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Physical Activity and Esophageal and Gastric Carcinoma in a Large Prospective Study

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Abstract

Background—Few studies have investigated the relationship of physical activity to esophageal and gastric carcinoma according to histology and anatomic site.

Methods—This study prospectively investigated the association between physical activity and esophageal and gastric carcinoma in a cohort of 487,732 U.S. men and women, followed from 1995–1996 to December 31, 2003. All analyses were performed in 2007– 2008.

Results—During 8 years of follow-up study, 523 cases of esophageal carcinoma (149 squamous cell and 374 adenocarcinoma) and 642 cases of gastric carcinoma (313 cardia and 329 noncardia) were documented. Physical activity was associated with reduced risk of esophageal and gastric adenocarcinomas but was unrelated to esophageal squamous cell carcinoma. The inverse association with physical activity was strongest for gastric noncardia adenocarcinoma (multivariate relative risk [RR] for highest versus lowest physical activity level=0.62, 95% CI=0.44, 0.87). Relationships were weaker but evident for gastric cardia adenocarcinoma (RR=0.83; 95% CI=0.58, 1.19) and esophageal adenocarcinoma (RR=0.75; 95% CI=0.53, 1.06). No significant relationship with physical activity was observed for esophageal squamous cell carcinoma (RR=1.05; 95% CI=0.64, 1.74). Exclusion of cases diagnosed during the first 2 follow-up years did not change those estimates, indicating that the findings are not due to decreased activity levels among participants with undiagnosed cancer at entry.

Conclusions—Physical activity may play a role in the prevention of upper gastrointestinal tract adenocarcinomas. No association was seen between physical activity and esophageal squamous cell carcinoma.

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Introduction

Cancers of the esophagus and stomach are a major source of morbidity and mortality worldwide, resulting in an estimated 460,000 esophageal and 870,000 gastric cancer cases and more than 1,085,000 deaths each year.[1–4] Both cancers have a poor prognosis with a 5-year survival rate below 20%.[5,6] Esophageal cancer comprises two major histologic types: squamous cell carcinoma and adenocarcinoma, which have distinct etiologies.[7–9] For example, BMI is associated with increased risk of esophageal adenocarcinoma[10] but may be related to decreased risk of esophageal squamous cell carcinoma.[11,12] Increases in the prevalence of obesity in recent decades in conjunction with rising incidence rates of esophageal adenocarcinoma have provided epidemiologic support for a role of lifestyle factors in the etiology of upper gastrointestinal tract cancers.[13]

Gastric tumors are predominantly adenocarcinomas (>90%). Certain risk factors for gastric cancer differ by anatomic site.[8,14] For example, *Helicobacter pylori* has been associated with divergent risks of gastric cardia and noncardia adenocarcinomas.[14] In contrast, esophageal adenocarcinoma and gastric cardia adenocarcinoma are adjacent tumors that are difficult to distinguish clinically, and they share common risk factors such as gastroesophageal reflux disease (GERD).[15]

Similarities regarding certain clinico-epidemiologic features coinciding with particular differences in the etiology of upper gastrointestinal tract cancers highlight the importance of investigating associations according to histology and anatomic site. However, available epidemiologic investigations[16–20] of physical activity in relation to upper gastrointestinal tract cancers according to histologic type or anatomic location are limited, and results are not entirely consistent.

Only one previous study[17] found a significant inverse association between physical activity and esophageal adenocarcinoma. In contrast, one study[18] found no relationship between the two, and a third study[20] was suggestive of an inverse association with physical activity but considered adenocarcinomas of the esophagus and gastric cardia as a combined endpoint and did not focus on esophageal adenocarcinoma specifically. Likewise, a significant inverse relationship to physical activity was noted in only one[16] of two[16,17] available reports of gastric cardia adenocarcinoma, whereas physical activity showed a significant association with gastric noncardia adenocarcinoma in three[16,17,19] of four[16,17,19,20] previous investigations.

Taken together, the scant epidemiologic data available suggest an inverse relationship between physical activity and upper gastrointestinal tract adenocarcinomas. Information on physical activity in relation to squamous cell esophageal cancer is unavailable. Thus, in this large prospective study, physical activity in relation to esophageal and gastric carcinomas was investigated according to histologic type and anatomic location.

Methods

Study Population

In 1995–1996, AARP (formerly known as the American Association of Retired Persons) members numbering 566,402 aged 50–71 years and residing in one of six U.S. states (CA, FL, LA, NJ, NC, or PA) or in one of two metropolitan areas (Atlanta, GA, or Detroit MI) completed and returned a mailed questionnaire on medical history, diet history, and physical activity to initiate the NIH–AARP Diet and Health Study.[21] The study was approved by the Special Studies IRB of the U.S. National Cancer Institute.

