come from Cox models adjusted for potential confounders. Use of any aspirin (HR, 95% CI: 0.64, 0.47 – 0.86) or other NSAIDs (0.68, 0.51 – 0.92) was associated with a significantly lower risk of gastric non-cardia adenocarcinoma. Neither aspirin (0.86, 0.61 – 1.20) nor other NSAIDs (0.91, 0.67 – 1.22) had a significant association with gastric cardia cancer. We found no significant association between using aspirin (1.00, 0.73 – 1.37) or other NSAIDs (0.90, 0.69 – 1.17) and oesophageal adenocarcinoma. We also performed a meta-analysis of the association between the use of NSAIDs and risk of gastric and oesophageal adenocarcinoma. In this analysis, aspirin use was inversely associated with both gastric and oesophageal adenocarcinomas, with summary odds ratios (95% CI) for non-cardia, cardia, and oesophageal adenocarcinomas of 0.64 (0.52 – 0.80), 0.82 (0.65 – 1.04), and 0.64 (0.52 – 0.79), respectively. The corresponding numbers for other NSAIDs were 0.68 (0.57 – 0.81), 0.80 (0.67 – 0.95), and 0.65 (0.50 – 0.85), respectively.

Keywords: aspirin; NSAIDs; oesophageal cancer; gastric cancer; cohort; meta-analysis

Aspirin may prevent heart disease (Hennekens and Schneider, 2008) and colon cancer (Dubé et al., 2007), but the US Preventive Services Task Force does not endorse an aspirin regimen for primary chemoprevention of colon cancer (US Preventive Services Task Force, 2007). Daily aspirin use carries the risk of gastrointestinal bleeding and haemorrhagic stroke and the expected benefits do not outweigh the risks, at least in individuals at average risk for colorectal cancer. If additional chemopreventive benefits at sites other than the colon could be included in the risk benefit analysis, this calculation may change.

Worldwide, gastric cancer remains the second leading cause of death due to cancer, with over 900 000 incident cases and about 700 000 deaths (Parkin et al., 2002). Although gastric cancer incidence rates are decreasing in the United States, about 21 000 incident cases occur each year (Ries and Melbert, 2007). In contrast, oesophageal adenocarcinoma rates have increased dramatically over the last 30 years in many Western countries, and there are about 9000 incident cases in the United States each year (Ries and Melbert, 2007). Both stomach and oesophageal cancers have high fatality rates, only 24 and 16% 5-year survival respectively, so preventive strategies are particularly important for these cancers. Earlier studies suggest that the incidence of adenocarcinomas of the oesophagus and stomach may be reduced by the use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) (Corley et al., 2003; Gonzalez-Perez et al., 2003; Wang et al., 2003), but few studies have been prospective, used data collected directly from subjects, and controlled for the many potential confounders.

We aimed to examine the association between aspirin and non-aspirin NSAID use and risk of oesophageal, gastric cardia, and gastric non-cardia adenocarcinoma in the NIH-AARP Diet and Health Study cohort, a large prospective study conducted in the United States.

METHODS

The NIH-AARP Diet and Health Study is a large prospective cohort study designed to investigate the association between diet and other factors and risk of cancer and has been described in detail previously (Schatzkin et al., 2001). Between 1995 and 1996, a questionnaire was mailed to 3.5 million AARP members (aged 50–71 years) in eight US states (California, Florida, Georgia,
In total, 617,119 individuals returned the questionnaire. A second mailed questionnaire (1996–1997) collected additional information including NSAID use and 334,908 individuals were available for analysis. We excluded subjects for whom either the baseline (N = 6959) or the follow-up questionnaire (N = 3424) was completed by proxies, those with prevalent cancer at the second questionnaire baseline (N = 4543), those with incomplete information about NSAID use (N = 6353), those with total energy intake more than twice the interquartile range from the median (N = 2506), and those who exited on the first day of follow-up (N = 8). The resulting cohort included 311,115 participants including 180,337 men and 130,778 women. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

As described earlier (Michaud et al, 2005), addresses for members of the NIH-AARP cohort were updated annually by matching the cohort database to that of the National Change of Address database maintained by the US Postal Service. We ascertained vital status by annual linkage of the cohort to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings. Incident cases of cancer through the year 2003 were identified by probabilistic linkage between the NIH-AARP cohort membership and the cancer registry databases of the states of residence at the time of mailing the questionnaire with the addition of Arizona, Nevada, and Texas, each of which has been certified by the North American Association of Central Cancer Registries for meeting the highest standards of data quality. For matching purposes, first and last name, address history, gender, date of birth, and Social Security number (available for 85% of our participants) were used. We estimate the sensitivity of case identification to be about 90%. Cancer sites were identified by anatomic site and histologic code as detailed earlier (Freedman et al, 2007), using the International Classification of Disease for Oncology, third edition. We classified tumours with site codes C15.0–C15.9 as oesophageal cancers, site code C16.0 as gastric cardia tumours, and site codes C16.1–C16.9 as non-cardia tumours. All included cancers were classified as adenocarcinomas.

