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Use of anti-inflammatory drugs and lower esophageal sphincter relaxing drugs and risk of esophageal and gastric cancers

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Abstract

Background and aims—The incidence of esophageal and gastric cardia adenocarcinoma has increased in western countries in recent decades for largely unknown reasons. We investigated whether use of lower esophageal sphincter (LES) relaxing drugs was related to an increased risk of esophageal and gastric cardia adenocarcinoma, and whether use of non-steroidal anti-inflammatory drugs was related to a reduced risk of esophageal and gastric cancers.

Methods—We examined these associations using administrative databases in a case-control study in two integrated health care delivery systems. Cases were incident esophageal adenocarcinomas (n= 163) and squamous cell carcinomas (n= 114), and gastric cardia (n= 176) and non-cardia adenocarcinomas (n= 320), diagnosed between 1980 and 2002 in one health system and between 1993 and 2002 in the other. Matched controls (n= 3996) were selected. Complete prescription information was available for the study period.

Results—Prescription of corticosteroids was associated with a decreased risk of esophageal adenocarcinoma (OR= 0.6, 95% CI= 0.4-0.9), esophageal squamous cell carcinoma (OR= 0.4, 95% CI= 0.2-0.6) and gastric non-cardia carcinoma (OR= 0.4, 95% CI=0.3-0.6). Ever use of pharmacy-purchased aspirin was associated with 30-60% decreased risks of the studied cancers. As a group, LES-relaxing drugs showed little evidence of association with increased risk of any esophageal or gastric cancer.

Conclusions—Corticosteroid and aspirin use were associated with significantly decreased risks of esophageal and gastric cancer. Lower esophageal sphincter relaxing drugs as a group did not affect

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these risks, although we had limited power to assess individual drugs. The possibility that corticosteroids and aspirin may reduce esophageal cancer risk warrants further consideration.

Introduction

The incidence of esophageal adenocarcinoma has markedly increased in the last few decades (1). The incidence per 100,000 person-years among white males in the United States rose from 0.7 in 1974-1976 to 3.2 in 1992-1994 (1). This increase was paralleled by an increase in the incidence of gastric cardia adenocarcinoma from 2.1/100,000 person-years in 1974-1976 to 3.3 in 1992-1994 (1). Interestingly, the incidence of esophageal squamous cell carcinoma slightly decreased during this period (1).

Risk factors for the two main subtypes of esophageal cancer differ. For adenocarcinoma of the esophagus, smoking, obesity and gastroesophageal reflux appear to be independent risk factors (2-4). The majority of esophageal adenocarcinomas arise from Barrett's esophagus, a precursor metaplasia resulting from chronic reflux (5). The use of drugs that relax the lower esophageal sphincter (e.g., nitrates, aminophyllin, β-receptor agonists, and benzodiazepines, among others) has been associated with risk of esophageal adenocarcinoma (6-8). Risk factors for esophageal squamous cell carcinoma include tobacco smoking and alcohol intake, but not gastroesophageal reflux.

In the stomach, risk factors for cardia adenocarcinoma are similar to those reported for esophageal adenocarcinoma (9), whereas risk factors for non-cardia adenocarcinoma include *Helicobacter pylori* carriage, ingestion of salted foods, and smoking, among others (2).

There is evidence that non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, may reduce the risk of esophageal cancer. A meta-analysis of epidemiological studies assessing the use of aspirin and other NSAIDs and risk of esophageal cancer found a significant 33% reduction in the risk of adenocarcinoma and a 42% reduction in the risk of squamous cell carcinoma (10). NSAIDs, including aspirin, were also shown in a meta-analysis to reduce the risk of non-cardia gastric cancer (11). Results for cardia carcinoma are less conclusive.

We conducted a case-control study using the pharmacy records of two integrated health care delivery systems in order to study the relation between the use of anti-inflammatory and LES-relaxing drugs and the risk of esophageal and gastric cardia cancers.

Methods

Study population

We conducted a case-control study using administrative databases linked to the populations served by the staff model component of two integrated health care delivery systems: Group Health Cooperative (GHC) in Seattle, and Henry Ford Health System's Health Alliance Plan (HFHS) in Detroit. These healthcare systems are part of the HMO Cancer Research Network, a consortium of research organizations affiliated with non-profit integrated healthcare delivery systems and the National Cancer Institute. Using comprehensive cancer registries maintained by these healthcare systems and feeding into the Surveillance, Epidemiology, and End Results (SEER) registries supported by the National Cancer Institute, all newly diagnosed cases of esophageal adenocarcinoma (n=163), gastric cardia carcinoma (n=176), esophageal squamous cell carcinoma (n=114), and gastric non-cardia carcinoma (n=320) since 1980 in GHC and since 1993 in HFHS, and through 2002 for both, were identified among all persons with at least three years of prior continuous membership in the two healthcare systems. The different starting dates allowed for maximum use of each center's computerized pharmacy records while

providing a minimum of three years exposure data for each subject. Subjects with a prior diagnosis of cancer (other than non-melanoma skin cancer) were excluded. From each healthcare system's base of enrolled individuals, 5 controls per case (n= 3996) were randomly selected and matched by age (2 year age strata), sex, health plan and duration of continuous enrollment in the health plan at the date of diagnosis of the case (2 year strata). For HFHS, cases and controls were also matched by race (White, Black, and Other). The index date was defined as the date of cancer diagnosis for cases and the same cutoff date for the matched controls. The study protocol was approved by the Institutional Review Boards of all participating institutions.

