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Aspirin and non-steroidal anti-inflammatory drug use and the risk of Barrett's Esophagus

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Abstract

Background—The use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease the risk of esophageal adenocarcinoma; however, it is unknown where these agents may act in the proposed pathway from normal mucosa to Barrett's esophagus to esophageal adenocarcinoma.

Aim—To evaluate the association between aspirin and NSAID use and Barrett's esophagus in a case-control study within a large community-based population.

Methods—We conducted a case-control study of aspirin/NSAID use and Barrett's esophagus within the Kaiser Permanente Northern California population. Cases had a new diagnosis of Barrett's esophagus between October 2002 and September 2005; controls were members without a diagnosis of Barrett's esophagus. Aspirin/NSAID "users" were persons with at least weekly use of either aspirin or NSAIDs in the year prior to the index date.

Results—Persons with Barrett's esophagus were less likely to use aspirin than population controls (odds ratio [OR]=0.59, 95% confidence interval [CI] 0.39–0.87); a stronger association was found among cases and controls with reflux symptoms (OR=0.49, 95% CI 0.32–0.75; p-value interaction=0.004). Similar associations were found with use of either aspirin and/or non-aspirin NSAIDs (OR= 0.53, 95% CI 0.35–0.81), although NSAID use alone was not significantly associated with Barrett's esophagus (OR=0.74, 95% CI 0.47–1.16). The strength of the association was highest among persons with at least moderate to high total medication intake.

Conclusions—Regular use of aspirin or NSAIDs was associated with a decreased risk of Barrett's esophagus, particularly among persons with GERD symptoms. These findings have implications for chemoprevention, as some of the previously described protective association

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between aspirin/NSAIDs and esophageal adenocarcinoma may be explained by events that occur prior to the development of Barrett's esophagus.

Keywords

Chemoprevention; Esophageal Cancer; NSAID; Barrett's Esophagus

INTRODUCTION

While incidence rates for most cancers have been decreasing in the US, the incidence of esophageal adenocarcinoma (EAC) has increased greater than six-fold over the last four decades.[1] Barrett's esophagus (BE), a metaplastic transformation from the normal squamous mucosa of the esophagus to a columnar lining, is the only known precursor for esophageal adenocarcinoma; its presence conveys a 30 to 40 fold increased risk of esophageal adenocarcinoma.[2–6] Thus, the identification of modifiable risk factors or preventive measures for Barrett's esophagus could potentially decrease cancer deaths.

Epidemiologic studies have suggested an inverse association between the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of esophageal adenocarcinoma; [7–14] however, it is not known where these agents may act in the proposed pathway from normal mucosa → gastroesophageal reflux disease (GERD) → Barrett's esophagus → esophageal adenocarcinoma. Animal models suggest that NSAIDs might act by decreasing the risk of esophagitis after injury from gastroesophageal reflux, by modifying the chance of esophagitis developing into Barrett's esophagus or by diminishing the chance of Barrett's esophagus progressing to esophageal adenocarcinoma.[15] A recent study comparing NSAIDs as a risk for BE, found that aspirin users, but not non-aspirin NSAID users, had a lower risk of BE than non-users[16]. However, very few population based studies, to our knowledge, have studied the relationship between NSAIDs and Barrett's esophagus and results are inconsistent. Understanding if and when aspirin or NSAIDs have a protective effect would allow for the identification of the appropriate risk group for potential chemoprevention studies.

We evaluated the association between aspirin and NSAID use and Barrett's esophagus in a case-control study within a large community-based population, comparing cases to population controls.

METHODS

We conducted a case-control study within the Kaiser Permanente Northern California (KPNC) population, an integrated health services delivery organization. KPNC contains approximately 3.3 million persons; its membership demographics closely approximate the underlying census population of northern California.[17] Details of the study design have been described previously.[18] Eligible subjects were all adult (ages 18 – 79 years) members who were continuously enrolled for at least 2 years prior to their index date. The index date for the cases was the date of diagnosis of Barrett's esophagus. The index date for controls was the midpoint of each 2–3 month selection interval for the cases.