Cohort Follow-Up Study

Study participants were traced by regular matching of the cohort database to the National Change of Address database maintained by the U.S. Postal Service and through processing of undeliverable mail, other address update services, and directly from participants. Vital status was ascertained by linkage of the cohort to the Social Security Administration Death Master File. Follow-up searches of presumed deaths in the National Death Index Plus provided verification and information on cause of death. For matching purposes, virtually complete data are available on first and last name, address history, gender, and date of birth. Social Security numbers are available for 85% of this cohort.

Endpoint Ascertainment

Incident cases of cancers of the upper gastrointestinal tract were identified by probabilistic linkage to the state cancer registries serving this cohort. The cancer registry ascertainment area was recently expanded by three states (TX, AZ, and NV) to capture cancer cases occurring among participants who moved to those states during the follow-up period. The North American Association of Central Cancer Registries certifies all 11 cancer registries from which follow-up cancer status was obtained. In a validation study comparing registry findings to self-reports and medical records, approximately 90% of all cancer cases in this cohort were validly identified using linkage to cancer registries.[22]

Cancers were identified by anatomic site and histologic code using the ICD for Oncology (ICD-O, second and third editions).[23] The endpoints considered were esophageal carcinoma (ICD-O C15) and gastric carcinoma (ICD-O C16). Esophageal carcinoma was further classified by histologic codes as squamous cell carcinoma (8050–8076) or adenocarcinoma (8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572). Gastric carcinoma was classified by tumor site as cardia adenocarcinoma (C16.0) or noncardia adenocarcinoma (C16.1–C16.9) when the histologic code unambiguously indicated an adenocarcinoma (8140–8576). Because of adjacent anatomic location,[15,24] the combination of esophageal adenocarcinoma and gastric cardia adenocarcinoma was also evaluated.

Assessment of Physical Activity

On the baseline questionnaire, participants were asked to report the average frequency (never; rarely; 1–3 times/month; 1–2 times/week; 3–4 times/week; and ≥5 times/week) during the past year that they engaged in activities of any type that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat. Although the measure of physical activity has not been directly validated and compared with reference instruments, a questionnaire similar to the one used in this cohort showed good reliability (percentage agreement=0.76; kappa=0.53) and reasonable validity (percentage agreement=0.71; kappa=0.40) as assessed by a Computer Science and Applications activity monitor.[25] The reliability and validity measures are comparable to other physical activity questionnaires.[26] Additional evidence of the validity of the physical activity instrument is its capability to predict lower risk of mortality from coronary heart disease.[27]

Statistical Analysis

Individuals with previously diagnosed cancer other than nonmelanoma skin cancer at baseline (n=52,561), those with emphysema (n=13,764), subjects with missing information on physical activity (n=5705), and those with missing or inconsistent information on smoking habits (n=6640) were excluded from the analyses. After these baseline exclusions, 487,732 participants (295,253 men and 192,479 women) remained to form the analytic cohort. Each participant accrued follow-up time beginning at the scan date of the baseline questionnaire and ending at the date of diagnosis of esophageal or gastric carcinoma, diagnosis of head or neck

cancer (as a diagnosis of one of those cancers would be associated with increased surveillance of the other sites), move out of the registry ascertainment area, death, or the end of the follow-up period on December 31, 2003, whichever occurred first.

Participants were divided into five categories according to their physical activity level: 0, <1, 1–2, 3–4, and ≥5 times/week. The group of subjects with the lowest physical activity level served as the reference group. Cox proportional hazards regression[28] was used to estimate hazard ratios and 95% CIs while controlling for multiple variables simultaneously. No departures from the proportional hazards assumption by age, calendar period, or duration of the follow-up period were observed.

Esophageal and gastric carcinoma risk was assessed in three models. One model adjusted for age and gender. A second model additionally adjusted for race/ethnicity; marital status; family history of any cancer; education; and intake of the combination of fruits and vegetables, red meat, and alcohol. A third model additionally adjusted for BMI. Tests of linear trend across categories were conducted by modeling the mean values of categories of physical activity as a single continuous variable in the multivariate model, the coefficient for which was evaluated using a Wald test.

In an additional analysis, upper gastrointestinal tract adenocarcinomas (i.e., esophageal and gastric adenocarcinomas) were combined. Because participants with esophageal and gastric adenocarcinoma could have decreased their level of physical activity due to disease-associated fatigue, the analyses were repeated excluding cases that were diagnosed during the first 2 follow-up years and excluding participants who reported poor health at study entry.