Drug information

Analyses focused on anti-inflammatory medications (i.e., corticosteroids, aspirin, and other NSAIDs), and on drugs affecting the lower esophageal sphincter pressure, such as benzodiazepines, antihistamines, or tricyclic antidepressants among others. We obtained the complete outpatient pharmacy records from both healthcare systems for cases and controls for the selected drugs. These included all prescriptions plus all non-prescription drugs dispensed at the health maintenance organization (HMO) pharmacy at GHC, and all prescriptions dispensed at HFHS. GHC provided records starting from 1977 while HFHS records were available from 1990. Both healthcare systems provided the composition of prescribed drugs. Ingredients were grouped into homogeneous categories and were further classified according to their more general effects: corticosteroids, all NSAIDs (including aspirin and non-aspirin NSAIDs), LES-relaxing drugs (beta-agonists, aminophyllin and related drugs, anticholinergics, antihistamines, benzodiazepines, calcium channel blockers, nitrates, tricyclic antidepressants), and proton pump inhibitors. For the main analysis, we considered all prescriptions up to one year prior to each case's and control's index date. Variables were created for analyses including: never/ever use of each particular ingredient and drug class, tertiles of numbers of fills, and tertiles of cumulative dose for selected drugs. All tertiles were based on the distribution among the control subjects matched with each cancer type studied. Cumulative dose was calculated for each drug using the number of pills per prescription times the dose of every specific ingredient per pill times the total number of prescriptions. Never users were defined as those having no prescription for the particular ingredient or drug class being examined in a given analysis.

Statistical Analysis

Odds ratios (ORs) with their 95% confidence intervals (CIs) were used to estimate the relative risk and were computed from conditional logistic regression models, matched by age, sex, healthcare system, years of enrollment in the healthcare system, and also for race at HFHS. Additionally, for each drug class examined, models were adjusted for ever-prescription of the other studied drug classes. Linear trends were tested in logistic regression models by including a single term for categorical exposures with values specified as median of tertiles cut-points of dose or number of prescriptions in the controls, using non-exposed subjects as the reference group. A lagged analysis excluding all drug prescriptions up to 5 years prior to each case's and control's index date was also performed.

Sensitivity analyses were performed to assess the possible impact of unmeasured potential confounders in this study (12). These analyses estimated the range of prevalences of smoking, obesity, and gastroesophageal reflux disease among subjects exposed and subjects unexposed to selected medications that would be necessary to produce the risk estimates observed in the present study if there were no true association between the medications and the disease, given estimates of association between these potential confounders and gastroesophageal cancers from previously published studies involving similar populations (4;13;14). Given the lack of published data, the prevalence of these factors among the non-exposed (to a given medication)

in the present study was assumed to be similar to that among controls in previously published studies assessing these factors in relation to gastroesophageal cancer (4;13;14). All analyses were conducted using Stata 9.2 (Stata Corp, College Station, Texas).

Results

Table 1 shows the demographic characteristics of cases and controls. Cases and controls showed no significant differences in gender, age, region or years of enrollment in the health plans, since these factors were individually matched in each case-control set. Among controls, 46% were ever prescribed a corticosteroid, 75% an NSAID (including aspirin), and 82% any LES-relaxing drug.

Table 2 shows the risk of the four types of studied cancers in relation to the use of prescribed drugs. Having at least one prescription of any corticosteroid was related to a significant reduction in the risk of esophageal adenocarcinoma (OR= 0.6, 95% CI= 0.4-0.9), esophageal squamous cell carcinoma (OR= 0.4, 95% CI= 0.2-0.6) and non-cardia gastric cancer (OR= 0.4, 95% CI= 0.3-0.6), and a non-significant reduction for gastric cardia carcinoma (OR= 0.7, 95% CI= 0.5-1.0). Results were similar for inhaled and oral corticosteroids, although an appreciable overlap existed between the two (data not shown). Having at least one prescription of any NSAID was also associated with decreased risks for the studied cancers. This decreased risk was accounted for primarily by aspirin use, which was associated with significantly decreased risks for esophageal adenocarcinoma (OR=0.6, 95% CI= 0.4-0.9), for cardia (OR= 0.4, 95% CI= 0.3-0.7) and non-cardia (OR= 0.5, 95% CI= 0.4-0.7) gastric cancers, and non-significantly for squamous cell carcinoma (OR= 0.7, 95% CI= 0.4-1.1). Other NSAID use did not appear to affect the risk of these cancers.

Prescription use of any LES-relaxing drugs was not related to any significant increase in the risk of esophageal or gastric cardia cancers, but was related to a decreased risk of gastric non-cardia adenocarcinoma (OR= 0.6, 95% CI= 0.4-0.8). The relation between individual LES-relaxing drugs and cancer risk varied according to the drug and type of cancer. Ipratropium bromide appeared to increase the risk of all cancers except esophageal adenocarcinoma, although risk estimates were imprecise. Prescriptions for benzodiazepines, nitrates, calcium channel blockers, and tricyclic antidepressants were inversely associated with both cardia and non-cardia gastric cancers. Prescriptions for theophyllin appeared to increase the risk for esophageal squamous cell carcinoma. When tertiles of number of prescriptions were assessed, corticosteroids showed a significant trend towards reduced risk for all cancers ($p \leq 0.03$ for all cancers), with the most apparent trends for esophageal squamous cell carcinoma and gastric non-cardia carcinoma (Table 2). Consistent statistically significant linear trends towards a decreased risk were also seen for all cancers in relation to the number of aspirin prescriptions filled. Subjects in the highest tertile of prescriptions of aspirin showed significant decreases in risk of esophageal adenocarcinoma (OR= 0.4, 95% CI= 0.2-0.7), gastric non-cardia carcinoma (OR= 0.4, 95% CI= 0.2-0.7), esophageal squamous cell carcinoma (OR= 0.4, 95% CI= 0.2-0.9), and gastric cardia carcinoma (OR= 0.3, 95% CI= 0.2-0.5). Other NSAIDs did not show a trend for any of these four tumor types, and were related to a decreased risk of gastric non-cardia carcinoma only among the highest tertile of users (OR=0.5, 95% CI= 0.3-0.7). For LES-relaxing drugs, a non-significant increase in the risk of esophageal adenocarcinoma was seen among the highest tertile of users of beta agonists (OR= 1.4, 95% CI= 0.7-2.6), theophyllin (OR= 1.8, 95% CI=0.7-4.6), antihistamines (OR= 1.5, 95% CI= 0.9-2.5) and tricyclic antidepressants (OR= 1.3, 95% CI= 0.6-2.5); but no major increases in risk were seen for gastric cardia carcinoma (i.e., the other reflux-related cancer). There was a significant trend towards an increased risk of esophageal squamous cell carcinoma in relation to the number of theophyllin prescriptions. Significantly decreased risks of gastric non-cardia cancers were seen for the highest tertile of users of several LES-relaxing drugs (beta-agonists, antihistamines,

benzodiazepines, calcium channel blockers, nitrates, and tricyclic antidepressants). Several drugs showed significant inverse trends, especially for gastric cancers. Table 3 shows the risks of the four cancers associated with the cumulative dose of individual drugs with at least 10 users among cases: aspirin, diazepam and amitriptyline. Associations with cumulative dose of aspirin were similar to those observed with number of prescriptions of aspirin. The highest tertile of cumulative dose of the benzodiazepine diazepam was related to an increase in the risk of esophageal adenocarcinoma (OR= 2.2, 95% CI= 1.1-4.4) and esophageal squamous cell carcinoma (OR=2.8, 95% CI= 1.2-6.8), but not of gastric cardia or non-cardia cancers.