Case Definition

Cases were eligible KPNC members who received a new diagnosis of Barrett's esophagus between October 2002 and September 2005. Potential cases were identified using the International Classification of Disease, Ninth Revision (ICD-9) code 530.2, which at KPNC is uniquely coded on reporting sheets as "Barrett's esophagitis." A single board certified gastroenterologist (D.A.C.) reviewed endoscopy and pathology records of potential cases; subjects were included if the endoscopist clearly described a visible length of columnar-type epithelium proximal to the gastro-esophageal junction/gastric folds, a biopsy was performed, and the biopsy showed specialized intestinal epithelium.

Controls

Population controls were eligible KPNC members without a diagnosis of Barrett's esophagus before the index date. Controls were randomly selected from the at-risk members of the entire KPNC membership roster using risk set sampling frequency matched to the cases by sex, age at the index date, and home medical facility.[19]

Exposure measurements

All study subjects completed (most commonly at the subject's home): an in-person interview that included questions about GERD symptoms and medication use (both historically and in the year prior to diagnosis)[20]; a validated food frequency questionnaire (the Block 1998, full length); phlebotomy; and anthropometric measurements. Subjects reported main exposures for the year prior to the index date. Additional data on demographics, medical history, and medication use were collected from electronic databases.

Aspirin/NSAID "users" were persons who, based on self-reported data, used either aspirin or NSAIDs at least weekly in the year prior to the index date. Subjects were asked to consider both prescription and over the counter medications when responding, "non-users" for the main analyses were defined as persons with less than weekly use of either aspirin or NSAIDs in the past year. Among users, total intake was calculated using the product of duration and average frequency of use, dose information was not collected. Average frequency was estimated using intake in the year prior to the index date. The duration of use was the interval between the age at initiation of regular use (defined as use at least once a week for more than 1 year) and the index date. High level intake was defined as at least weekly use for more than 5 years duration, medium level intake was defined as at least weekly use for 1 year to 5 years duration, and low level intake was less than weekly use for 1 year to 5 years. "Non-users" for the total intake analyses were defined as persons who reported no use of either aspirin or NSAIDs in the past year.

Statistical Analysis

Unconditional logistic regression was used to analyze the association between aspirin and/or NSAID use and Barrett's esophagus; results are presented as odds ratios (OR) with 95% confidence intervals (CI's). All tests of statistical significance are 2-sided.

We evaluated as potential confounders: sex, race (white vs. non-white), age, education (< college vs. at least some college), smoking status (ever vs. never smoker), alcohol use, body mass index, waist circumference, total fat intake, vitamin use (>2 years use vs. less or none), statin use (rx year before reference date vs. none), history of prior cardiovascular disease (history of acute coronary syndrome, ischemic or hemorrhagic stroke, MI, CABG, peripheral arterial disease, or heart failure), H. pylori status, an index of anti-oxidant intake from diet and supplements, total fruit and vegetable servings, serum ferritin level, GERD symptoms, and a co-morbidity index (the DxCG score[21,22]).

None of the potential confounders evaluated altered the OR by 10%; therefore, we included in the main models only those variables previously studied with a known or probable association with aspirin use, Barrett's esophagus or esophageal adenocarcinoma (race, smoking, ferritin, H. pylori status, GERD, and cardiovascular disease history), and frequency matched variables (age and sex). Effect modification was assessed using cross product terms in the logistic regression models as well as by evaluation of stratum-specific ORs. Interactions were considered present if the p-value of the beta coefficient on the cross-product term was <0.1. Analyses which combined use of either aspirin or non-aspirin NSAID evaluated the agent with the greatest duration or total intake in each person. The study and analyses were approved by the institutional review board. All analyses were performed using SAS v9.1 statistical software (SAS Institute, Cary, NC).

Supplemental Analyses

We explored whether the severity of GERD symptoms, instead of simply the presence of any GERD symptoms, had an effect on the association between Barrett's esophagus and aspirin or NSAID use. GERD of at least moderate severity was defined as at least weekly heartburn or acid regurgitation that could not be ignored, but that did not affect the person's lifestyle; any GERD was defined as any heartburn or acid regurgitation in the last year. Since aspirin and NSAIDs may act through different mechanisms and some subjects may use both, we also evaluated separately effects of aspirin only (among persons not using NSAIDs) and NSAIDs only (among persons not using aspirin). We also evaluated whether the associations varied by Barrett's esophagus segment length (<3cm vs. ≥3cm).