Our questionnaire assessed aspirin (generic aspirin and trade names) use and non-aspirin NSAID use separately and the latter named 19 non-aspirin NSAIDs (e.g., ibuprofen, sulindac etc., using both generic and trade names) and specifically excluded Tylenol, acetaminophen, and other pain relievers. Both questions asked about any use in the past 12 months and asked users to mark how often they took any aspirin or non-aspirin NSAID. Aspirin users and non-aspirin NSAID users appeared throughout the day. A small number of subjects were missing values for some adjusting covariates and these subjects were retained using dummy variables in the models. We modelled the HR (95% CI) for any use of aspirin and of non-aspirin NSAIDs in a single model (i.e., mutually adjusted models) and for frequency of use with adjustment for the other category of NSAIDs. We tested the proportional hazards assumption using cross-product terms for interaction between follow-up time and any use of NSAIDs and found no significant deviations from proportionality. Furthermore, we dropped 1, 2, or 3 years of initial follow-up and refitted the models to assess lag effects and found none. Age-standardised incidence rates were calculated as in Breslow and Day (1987) with 5-year age bands and age- and sex-specific rates standardised to the entire NIH-AARP Diet and Health Study population.

Meta-analysis

To conduct the meta-analysis, we searched PubMed on 20 November 2008, with the following terms: (aspirin OR nsaid OR nsaids OR non-steroidal) AND (gastric cancer OR oesophageal cancer) AND (case-control OR cohort OR epidemiologic). We reviewed the 128 retrieved abstracts to find relevant papers, reading those in full in which the abstracts were not entirely informative. We also reviewed earlier meta-analyses on aspirin and NSAIDs in relation to oesophageal and gastric cancers (Corley et al, 2003; Gonzalez-Perez et al, 2003; Wang et al, 2003) and other review articles (Baron, 2003; Bosetti et al, 2003). We limited our analysis to papers reporting case–control or cohort studies of the association between the use of either aspirin or non-aspirin NSAIDs and the risk of oesophageal or gastric adenocarcinomas. We included the following studies for the oesophagus (Farrow et al, 1998; Cheng et al, 2000; Lindblad et al, 2005; Anderson et al, 2006; Jayaprakash et al, 2006; Ranka et al, 2006; Fortuny et al, 2007; Duan et al, 2008; Sadeghi et al, 2008), cardia (Farrow et al, 1998; Zardie et al, 1999; Akre et al, 2001; Fortuny et al, 2007; Duan et al, 2008; Sadeghi et al, 2008), non-cardia (Farrow et al, 1998; Zardie et al, 1999; Akre et al, 2001; Fortuny et al, 2007; Duan et al, 2008), and gastric NOS (Thun et al, 1993; Schreinemachers and Everson, 1994; Coogan et al, 2000; Langman et al, 2000; Akre et al, 2001; Sorensen et al, 2003; Ratnasingham et al, 2004; Lindblad et al, 2005) and excluded a few studies from certain sections that did not specify the agent (Garidou et al, 1996; Suleiman et al, 2000) or the histology of the oesophageal tumours (Funkhouser and Sharp, 1995; Langman et al, 2000). Two other studies, one prospective and one retrospective, reported on the association between aspirin and oesophageal adenocarcinoma but included only Barrett’s oesophagus in the reference group (Tsibouris et al, 2004; Vaughan et al, 2005) and these papers are discussed separately. From each selected paper, the effect measures (odds ratio (OR) or HR) and 95% CIs were tabulated by two investigators. In each case, we selected the most expansive measure of NSAID use and the maximally adjusted model that did not include adjustment for reflux symptoms (where possible). In some cases, we collapsed multiple exposure groups into a single measure of association using fixed effects models, and these are indicated by asterisks in the figure. We used Stata/SE version 8.0 (Stat Corp., College Station, TX, USA) and the meta and metabias commands to complete the analyses. We report the results from random effects models, but the results for fixed effects are similar in each case. Plots were created using SigmaPlot 8.0 (Systat Corp., Chicago, IL, USA).