Proton pump inhibitors (PPI) (e.g., omeprazol) are used to treat gastroesophageal reflux symptoms. PPI use was associated with an increased risk of esophageal adenocarcinoma (OR= 2.1, 95%CI= 1.0-4.6), most likely as a marker of severe GERD, but was not associated with any significant risk of the other cancers. Adjustment for PPI use in the models had little impact on the risk estimates observed for corticosteroids or aspirin, with an OR of 0.6 (95%CI= 0.4-0.9) and 0.6 (95%CI= 0.4-0.8) respectively in relation to esophageal adenocarcinoma. Adjusted results for the other tumors were also unchanged (data not shown). We conducted an alternative analysis restricted to non-users of PPI that likely excluded most subjects with severe GERD. This analysis yielded results similar to those reported in Table 2, which did not take PPI use into account (data not shown).

We conducted sensitivity analyses in order to assess the possible effect of unmeasured confounding by obesity, smoking, and GERD. Based on the literature (4), we assumed a relative risk of 2 to 3 from BMI greater than 25 in men or 24 in women in relation to esophageal adenocarcinoma, and a prevalence of obesity of 40% among non-users of corticosteroids or aspirin. Based on these assumptions, a prevalence of obesity among corticosteroid or aspirin users would need to be as low as 4% to fully explain the results of our study. The literature suggests that smoking is related to a 3 to 5-fold increased risk of esophageal squamous cell carcinoma, and that ever-smoking prevalence among non-users of corticosteroids is close to 65% (14). A prevalence of ever-smoking of 6% among users of corticosteroids would be necessary to explain the observed association between corticosteroid use and esophageal squamous cell carcinoma in our study. To explain through confounding by unmeasured smoking the association seen for theophyllin use and esophageal squamous cell carcinoma, the prevalence of smoking among users of theophyllin would need to exceed 90%. Experiencing frequent GERD symptoms (>105 episodes per year) conferred a 4.5-fold increased risk of esophageal adenocarcinoma and was observed in up to 25% of control subjects from a population similar to ours (15). In order for GERD symptoms to be responsible for the association seen in our study between corticosteroid or aspirin use and risk of esophageal adenocarcinoma, GERD prevalence among users of these drugs would need to be a very low 4%.

Finally, we also performed a 5-year lag-time analysis of the risks of the four cancers associated with major categories of drugs (e.g., corticosteroids, NSAIDs, LES-relaxing drugs). Risks that were decreased in the previous analyses (which excluded only the 1 year prior to the index date) tended to be more so in these 5-year lagged analyses, but with wider confidence intervals. In this alternate analysis, LES-relaxing drugs showed no evidence of an increase in risk of any of the studied cancers (data not shown).

Discussion

In this case-control study using population-defined administrative databases, we found an inverse association between prescription of anti-inflammatory medications, especially corticosteroids and aspirin, and the risk of esophageal and gastric cancers, with significant dose-response trends. As a group, drugs that relax the lower esophageal sphincter were not

related to increased risk of the reflux-related cancers, although a dose-response trend for esophageal squamous cell carcinoma was seen among theophyllin users.

To our knowledge, only one study to date has assessed the risk of esophageal cancer in relation to the use of corticosteroids (16). That records-based study, performed in a cohort of corticosteroids users in Denmark, observed a twofold increase in risk of esophageal cancer. In contrast, recent animal experimental research on corticosteroids, and especially on inhaled budesonide, has suggested that budesonide could reduce oxidative stress and act as a lung cancer chemopreventive drug in mice (17). In our study, corticosteroids appeared to be inversely associated with both esophageal carcinomas and gastric carcinomas.

Previous evidence supports a protective effect of aspirin and other NSAIDs for esophageal and gastric cancers. A meta-analysis of studies assessing use of aspirin or NSAIDs and risk of esophageal cancer, including seven case-control and two cohort studies, for a total of 1813 esophageal cancer cases (adenocarcinoma and squamous cell carcinoma), found combined summary risk estimates of esophageal cancer of 0.50 for ever use of aspirin versus never, and 0.75 for any use of other NSAIDs versus none (10). In contrast, a recent case-control study nested within the General Practitioners Research Database in the UK (18) found no evidence of a significant protective effect of aspirin or other NSAIDs for esophageal cancer. However, the exposure window in that study may have been too short to adequately assess this relationship. Interestingly, subjects that had used aspirin or other NSAIDs for more than 3 years showed slightly decreased risks of esophageal cancer. A randomized clinical trial conducted in high risk patients in China that assessed the effect of the NSAID celecoxib on the risk of progressing from esophageal dysplasia to esophageal carcinoma also found no evidence of a protective effect (19). However, the study did not evaluate the effect of aspirin, which has been reported to have a stronger protective effect in most studies. A meta-analysis assessing the risk of gastric cancer showed a protective effect for both aspirin and other NSAIDs, the protection being stronger among regular users and for non-cardia cancers (20). In the present study, we found stronger inverse associations for aspirin than for other NSAIDs for the four types of esophageal and gastric cancer studied. Additionally, we found consistent dose-response relationships between aspirin, but not other NSAIDs, and all four cancers.