RESULTS

The baseline characteristics of the cases and controls were similar (Table 1), except that cases were more likely to smoke ($p=0.005$), to consume fewer daily servings of fruits and vegetables ($p=0.004$), to have GERD symptoms ($p<0.0001$), to have lower serum ferritin levels ($p<0.0001$), and to lack antibodies to *Helicobacter pylori* ($p=0.0005$).

Weekly Aspirin or NSAID Use

Persons with Barrett's esophagus were less likely to use aspirin than were all population controls (OR=0.59, 95% CI 0.39–0.87). The inverse association between aspirin use and Barrett's esophagus was stronger among the cases and population controls with GERD symptoms (OR=0.49, 95% CI 0.32–0.75; p-value interaction term for GERD symptoms=0.004). Analyses of cases and controls without GERD provided unstable

estimates with wide confidence intervals (aspirin OR: 2.39, 95% CI 0.84–6.82 and NSAIDs OR: 3.9, 95% CI 1.10–13.77), given few Barrett's esophagus patients (n=22) lacked GERD symptoms. Thus, for the subsequent analyses, we only present results for cases and population controls who reported GERD symptoms (Tables 2 and 3).

There was a nonsignificant inverse trend between NSAID use and the risk of Barrett's esophagus (OR=0.74, 95% CI 0.47–1.16), among cases and controls with GERD symptoms. The association observed between Barrett's esophagus and combination use (either aspirin and/or non-aspirin NSAIDs) was similar to that found for weekly users of aspirin (OR=0.53, 95% CI 0.35–0.81).

Duration of Use

The magnitude of the association between Barrett's esophagus and aspirin use did not differ by duration of use alone, separate from total use (1 year – <5 years, 5–10 years or greater than 10 years) (Table 3). There was a significant test for trend across all duration categories for aspirin, including nonusers (P-trend 0.003), although not among analyses confined to those using aspirin, for at least one year (p=1.0). Neither test for trend was significant for non-aspirin NSAID users.

Total Intake (Combination of Frequency and Duration)

The risk of Barrett's esophagus was significantly lower among persons with moderate total aspirin intakes (at least weekly use for <5 years; OR=0.41, 95% CI 0.23–0.73) and high total intakes of aspirin (>=weekly use for >5 years; OR=0.46, 95% CI 0.26–0.79), but not among persons with low total intakes (<weekly use for <5 years; OR=0.58, 95% CI 0.28–1.24) (Table 4). The result for the use of either aspirin or NSAIDs was similar to that of aspirin use alone. For NSAID use alone, a significant association was observed only at the lowest level of use (OR=0.54, 95% CI 0.32–0.90). There was a significant test for trend in analyses across all intake categories for aspirin, including nonusers (P-trend 0.001), although not among analyses confined only to aspirin users (p=.7). Neither test for trend was significant for non-aspirin NSAID users.

Interaction

There was no statistically significant evidence of interaction between age, sex, smoking, race, or H. pylori status and the main predictors (at least weekly aspirin, NSAIDs, or combination use) in any comparisons of Barrett's to population controls (with GERD), with the exception of H. pylori. The association between aspirin use and Barrett's esophagus was stronger among people who were H. pylori antibody negative (OR=0.54, 95% CI 0.35–0.84) than among people who were H. pylori positive (OR=0.82, 95% CI 0.30–2.23; p-value interaction =0.004). There was no significant interaction present between H. pylori and NSAID use (p=0.17).

Supplemental Analyses

The significant inverse association between Barrett's esophagus and aspirin use persisted in analyses limited to aspirin only users (no reported NSAID use) (OR=0.58, 95% CI 0.37–0.93). Similarly, a lack of significant association between Barrett's and NSAID use persisted

in analyses limited to non-aspirin NSAID only users (no reported aspirin use) (OR=0.93, 95% CI 0.52–1.67) (Table 4). Similar models that adjusted for, rather than stratified by, the use of the other medication (aspirin or NSAIDs) resulted in comparable associations (data not shown). The subsets of cases that were aspirin only or non-aspirin only users were 87 and 54, respectively. There were 95 and 44 controls in each of those categories, respectively. The results were similar when stratified or adjusted for GERD symptom severity compared with the baseline model of GERD as a yes/no variable.