RESULTS

In the 12 months before baseline, 73% of the cohort had used aspirin and 56% had used non-aspirin NSAIDs (Table 1), 25% reported daily aspirin use and 10% reported daily non-aspirin NSAID use. Aspirin users and non-aspirin NSAID users appeared throughout the day. A small number of subjects were missing values for some adjusting covariates and these subjects were retained using dummy variables in the models. We modelled the HR (95% CI) for any use of aspirin and of non-aspirin NSAIDs in a single model (i.e., mutually adjusted models) and for frequency of use with adjustment for the other category of NSAIDs. We tested the proportional hazards assumption using cross-product terms for interaction between follow-up time and any use of NSAIDs and found no significant deviations from proportionality. Furthermore, we dropped 1, 2, or 3 years of initial follow-up and refitted the models to assess lag effects and found none. Age-standardised incidence rates were calculated as in Breslow and Day (1987) with 5-year age bands and age- and sex-specific rates standardised to the entire NIH-AARP Diet and Health Study population.
similar to each other and to the cohort as a whole in their age, smoking histories, alcohol-drinking habits, education, diet, BMI, and amount of physical activity.

The cohort members had an average of 6.7 years of follow-up and we collected 2,078,248 person years of follow-up in total. The HRs and 95% CIs for both any use and the frequency of aspirin or non-aspirin NSAID use are given in Table 2. Models adjusted for only age and sex produced similar results to these fully adjusted models. For gastric non-cardia cancer, we found a strong dose-dependent protective association for aspirin. Any aspirin use had an HR (95% CI) of 0.64 (0.52 – 0.86). The HRs decreased from 0.74 for monthly use to 0.57 for weekly or daily use and the test for trend across categories was significant (P < 0.050). We saw no evidence of a significant interaction between sex and NSAID use. Finally, we deleted the first 1, 2, and 3 years of follow-up and found similar results to those for the full follow-up period.

We calculated age-standardised incidence rates for non-cardia gastric cancer in aspirin users and non-users. The rates (95% CI) per 100,000 person years dropped from 11.0 (8.4 – 13.6) in non-aspirin users to 7.0 (5.7 – 8.3) in users. We also calculated rates in men and women separately because of the underlying difference in risk for this cancer. The number of non-cardia gastric cases in women in our cohort was small (N = 53), and among aspirin non-users and users we found rates of 6.4 (3.7 – 9.1) and 5.1 (3.3 – 6.9), respectively. In men (N = 129), we found rates of 16.4 (11.6 – 21.1) and 8.2 (6.4 – 9.9), respectively.

To put our results in a larger perspective, we completed a meta-analysis of 49 risk estimates from 17 published studies reporting the association between either aspirin (Figure 1A) or non-aspirin NSAID (Figure 1B) use and the risk of oesophageal adenocarcinoma. We combined aspirin and non-aspirin NSAIDs into a single category and found statistically significantly reduced risk of non-cardia gastric cancer, 0.64 (0.44 – 0.91), compared with never using either agent, but no significant associations with risk of cancer at the other two sites. As adenocarcinomas of the oesophagus and cardia can be difficult to separate, we combined these two sites into a single outcome, but still found no significant associations with either aspirin or non-aspirin NSAID use. We adjusted for and also stratified by reported use of antacids, a proxy marker for reflux disease or heartburn, and found no differences compared with the presented results (data not shown). We tested for and found no evidence of a significant interaction between sex and NSAID use.
DISCUSSION

We found that reported use of aspirin or non-aspirin NSAIDs was associated with a significant 36% reduction in the risk of non-cardia gastric cancer consistent with the earlier studies. For ever use of aspirin in the previous 12 months, age-adjusted rates of gastric non-cardia cancer dropped from 11.0 in non-users to 7.0/100,000 person years in users. Although we did not find a significant association between use of aspirin or other NSAIDs with cardia cancer, the point estimate in our study was very close to the summary estimate from the meta-analysis, which showed a protective effect. Unlike most earlier observational studies, we found no such association with oesophageal adenocarcinoma.