Inflammation has been shown to play an important role in carcinogenesis of the digestive tract (21). Over-expression of COX-2 has been one of the identified culprits and efforts have been made to study the efficacy of COX-inhibiting drugs on the risk of digestive cancers. Non-selective COX drugs (e.g., aspirin, sulindac) and COX-2 selective drugs (e.g., celecoxib, rofecoxib) have been shown to decrease the risk of colorectal cancer (21) or of conditions closely related to it (i.e., polyps in familial adenomatous polyposis) (22). Our results are in general accord with the inflammation-driven carcinogenesis hypothesis, as both corticosteroids and NSAIDs (including aspirin) are potent anti-inflammatory drugs, albeit through different mechanisms.

Drugs favoring reflux have been hypothesized to increase the risk of adenocarcinoma through the induction by reflux of premalignant dysplastic changes in the esophageal and gastric-cardia mucosa. Most, but not all, studies have found evidence of increased risk of esophageal adenocarcinoma in relation to LES-relaxing drugs, especially aminophyllin, beta receptor agonists, anticholinergics and tricyclic antidepressants (6-8;23). In our study, most risk estimates for esophageal cancers were close to unity. We did, however, find a suggestion of increased risk of esophageal carcinomas for some of the LES-relaxing drugs, especially among the heaviest users, but without a clear dose-response relationship. Carcinogenesis related to reflux probably requires a long period of exposure to allow for progression to metaplasia, then dysplasia, and finally invasive cancer (2). The exposure window in our study might have been too short to detect such increased risks. We found a decrease of non-cardia gastric cancer risk

associated with the use of most LES-relaxing drugs that, to our knowledge, has not been previously reported and requires further study.

Our study has some limitations. Most importantly, we lacked information on potential confounders such as BMI, gastroesophageal reflux, and smoking. We conducted sensitivity analyses to examine the potential impact of this issue. For example, we found that the prevalence of BMI greater than 24 to 25 among users of corticosteroids or aspirin would need to be 4% in order to explain our results through confounding by unmeasured obesity. Given that overweight/obesity in the general population is likely to be close to 40% (4), such a large difference in overweight/obesity prevalence (40% vs. 4%) is unlikely because (a) corticosteroid use may in fact contribute to obesity (i.e., Cushing's syndrome), and (b) while corticosteroids are used to treat, among other indications, pulmonary emphysema, which is more common among lean subjects (24), they are also used for asthma and chronic bronchitis, which are related to obesity (24). The other three studied cancers are less strongly related to obesity and, therefore, any confounding by obesity is likely to be even smaller. For smoking and GERD, the necessary differences in prevalence between exposure groups were similarly unlikely. Consequently, confounding by GERD, smoking or overweight/obesity is unlikely to explain the observed results, although some confounding by these factors is possible. Analyses accounting for PPI use also suggested that GERD is unlikely to be an important confounder in this study. Moreover, age, BMI, and smoking status did not substantially alter associations between use of medications, including LES-relaxing drugs, and risk of esophageal and gastric cardia adenocarcinomas in a previous case-control study (7) and there was no relation between NSAID use and education, BMI, or cigarette use in a prospective study of NSAID use and risk of progression of Barrett's esophagus (25). Also, aspirin was similarly protective for all four cancers studied, despite differences among these cancers in the predisposing conditions and their symptoms, suggesting that confounding by indication is unlikely. Moreover, other NSAIDs were largely unrelated to cancer risk, despite the likelihood that subjects avoiding aspirin would also avoid other NSAIDs. Similarly, neither antihistamines nor benzodiazepines, which were associated with increased risk of esophageal adenocarcinoma, are used to treat reflux-related conditions. On the other hand, confounding by smoking could, at least partially, explain the elevated risks of esophageal squamous cell carcinoma and gastric cancers found for theophyllin and ipratropium bromide. Theophyllin is used to treat chronic obstructive pulmonary disease, a condition related to smoking, and thus confounding by unmeasured smoking could account for a substantial part of the association between theophyllin and esophageal squamous cell carcinoma seen in our study.

In addition, the automated pharmacy database probably underascertains aspirin and NSAID use. Although these medications are frequently obtained over-the-counter from the healthcare system's pharmacy, and are thus recorded in the automated database, it is likely that much aspirin and other NSAIDs is acquired elsewhere and is not captured by this automated pharmacy database. Some subjects using non-prescription NSAIDs may have been misclassified in the reference (i.e., non-users) category. However, any such misclassification would tend to be non-differential by case status, diluting the true association between NSAIDs and aspirin (26): a survey on aspirin use done in 1993-1994 at GHC showed that the difference between self-reported use (including prescription and non-prescription drugs) and pharmacy database-ascertained use was similar among myocardial infarction cases and controls ($p= 0.9$) (S. Heckbert, personal communication). Other drugs assessed in the present study, with the exception of antihistamines, can only be acquired by prescription.

In our study, left censoring of some prescription data is likely, due to the time frames of the automated pharmacy databases. Nevertheless, this censoring is likely to be non-differential by case status and thus would tend to dilute the true estimates of the associations of drug use and upper gastrointestinal cancers.

We lacked the necessary data to match on race at GHC. Nevertheless we can infer the racial makeup of the GHC enrollees through the racial distribution of women enrolled in the Breast Cancer Screening Program, which is promoted to all GHC members (27). This subpopulation of the GHC base of enrollees is composed of 90% Whites, 4% Blacks, 4% Asian or Pacific Islanders, 1% Hispanic and 1% other races. The racial distribution of our 4 case groups, as described in Table 1, suggests that, while racial distributions varied somewhat across case groups, the large majority of Whites in each group and in the GHC membership as a whole would result, by chance, in cases being correctly matched by race to their controls. Moreover, we observed similar associations at GHC and at HFHS, where cases and controls were matched for race, suggesting that race was not an important confounder in this study. Finally, some associations may have occurred by chance due to multiple comparisons and the small number of subjects in some exposure categories.