The associations were comparable for persons with short segments (<3cm) (e.g. weekly aspirin use OR=0.57, 95% CI 0.34–0.95) vs. long segments (≥3cm) of Barrett's esophagus cases vs. population controls with GERD (OR=0.66, 95% CI 0.42–1.03). Analyses which excluded from the "nonuser" group those with infrequent use (< 1/week) also provided similar results (data not shown).

DISCUSSION

We found a lower risk of Barrett's esophagus among persons with a prior use of aspirin or NSAIDs, particularly among persons who reported GERD symptoms. The risk of Barrett's esophagus was lowest among those with at least moderate to high total use, and the associations were primarily related to aspirin use; no strong or consistent significant associations were found among persons who only used NSAIDs, raising the possibility of a difference between these two classes of medications.

The current study is the first population or community-based study in the United States, to our knowledge, to specifically evaluate the association between aspirin and NSAID use and the risk of Barrett's esophagus. A recent case-control study compared BE patients to controls that had undergone an EGD.[16] In that study, the authors found that aspirin, but not non-aspirin NSAIDs, was associated with a reduced risk of BE compared with other patients who had received an upper endoscopy; however, no comparisons were available with population-based controls. Two prior population-based studies in other countries have evaluated aspirin use and Barrett's esophagus, although they had conflicting results. One conducted in Ireland found an inverse association between Barrett's esophagus and aspirin use; but no difference among various durations or frequencies of use.[10] In contrast, an Australian study found no significant association between aspirin use and BE. [23] Other previous studies, to our knowledge, have analyzed the association of these medications only with the development of esophageal adenocarcinoma[7,9] or have used convenience samples and endoscopy controls, without population controls.[16,24–26]

Our findings for aspirin are fairly similar to those found in a recent individual-level pooled analysis of esophageal adenocarcinoma studies[12], in which weekly aspirin users had a significantly reduced risk of EAC (OR=0.77; 95% CI 0.59–0.99); similar associations were found in a separate meta-analysis of all published studies of esophageal adenocarcinoma[8]. Our risk estimate of 0.49 (95% CI 0.32–0.75) for weekly aspirin use for Barrett's esophagus raises the question of whether much of the association between aspirin use and esophageal adenocarcinoma may be explained by aspirin's association with Barrett's esophagus.

An inverse association between aspirin/NSAID use and Barrett's esophagus is biologically plausible. Aspirin/NSAID use is associated with a reduction in the risk of other cancers and precancerous lesions, such as colon adenomas;[27–30] however, adenomas already represent a dysplastic condition and less is known about how aspirin/NSAIDs may modify the development of metaplasia, such as is found with Barrett's esophagus. Potential mechanisms for modifying a metaplastic response to inflammation include the inhibition of prostaglandin production.[31] Supporting this hypothesis, animal models of reflux suggest that anti-inflammatory medications can both decrease the risk of esophagitis resulting from reflux-induced damage and the risk of Barrett's-like changes.[32,33] The mechanisms of action for aspirin and other NSAIDs are different, however, and our results and those of other recent studies suggest that they may have different effects on prevention of BE. [8,16] The exact biologic mechanism of chemoprevention for each agent is not known, though it may be related to differing inhibition of cyclooxygenase 1 vs. cyclooxygenase 2, or differences in modification of other pathways that modify cell growth, apoptosis or angiogenesis;[34,35] such differences have resulted in biologic differences between these classes of agents for other conditions, such as cardiovascular disease.[36]