Our finding in the NIH-AARP cohort study that aspirin or other NSAIDs had a protective association with gastric non-cardia adenocarcinoma is consistent with the literature published earlier, which is summarised in Figure 1. It appears that aspirin and non-aspirin NSAIDs have similar effects, which may have implications for cancer prevention. Eradication of Helicobacter pylori, the strongest risk factor for gastric non-cardia adenocarcinoma, may reduce its incidence (Talley, 2008). However, recent studies suggest that H. pylori may have health benefits, such as preventing asthma (Blaser et al, 2008) or oesophageal adenocarcinoma (Islami and Kamangar, 2008). Beyond the direct benefits and risks of eradication to the individual, the methods and consequences of attempted widespread eradication, such as increasing antibiotic resistance, must also be considered (Graham and Shiotani, 2008). A single trial has tested the effect of the NSAID rofecoxib on subjects with gastric pre-neoplastic lesions over 24 months and found no evidence of benefit, but this study was small and did not use cancer as an end point (Leung et al, 2006). The remarkably consistent observational results showing that NSAID use is associated with a reduced risk of gastric cancer may warrant a randomised trial in a suitable population at high risk for the disease in which side effects can be monitored closely.

The epidemiology of gastric cardia tumours in the United States is similar to that of oesophageal adenocarcinoma. The incidence of this tumour may have increased in recent years, but this change may have occurred because of changing patterns of diagnosis or because of the difficulty of separating adenocarcinomas in the gastric cardia from those in the oesophagus (Kubo and Corley, 2002). We found no significant association between use of either aspirin or non-aspirin NSAIDs and risk of gastric cardia adenocarcinoma, but our point estimates are similar to the summary estimates from our meta-analysis, which suggests a significant protective effect.

We found no evidence that ever or daily aspirin use lowered the risk of oesophageal adenocarcinoma, for which, as shown in Figure 1, our results are discordant with many earlier studies. Most of these showed some evidence, albeit not always significantly, that use of aspirin or non-aspirin NSAIDs was associated with reduced risk.

The reasons for these differences are not clear. Most earlier studies had retrospective designs and may be prone to reverse
causality for NSAIDs, as subjects with reflux symptoms, and therefore at higher risk of oesophageal adenocarcinoma, may avoid using NSAIDs producing the appearance of protection among users. But at least one earlier prospective study found that NSAID use reduced risk of progression to oesophageal adenocarcinoma among subjects with Barrett’s oesophagus (Vaughan et al., 2005). Recently, in the same cohort, the association is found strongest among subjects with multiple molecular abnormalities that confer the greatest risk of progressing to cancer, but absent in those at the lowest risk (Galipeau et al., 2007). One study using subjects with Barrett’s oesophagus as controls found that oesophageal adenocarcinoma cases and subjects with Barrett’s used aspirin and NSAIDs at similar rates, but this differed with long-term reflux symptoms (Tsibouris et al., 2004). One small, short-term trial tested the effect of twice-daily treatment with 200 mg of celecoxib for 48 weeks on the proportion of dysplastic biopsies in subjects with Barrett’s oesophagus and did not find any benefit (Heath et al., 2007). A large trial of proton pump inhibitors with or without aspirin for the chemoprevention of oesophageal adenocarcinoma in men with Barrett’s oesophagus is underway (Jankowski and Moayyedi, 2004).

Our study has several strengths, being based on a large prospective cohort that provided adequate power and minimised recall bias, which may alter the associations found in case–control studies. We used subject-completed questionnaires that captured both over-the-counter and pharmacy-provided NSAIDs and...
information on many potentially confounding exposures, many of which (e.g., age, tobacco smoking, and physical activity) were similar among NSAID users and non-users. On the other hand, we captured only NSAID use over the previous 12 months and did not collect the duration of use, which could have caused misclassification of subjects who, for example, recently ceased NSAID use due to upper gastrointestinal symptoms. But, we did adjust for and stratify by antacid use without change in our risk estimates. We could not assess infection with \textit{H. pylori} and infected subjects may have different patterns of NSAID use, which would lead to different confounding effects in the stomach and oesophagus. Finally, this study, being observational, is susceptible to confounding by other unmeasured or poorly measured confounders, supporting the need for randomised controlled trials.

In this large prospective cohort study, we found further evidence that regular use of aspirin or non-aspirin NSAIDs may reduce the risk of non-cardia gastric cancer; in contrast, this was not associated with reduced risk of oesophageal adenocarcinoma, thereby differing from most earlier studies.

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CCA had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. All authors have given full approval to the final paper. CCA, NDF, FK, MFL, and AS were involved in the study design, analysis, and interpretation of the data. CCA, NDF, FK, MFL, ARH, and AS were all involved in the critical revision of the paper.

**Competing interests**

The authors declare that no competing interests exist.

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