On the other hand, our study has several strengths. The most important is the complete, detailed and accurate information on drug prescriptions obtained within a defined population base, including number, dose and timing of prescriptions for drugs other than non-prescription NSAIDs, for which we lacked information on purchases outside the healthcare system. These computerized, prospectively-collected drug records overcome possible recall bias associated with interview-based case-control studies. In addition, we have information on all prescription drugs purchased since 1980 by most of the cases and controls included in this study (i.e., GHC subjects), allowing for a long period of exposure and/or follow-up. It has been previously shown that the comprehensiveness of the automated prescription medication databases at GHC is very high: subjects in the closed group delivery system of GHC (100% of GHC subjects included in the present study) obtain more than 80% of their prescription medications at GHC pharmacies where the automated registry system is implemented (28;29). HFHS has 65% of its enrollees included in a closed group delivery system (28) and all subjects included in this study came from this closed group. To receive payment, HMO-contracted pharmacies, which include several major chains, must file a claim for each prescription filled. The payment incentive (i.e., the pharmacy does not get reimbursed and the patient does not receive subsidized medications unless a claim is filed) and the fact that members can use local pharmacies promotes the validity and completeness of the pharmacy data. We were also able to look at associations with the four types of esophageal and gastric cancers separately, which was not done in several previous studies. This study benefited from high quality case ascertainment provided by the SEER registry at GHC and from an ad-hoc registry feeding into the Detroit SEER program at HFHS.

In conclusion, corticosteroid and aspirin use were associated with significantly decreased risks of esophageal and gastric cancer. In contrast, lower esophageal sphincter relaxing drugs as a group did not affect these risks and no clear evidence was seen for individual drugs in that group, although we had limited power to assess the effect of most individual drugs. The possibility that corticosteroids and aspirin may reduce esophageal cancer risk warrants further consideration.

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The Cancer Research Network (CRN) consists of the research programs, enrollee populations and databases of 12 integrated healthcare organizations that are members of the HMO Research Network. The health care delivery systems participating in the CRN are: Group Health Cooperative, Harvard Pilgrim Health Care, Henry Ford Health System/ Health Alliance Plan, HealthPartners Research Foundation, the Meyers Primary Care Institute of the Fallon Healthcare System/University of Massachusetts, Kaiser Permanente in six regions: Colorado, Georgia, Hawaii, Northwest (Oregon and Washington), Northern California and Southern California, and Lovelace Health System. The 12 health plans, with nearly ten million enrollees, are distinguished by their long-standing commitment to prevention and research, and collaboration among themselves and with affiliated academic institutions.

The *overall goal* of the CRN is to increase the effectiveness of preventive, curative and supportive interventions that span the natural history of major cancers among diverse populations and health systems, through a program of collaborative research. This overarching aim of the CRN, coupled with the expertise of the investigative team, and geographically-dispersed population base, fosters efficient and effective research on variations in cancer prevention and treatment policies and practices.

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Table 1

Demographic characteristics of study subjects

	Controls* N (%)	Esophageal Adenocarcinoma Cases N(%)	Gastric cardia Adenocarcinoma Cases N (%)	Esophageal Squamous Cell Carcinoma Cases N (%)	Gastric Non-Cardia Adenocarcinoma Cases N (%)
Total No	3996	163	176	114	320
Sex					
Female	1266 (32)	22 (13)	39 (22)	58 (51)	125 (39)
Male	2730 (68)	141 (86)	137 (78)	56 (49)	195 (61)
Mean age (SD)	66.8 (12.5)	65.7 (12.1)	66.8 (11.8)	71.1 (10.0)	70.7 (13.4)
HMO					
Group Health Cooperative	3096 (77)	125 (77)	137 (78)	88 (77)	254 (79)
Henry Ford Health System	900 (23)	38 (23)	39 (22)	26 (23)	66 (21)
Race†					
White	590 (66)	157 (96)	157 (89)	87 (76)	237 (74)
Black	300 (33)	3 (2)	13 (7)	20 (18)	46 (14)
Other	10 (1)	3 (2)	6 (4)	7 (6)	37 (11)

*Cases and controls were individually matched for age (2 year age strata), sex, health plan and duration of continuous enrollment in the health plan (2 year strata). We present, however, all controls pooled, and thus, small differences of matching variables distribution are expected.

†Percentages of race among the controls are based on the total number of controls from Henry Ford Health System, since race information for controls was available only at this HMO. Race percentages for cases are based on cases provided by both HMOs.

Table 2

Ever/never use and number of prescriptions of selected drugs by tertiles and risk of Esophageal Adenocarcinoma, Gastric Cardia Carcinoma, Esophageal Squamous Cell Carcinoma and Gastric Non-Cardia Carcinoma