There are several limitations to the current study. First, we cannot exclude the possibility of uncontrolled confounding. Patients with GERD symptoms, especially those who have sufficient symptoms to undergo endoscopy, may be less likely to take aspirin/NSAIDs than the average population; however, we saw no evidence for this in the current study. On the contrary, among our population controls, those with GERD symptoms were somewhat more likely than those without such symptoms to report at least weekly aspirin use (42% vs. 32%) and there was no difference in unadjusted weekly aspirin use in all cases compared with all population controls (38% vs. 41%, p-value=0.4). This suggests GERD symptoms alone did not deter people in our population from taking aspirin; this is similar to findings from a previous study.[37] Our findings could also be biased if the frequency of aspirin use among our study population differed from the general population. However, a recent national population-based survey reported that 35% of adults in the United States use aspirin daily or every other day.[38] Additionally, in a survey of over 7000 KPNC members aged 65 and older in 2005, 42% of male respondents aged 65–74 indicated they had taken aspirin to prevent stroke or heart attack in the past year.[39] These numbers are very comparable to the prevalence of at least weekly use in the last year among our cases (38%) and population controls (41%). In addition, we adjusted for a history of cardiovascular disease, the most commonly reported reason for use in that survey (74%), given its known associations with both aspirin use and Barrett's esophagus. [40] Our analyses of duration of use were limited, given the need to assume that current regular users had a consistent pattern of use from the reported start date until the current date. It is likely that the pattern of use fluctuated over time for at least some of the patients, therefore the current results may underestimate the observed effects if patients did not use aspirin/NSAIDs for periods of time; this would be more likely to influence analyses of longer intervals of use. By relying on self-reported data for medication use, a necessity to capture over the counter use, recall bias must be acknowledged. To minimize the effect, the cases and controls were not aware of the exact subject of the study when they were interviewed. We did not perform EGDs on the cases, therefore misclassification bias is possible, however given the rarity of BE and the fact that

controls were pulled from the general population, we believe it would be small. Finally, we do not know when Barrett's esophagus developed, only when the diagnosis was made; thus, we cannot assess the exact temporal relationship between aspirin/NSAID use and development of Barrett's esophagus. This is a limitation of all Barrett's esophagus studies and may influence the duration analyses.

There are several strengths to the current study. The cases all had a new diagnosis of Barrett's esophagus; thus, they were less likely to have enacted behavior changes that could alter measurement of the exposures. The medication use periods evaluated were all from prior to the diagnosis of Barrett's esophagus, minimizing the risk of protopathic bias (e.g. if the medications were started or stopped because of a diagnosis of the disease under study). The community-based nature of our population can also provide results that are more generalizable to the population at large, as the demographics of the studied population closely resemble those of the underlying population in the region.[17] Finally, the relatively large number of cases provided sufficient power to evaluate moderate differences in medication use.

In summary, aspirin use is inversely associated with the risk of Barrett's esophagus, compared to population controls, especially among persons with GERD symptoms. The association was strongest with moderate to high total dosages of use. There was no strong significant association between the risk of Barrett's esophagus and the use of non-aspirin NSAIDs. A clear understanding of where aspirin/NSAIDs may influence the neoplastic pathway is critical for the timing of potentially protective interventions. Aspirin has been suggested as a form of chemoprevention for patients with established Barrett's esophagus; however, this assumes that it acts by decreasing the risk of Barrett's esophagus progressing to cancer.[41] Given the strength of the associations between aspirin/NSAIDs and Barrett's esophagus are similar to those reported between aspirin use and esophageal adenocarcinoma overall, the prior positive findings with cancer may be at least partially explained by aspirin's associations with early events in esophageal carcinogenesis (i.e. inflammation and Barrett's esophagus) rather than solely with later events (i.e. progression of Barrett's esophagus to cancer). If true, this may decrease the hypothesized effectiveness of aspirin as a chemopreventive agent for persons with established Barrett's esophagus.

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Table 1

Characteristics of study groups

	Cases	Population Controls
	Number (%) or Mean (SD)	Number (%) or Mean (SD)
	(n=320)	(n=317)
Age	61.9 (11.0)	62.5 (10.3)
20–39	9 (3%)	9 (3%)
40–59	120 (37%)	105 (33%)
60–79	191 (60%)	203 (64%)
Race		
White	277 (87%)	268 (85%)
Black	5 (2%)	17 (5%)
Hispanic	25 (8%)	13 (4%)
Asian or Pacific Islander	4 (1%)	11 (3%)
Other	7 (2%)	7 (2%)
Unknown	2	1
Male	234 (73%)	214 (68%)
BMI (kg/m ²)	29.5 (6.1)	29.5 (5.8)
Waist circumference (cm)	100.8 (14.8)	99.1 (17.6)
Smoking status (ever smoked)	212 (66%)	176 (56%)
Statin use	108 (34%)	95 (30%)
Heart condition	67 (21%)	52 (16%)
Fruit and vegetable servings (daily)	4.2 (2.6)	5.0 (2.9)
H. pylori serum antibody (yes/no)	36 (12%)	67 (23%)
Serum ferritin (ng/mL)	116 (132)	156 (137)
GERD (any)	298 (93%)	193 (61%)
GERD (moderate severity)	239 (75%)	83 (26%)
Aspirin use (at least weekly in past year)	121 (38%)	131 (41%)
NSAID use (at least weekly in past year)	88 (28%)	80 (25%)