		Esophageal Adenocarcinoma (n= 163)			Gastric Cardia Adenocarcinoma (n= 176)			Esophageal Squamous Cell Carcinoma (n= 114)			Gastric Non-Cardia Adenocarcinoma (n= 320)		
	Tertiles of number of prescriptions *	**N Cases/ Controls**	**OR†**	**95% CI**	**N Cases/ Controls**	**OR†**	**95% CI**	**N Cases/ Controls**	**OR†**	**95% CI**	**N Cases/ Controls**	**OR†**	**95% CI**
Corticosteroids	None	104/417	1.0	Ref.	122/489	1.0	Ref.	85/282	1.0	Ref.	240/821	1.0	Ref.
	Ever use	59/398	**0.6**	0.4-0.9	54/391	0.7	0.5-1.0	29/288	**0.4**	0.2-0.6	80/775	**0.4**	0.3-0.6
	1st	23/152	0.7	0.4-1.1	34/173	1.0	0.6-1.5	16/122	0.5	0.3-0.9	38/333	**0.5**	0.4-0.8
	2nd	16/118	0.6	0.3-1.1	5/92	**0.3**	0.1-0.7	8/73	0.4	0.2-1.0	22/190	**0.5**	0.3-0.9
	3rd	20/128	0.8	0.4-1.4	15/126	0.8	0.4-1.5	5/93	0.2	0.1-0.6	20/252	**0.4**	0.3-0.7
	P for linear trend ‡		**0.03**			**0.01**			**0.0002**			**0.0000002**	
NSAIDs	None	56/222	1.0	Ref.	63/213	1.0	Ref.	42/135	1.0	Ref.	119/361	1.0	Ref.
	Ever use	107/593	0.8	0.5-1.1	113/667	0.6	0.4-1.0	72/435	0.7	0.4-1.1	201/1235	0.6	0.4-0.8
	1st	55/230	0.9	0.6-1.4	56/241	0.9	0.6-1.4	28/142	0.7	0.4-1.3	102/423	0.8	0.6-1.1
	2nd	24/167	0.5	0.3-1.0	32/205	0.6	0.3-1.0	26/145	0.8	0.4-1.6	64/396	**0.6**	0.4-0.9
	3rd	28/196	0.5	0.3-1.0	25/221	**0.5**	0.3-0.9	18/148	0.6	0.3-1.1	35/416	**0.4**	0.2-0.6
	P for linear trend ‡		**0.02**			**0.002**			0.1			**0.0000001**	
Aspirin	None	100/408	1.0	Ref.	110/393	1.0	Ref.	63/242	1.0	Ref.	186/651	1.0	Ref.
	Ever use	63/407	**0.6**	0.4-0.9	66/487	**0.4**	0.3-0.7	51/328	0.7	0.4-1.1	134/945	**0.5**	0.4-0.7
	1st	29/147	0.7	0.4-1.1	37/179	0.6	0.4-1.0	26/108	1.0	0.6-1.9	61/324	**0.6**	0.4-0.9
	2nd	19/125	**0.5**	0.3-0.9	11/152	**0.2**	0.1-0.4	16/117	0.6	0.3-1.2	48/311	**0.5**	0.3-0.8
	3rd	15/135	**0.4**	0.2-0.7	18/156	**0.4**	0.2-0.7	9/103	**0.4**	0.2-0.9	25/310	**0.3**	0.2-0.5
	P for linear trend ‡		**0.002**			**0.00002**			**0.009**			**0.0000002**	
Other NSAIDs	None	78/355	1.0	Ref.	86/380	1.0	Ref.	60/236	1.0	Ref.	167/667	1.0	Ref.
	Ever use	85/460	0.9	0.6-1.3	90/500	1.0	0.7-1.4	54/334	0.8	0.5-1.3	153/929	0.8	0.6-1.1
	1st	40/211	0.9	0.6-1.4	46/223	1.0	0.7-1.5	19/140	0.6	0.3-1.1	77/370	0.9	0.7-1.2
	2nd	19/106	0.9	0.5-1.6	26/127	1.1	0.7-1.8	13/80	0.8	0.4-1.7	48/246	1.0	0.7-1.5
	3rd	26/143	1.0	0.6-1.6	18/150	0.7	0.4-1.2	22/114	1.2	0.7-2.2	28/313	**0.5**	0.3-0.7
	P for linear trend ‡		0.8			0.4			0.7			**0.008**	
LES-relaxing drugs	None	39/170	1.0	Ref.	48/158	1.0	Ref.	30/87	1.0	Ref.	100/265	1.0	Ref.
	Ever use	124/645	1.1	0.7-1.7	128/722	0.8	0.5-1.2	84/483	0.7	0.4-1.3	220/1331	**0.6**	0.4-0.8
	1st	52/216	1.2	0.7-2.0	61/261	0.8	0.5-1.3	37/161	0.7	0.4-1.3	119/441	0.8	0.5-1.1
	2nd	45/206	1.3	0.7-2.2	42/219	0.9	0.5-1.5	24/148	0.7	0.5-1.5	55/428	**0.5**	0.3-0.7
	3rd	27/223	0.7	0.4-1.3	25/242	**0.5**	0.3-0.9	23/174	0.7	0.3-1.5	46/462	**0.4**	0.3-0.7
	P for linear trend ‡		0.2			**0.009**			0.4			**0.0000001**	
Beta agonists	None	132/612	1.0	Ref.	143/645	1.0	Ref.	98/420	1.0	Ref.	284/1166	1.0	Ref.
	Ever use	31/203	0.9	0.5-1.4	33/235	0.8	0.5-1.3	16/150	0.7	0.4-1.2	36/430	**0.5**	0.3-0.7
	1st	12/80	0.8	0.4-1.6	17/93	1.0	0.5-1.7	8/53	0.8	0.3-1.7	18/156	0.6	0.4-1.0
	2nd	5/58	0.5	0.2-1.2	3/62	**0.3**	0.1-0.9	3/46	0.4	0.1-1.5	13/139	0.5	0.3-1.0
	3rd	14/65	1.4	0.7-2.6	13/80	1.0	0.5-2.0	5/51	0.8	0.3-2.2	5/135	**0.3**	0.1-0.7
	P for linear trend ‡		0.9			0.5			0.3			**0.0002**	
Theophylline	None	149/741	1.0	Ref.	159/796	1.0	Ref.	101/516	1.0	Ref.	296/1408	1.0	Ref.
	Ever use	14/74	1.3	0.7-2.4	17/84	1.4	0.8-2.4	13/54	**2.2**	1.1-4.5	24/188	0.8	0.5-1.3
	1st	5/28	1.1	0.4-3.1	8/27	1.9	0.8-4.3	4/18	1.5	0.5-4.7	10/77	0.7	0.3-1.4