Table 2

Risk of Barrett's esophagus associated with frequency of nonsteroidal anti-inflammatory drug use

	Barrett's Esophagus/Population/ (with GERD symptoms)	Barrett's Esophagus vs. Population Odds Ratio (95% CI) *	Barrett's Esophagus vs. Population with GERD symptoms Odds Ratio (95% CI) **
Aspirin	n		
non users (referent < weekly use in last year)	199/186/97	1.0	1.0
At least weekly use in the past year	121/131/96	0.59 (0.39–0.87)	0.49 (0.32–0.75)
NSAID Use			
non users (referent)	232/237/137	1.0	1.0
At least weekly use in the past year	88/80/56	0.89 (0.58–1.36)	0.74 (0.47–1.16)
Aspirin or NSAID Use			
non users (referent)	145/142/70	1.0	1.0
At least weekly use in the past year	175/175/123	0.67 (0.45–0.97)	0.53 (0.35–0.81)

* Adjusted for age, sex, race, smoking, H. pylori, ferritin, CVD history, and GERD symptoms

** Adjusted for age, sex, race, smoking, H. pylori, ferritin, and CVD history

Table 3

Risk of Barrett's esophagus associated with duration of use (at least weekly use of aspirin or NSAIDs) (cases with GERD symptoms vs. population controls with GERD symptoms)

	Barrett's Esophagus/Population	Barrett's Esophagus vs. Population with GERD symptoms
	N	OR (95% CI)*
Aspirin Use		
non users (referent <weekly use in last year)	190/97	1.0
1 year - <5 years	43/38	0.46 (0.26–0.80)
5– 10 years	32/28	0.50 (0.26–0.96)
> 10 years	33/30	0.45 (0.23–0.86)
		P trend (includes non users)= 0.003 P trend (among users) = 1.0
NSAID Use		
non users (referent)	218/137	1.0
1 year - <5 years	44/29	0.71 (0.40–1.25)
5– 10 years	19/14	0.66 (0.29–1.49)
> 10 years	17/13	0.82 (0.34–2.00)
		P trend (includes non users) = 0.24 P trend (among users) = 0.9
Aspirin/NSAID Use		
non users (referent)	140/70	1.0
1 year - <5 years	64/47	0.51 (0.30–.87)
5– 10 years	46/36	0.50 (0.27–0.90)
> 10 years	48/40	0.48 (0.26–0.88)
		P trend (includes non users)= 0.005 P trend (among users) = 0.8

* Adjusted for age, sex, race, smoking, H. pylori, ferritin, and CVD hx

Table 4

Risk of Barrett's esophagus associated with total medication intake (cases with GERD symptoms vs. population controls with GERD symptoms)

	Barrett's Esophagus/Population	Barrett's Esophagus vs. Population with GERD symptoms
	n	OR (95% CI)*
<u>Aspirin Use</u>		
non users (referent no use in past year)	170/82	1.0
**		
Low	25/19	0.58 (0.28–1.24)
Med	44/44	0.41 (0.23–0.73)
High	58/48	0.46 (0.26–0.79)
		P trend (includes non users)= 0.001 P trend (among users) = 0.7
<u>NSAID Use</u>		
non users (referent)	180/101	1.0
Low	54/49	0.54 (0.32–0.90)
Med	34/26	0.59 (0.31–1.11)
High	29/17	0.82 (0.38–1.74)
		P trend (includes non users)= 0.12 P trend (among users) =0.24
<u>Aspirin/NSAID Use</u>		
non users (referent)	106/47	1.0
Low	45/30	0.67 (0.35–1.30)
Med	62/56	0.38 (0.21–0.67)
High	83/60	0.45 (0.26–0.80)
		P trend (includes non users)= 0.002 P trend (among users) =0.7

* Adjusted for age, sex, race, smoking, H. pylori, ferritin, and CVD hx

** Total intake low = <weekly use for <5 years; med = >weekly use for <5 years or weekly or less than weekly use for >5 years; high=>weekly use for >5 years