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		Esophageal Adenocarcinoma (n= 163)			Gastric Cardia Adenocarcinoma (n= 176)			Esophageal Squamous Cell Carcinoma (n= 114)			Gastric Non-Cardia Adenocarcinoma (n= 320)		
	Tertiles of number of prescriptions *	**N Cases/ Controls**	**OR** †	**95% CI**	**N Cases/ Controls**	**OR** †	**95% CI**	**N Cases/ Controls**	**OR** †	**95% CI**	**N Cases/ Controls**	**OR** †	**95% CI**
	2nd	3/23	0.9	0.3-3.0	6/31	1.4	0.5-3.4	3/15	2.0	0.5-7.4	9/49	1.2	0.6-2.5
	3rd	6/23	1.8	0.7-4.6	3/26	0.8	0.2-2.7	6/21	**3.7**	1.3-10.6	5/62	0.7	0.3-1.8
	P for linear trend ‡		0.4			0.2			**0.01**			0.5	
Antihistamines	None	69/330	1.0	Ref.	89/339	1.0	Ref.	52/204	1.0	Ref.	167/555	1.0	Ref.
	Ever use	94/485	1.2	0.8-1.8	87/541	0.7	0.5-1.1	62/366	1.0	0.6-1.8	153/1041	**0.6**	0.4-0.8
	1st	45/202	1.2	0.8-1.9	48/240	0.8	0.5-1.3	23/138	0.9	0.5-1.7	70/389	**0.6**	0.4-0.9
	2nd	17/130	0.8	0.4-1.5	22/137	0.7	0.4-1.2	20/104	1.3	0.6-2.4	43/316	**0.5**	0.4-0.8
	3rd	32/153	1.5	0.9-2.5	17/164	0.5	0.3-1.0	19/124	1.2	0.6-2.4	40/336	**0.5**	0.4-0.9
	P for linear trend ‡		0.3			**0.03**			0.5			**0.002**	
Benzodiazepines	None	118/544	1.0	Ref.	137/564	1.0	Ref.	18/349	1.0	Ref.	248/982	1.0	Ref.
	Ever use	45/271	0.9	0.6-1.3	39/316	**0.6**	0.4-0.9	36/221	1.0	0.6-1.5	72/614	**0.6**	0.4-0.8
	1st	18/95	1.0	0.5-1.7	23/143	0.8	0.5-1.3	11/95	0.6	0.3-1.2	33/261	**0.6**	0.4-0.8
	2nd	15/95	0.8	0.5-1.5	5/73	**0.4**	0.1-0.9	7/54	0.8	0.4-1.9	19/150	0.6	0.4-1.0
	3rd	12/81	0.8	0.4-1.5	11/100	0.6	0.3-1.1	18/72	1.7	0.9-3.1	20/203	**0.5**	0.3-0.8
	P for linear trend ‡		0.4			**0.02**			0.3			**0.001**	
Calcium channel blockers	None	134/619	1.0	Ref.	142/599	1.0	Ref.	82/371	1.0	Ref.	267/1079	1.0	Ref.
	Ever use	29/196	0.7	0.5-1.2	34/281	**0.6**	0.4-0.9	32/199	1.0	0.6-1.6	53/517	**0.5**	0.4-0.7
	1st	10/67	0.7	0.4-1.5	13/96	0.7	0.4-1.2	13/70	1.1	0.6-2.1	19/177	**0.4**	0.3-0.7
	2nd	9/60	0.8	0.4-1.6	12/100	0.6	0.3-1.2	14/60	1.5	0.8-2.9	17/164	**0.4**	0.2-0.7
	3rd	10/69	0.7	0.4-1.5	9/85	0.5	0.2-1.0	5/69	0.5	0.2-1.3	17/176	**0.4**	0.2-0.6
	P for linear trend ‡		0.2			**0.01**			0.6			**0.0002**	
Nitrates	None	118/588	1.0	Ref.	147/600	1.0	Ref.	97/391	1.0	Ref.	263/1104	1.0	Ref.
	Ever use	45/227	1.1	0.8-1.7	29/280	**0.5**	0.3-0.7	17/179	**0.5**	0.3-0.8	57/492	0.6	0.4-0.8
	1st	11/77	0.8	0.4-1.6	15/111	0.6	0.3-1.0	8/78	0.5	0.2-1.1	24/199	**0.5**	0.3-0.8
	2nd	20/81	1.4	0.8-2.4	5/76	**0.3**	0.1-0.8	1/41	0.1	0.0-0.9	16/137	**0.5**	0.3-0.8
	3rd	14/69	1.2	0.7-2.4	9/93	**0.4**	0.2-0.9	8/60	0.7	0.3-1.5	17/156	**0.5**	0.3-0.9
	P for linear trend ‡		0.3			**0.001**			**0.04**			**0.006**	
Tricyclic antidepressants	None	129/648	1.0	Ref.	150/648	1.0	Ref.	83/392	1.0	Ref.	276/1108	1.0	Ref.
	Ever use	34/167	1.0	0.7-1.6	26/232	0.5	0.3-0.8	31/178	1.3	0.8-2.1	44/488	**0.4**	0.3-0.6
	1st	17/62	1.6	0.9-2.9	7/91	**0.4**	0.2-0.8	12/63	1.5	0.7-3.2	20/186	**0.5**	0.3-0.8
	2nd	6/56	0.6	0.2-1.5	10/64	0.7	0.3-1.5	14/55	1.7	0.8-3.3	12/143	**0.4**	0.2-0.8
	3rd	11/49	1.3	0.6-2.5	9/77	0.6	0.3-1.2	5/60	0.6	0.2-1.7	12/159	**0.4**	0.2-0.7
	P for linear trend ‡		0.8			**0.05**			0.9			**0.00004**	
Ipratropium bromide	None	159/792	1.0	Ref.	170/859	1.0	Ref.	110/550	1.0	Ref.	314/1567	1.0	Ref.
	Ever use	4/23	1.3	0.4-3.9	6/21	**3.1**	1.1-8.8	4/20	3.1	0.9-9.9	6/29	2.0	0.8-5.3
Anticholinergics	None	146/722	1.0	Ref.	158/749	1.0	Ref.	99/459	1.0	Ref.	283/1311	1.0	Ref.
	Ever use	17/93	1.0	0.6-1.8	18/131	0.8	0.5-1.4	15/111	0.9	0.5-1.7	37/285	0.8	0.5-1.1

* Cut points for number of prescriptions tertiles were as follow: **esophageal adenocarcinoma**: corticosteroids <2, 2-5, >5, all NSAIDs: <4, 4-15, >15, aspirin: <1, 1-7, >7, other NSAIDs: <2, 2-5, >5, any LES relaxing drug: <3, 3-19, >19, beta agonists: >1, 1-4, >4, theophyllin: >1, 1-13, >13, anticholinergics: <1, 1-2, >2, antihistamines: <1, 1-4, >4, benzodiazepines: <1, 1-5, >5, calcium channel blockers:<7, 7-27, >27, proton pump inhibitors <1, 1-4, >4, tricyclic antidepressants: <2, 2-6, >6. **Gastric cardia adenocarcinoma**: corticosteroids <2, 2-5, >5, all NSAIDs: <5, 5-20, >20, aspirin: <2, 2-11, >11, other NSAIDs: <2, 2-6, >6, any LES relaxing drug: <4, 4-24, >24, beta agonists: >1, 1-4, >4, theophyllin: <2, 2-16, >16, anticholinergics: <1, 1-3, >3, antihistamines: <2, 2-4,

>4, benzodiazepines: <1, 1-5, >5, calcium channel blockers:<7, 7-27, >27, proton pump inhibitors <2, 2-5, >5, tricyclic antidepressants: <2, 2-8, >8. **Esophageal squamous cell carcinoma**: corticosteroids <1, 1-5, >5, all NSAIDs: <6, 6-20, >20, aspirin: <2, 2-8, >8, other NSAIDs: <2, 2-6, >6, any LES relaxing drug: <4, 4-20, >20, beta agonists: >1, 1-4, >4, theophyllin: >2, 2-17, >17, anticholinergics: <1, 1-2, >2, antihistamines: <1, 1-4, >4, benzodiazepines: <1, 1-5, >5, calcium channel blockers:<8, 8-28, >28, proton pump inhibitors <2, 2-5, >5, tricyclic antidepressants: <2, 2-7, >7. **Gastric non-cardia adenocarcinoma**: corticosteroids <1, 1-5, >5, all NSAIDs: <4, 4-15, >15, aspirin: <2, 2-7, >7, other NSAIDs: <2, 2-5, >5, any LES relaxing drug: <4, 4-21, >21, beta agonists: >1, 1-4, >4, theophyllin: >2, 2-17, >17, anticholinergics: <1, 1-3, >3, antihistamines: <1, 1-4, >4, benzodiazepines: <1, 1-5, >5, calcium channel blockers:<8, 8-28, >28, proton pump inhibitors <2, 2-5, >5, tricyclic antidepressants: <2, 2-7, >7.

† Based on conditional logistic regression analyses with matching factors: age, sex, HMO, years of enrollment in the HMO, race at HFHS and adjusted for use of drug classes other than the studied one

‡ Linear trends were tested by including a single term for categorical exposures with weights specified as terciles of dose or duration of use in the controls in logistic regression models, using subjects not exposed to the drugs of interest as the reference group.

Table 3

Cumulative dose of selected drugs by tertiles and risk of Esophageal Adenocarcinoma, Gastric Cardia Carcinoma, Esophageal Squamous Cell Carcinoma and Gastric Non-Cardia Carcinoma

		Esophageal Adenocarcinoma (n= 163)			Gastric Cardia Adenocarcinoma (n= 176)			Esophageal Squamous Cell Carcinoma (n= 114)			Gastric Non-Cardia Adenocarcinoma (n= 320)		
	Tertiles of cumulative dose*	**N Cases/ Controls**	**OR†**	**95% CI**	**N Cases/ Controls**	**OR†**	**95% CI**	**N Cases/ Controls**	**OR†**	**95% CI**	**N Cases/ Controls**	**OR†**	**95% CI**
Aspirin	None	100/408	1.0	Ref.	110/393	1.0	Ref.	63/242	1.0	Ref.	186/651	1.0	Ref.
	1	11/71	**0.4**	0.2-0.9	11/94	**0.3**	0.1-0.5	11/74	0.6	0.2-1.2	23/160	**0.4**	0.2-0.6
	2	17/82	0.6	0.3-1.1	10/96	**0.3**	0.1-0.5	13/68	0.8	0.4-1.8	30/168	**0.5**	0.3-0.8
	3	11/87	**0.3**	0.2-0.7	16/97	**0.4**	0.2-0.8	12/79	0.7	0.3-1.4	15/181	**0.2**	0.1-0.4
	P for linear trend ‡		**0.01**			**0.001**			0.3			**0.0000005**	
Diazepam	None	118/499	1.0	Ref.	137/515	1.0	Ref.	78/307	1.0	Ref.	247/883	1.0	Ref.
	1	8/38	1.1	0.5-2.4	8/42	0.8	0.4-1.9	6/24	1.2	0.5-3.4	13/82	0.7	0.4-1.3
	2	7/32	1.1	0.5-2.6	8/40	1.0	0.4-2.3	3/30	0.5	0.1-1.8	11/72	0.7	0.3-1.3
	3	17/38	**2.2**	1.1-4.4	7/40	0.8	0.3-1.8	12/28	**2.8**	1.2-6.8	16/81	1.0	0.5-1.7
	P for linear trend ‡		**0.04**			0.5			0.1			0.4	
Amitriptyline	None	129/547	1.0	Ref.	150/596	1.0	Ref.	83/333	1.0	Ref.	276/1007	1.0	Ref.
	1	4/20	0.9	0.3-3.0	2/28	0.3	0.1-1.2	4/21	1.0	0.3-3.3	4/65	**0.3**	0.1-0.8
	2	4/19	0.9	0.3-3.0	6/31	0.7	0.3-1.9	6/18	0.6	0.5-5.1	4/68	**0.3**	0.1-0.7
	3	1/19	0.2	0.0-0.9	3/32	0.4	0.1-1.3	3/22	0.9	0.2-3.2	5/66	**0.4**	0.1-0.9
	P for linear trend ‡		0.2			0.07			0.8			**0.001**	

* Cut points for cumulative dose tertiles were as follow: **Esophageal adenocarcinoma**: aspirin: <260g, 260-1600g, >1600g, diazepam: <150mg, 150-665mg, >665mg, amitriptyline: <860mg, 860-7044mg, >7044mg. **Gastric cardia adenocarcinoma**: aspirin: <320g, 320-1440g, >1440g, diazepam: <200mg, 200-964mg, >964mg, amitriptyline: <1500mg, 1500-9790mg, >9790mg **Esophageal squamous cell carcinoma**: aspirin: <390g, 390-2270g, >2270g, diazepam: <200mg, 200-763mg, >763mg, amitriptyline: <1500mg, 1500-6000mg, >6000mg. **Gastric non-cardia adenocarcinoma**: aspirin<400g, 400-2140g, >2140g, diazepam: <250mg, 250-942mg, >942mg.

† Based on conditional logistic regression analyses with matching factors: age, sex, HMO and years of enrollment in the HMO, and adjusted for use of drugs other than the studied one.

‡ Linear trends were tested by including a single term for categorical exposures with weights specified as terciles of dose or duration of use in the controls in logistic regression models, using the lower exposed category as the reference group