To examine whether the association between physical activity and risk of upper gastrointestinal tract adenocarcinomas was modified by other potential risk factors for esophageal or gastric adenocarcinomas, both stratified analyses and tests for multiplicative interaction were conducted. Physical activity, the variable of interest, and the products of physical activity and the variable of interest (the interaction terms) were modeled simultaneously; the significance of the latter was evaluated using a likelihood-ratio test. In a subset of study participants, an assessment was also made of whether relationships with physical activity were confounded or modified by use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antacids (the latter was considered a proxy measure of GERD). All analyses were conducted in 2007–2008 using SAS release 9.1.

Results

During 3,518,484 follow-up person-years between 1995 and 2003, a total of 523 esophageal and 642 gastric carcinomas were documented. About one third (28.5%) of esophageal carcinomas were squamous cell carcinoma and about two thirds (71.5%) were adenocarcinoma. Gastric carcinoma showed a fairly even split of 48.8% cardia and 51.2% noncardia adenocarcinomas.

The potential risk factors for upper gastrointestinal tract cancer across increasing levels of physical activity were evaluated to assess their potential for confounding (Table 1). Men and women who reported greater physical activity tended to be leaner, have graduated from college, be married, and smoke less than those who reported less physical activity. In addition, participants who were physically more active tended to have higher intakes of fruits, vegetables, and alcohol but a lower intake of red meat than their less-active counterparts.

The relationship of physical activity to esophageal carcinoma was examined according to its major histologic types (Table 2). No significant relationship with physical activity emerged for squamous cell carcinoma (multivariate RR comparing highest versus lowest physical

activity category=1.05; 95% CI=0.64, 1.74). In contrast, a significant inverse association was noted for esophageal adenocarcinoma in a multivariate model that did not include BMI (multivariate RR=0.68; 95% CI=0.48, 0.96). However, that relationship became nonsignificant after adjustment for BMI (RR=0.75; 95% CI=0.53, 1.06).

Next, the relationship of physical activity to gastric carcinoma was explored by anatomic site (Table 2). For gastric cardia adenocarcinoma, the age- and gender-adjusted RR comparing extreme physical activity categories was 0.62 (95% CI=0.44, 0.88). That association was slightly attenuated after multivariate adjustment that did not include BMI (RR=0.74; 95% CI=0.52, 1.06) and became nonsignificant in a further multivariate model that included BMI (RR=0.83; 95% CI=0.58, 1.19). In contrast, a significant inverse association was noted for gastric noncardia adenocarcinoma, regardless of whether the multivariate model included BMI (RR=0.62; 95% CI=0.44, 0.87) or did not (RR=0.61; 95% CI=0.43, 0.86).

Because no relationship had been noted between physical activity and esophageal squamous cell carcinoma, subsequent analyses were restricted to adenocarcinomas of the upper gastrointestinal tract (i.e., esophageal and gastric adenocarcinomas; Table 3). A significant inverse association was detected between physical activity and adenocarcinomas of the upper gastrointestinal tract that held after multivariate adjustment, with (RR=0.73; 95% CI=0.59, 0.89) or without (RR=0.67; 95% CI=0.55, 0.82) inclusion of BMI in the model. A similarly reduced risk was evident in the top four categories of physical activity. Addition of covariates representing use of antacids or NSAIDs had no impact on the risk estimates. The corresponding RRs comparing extreme physical activity categories were 0.72 (95% CI=0.55, 0.95) and 0.72 (95% CI=0.54, 0.96) after controlling for antacids and NSAIDs, respectively.

The inverse association between physical activity and upper gastrointestinal tract adenocarcinoma was comparable across subgroups defined by gender; age; smoking status; BMI; race/ethnicity; education; intakes of fruits and vegetables, red meat, and alcohol; and antacid and NSAID use (all p values for interaction were >0.05), indicating no meaningful effect modification (Table 3).

Results did not change materially after exclusion of all cases that occurred during the first 2 follow-up years (n=263 cases excluded), with a multivariate RR for the highest versus lowest category of physical activity of 0.67 (95% CI=0.53, 0.85). Findings also remained essentially unaltered when participants who reported poor health at baseline were eliminated (n=283 cases excluded; RR=0.65; 95% CI=0.51, 0.83).

Discussion

In this large prospective study of U.S. men and women, increased physical activity was associated with decreased risk of adenocarcinomas of the upper gastrointestinal tract. The inverse relationship with physical activity was strongest for gastric noncardia adenocarcinoma, but inverse associations were also evident for gastric cardia adenocarcinoma and esophageal adenocarcinoma. No relationship with esophageal squamous cell carcinoma was detected.

Similarly reduced risks were evident in the top four categories of physical activity. This finding suggests that the apparent protection provided by physical activity is reached at a very low threshold (i.e., any exercise versus no exercise is a benefit). Alternatively, noncausal mechanisms, such as residual confounding by a healthy lifestyle or confounding by unmeasured or unknown factors, may be responsible for the findings.

A strength of the present study was the availability of information on tumor histology and anatomic location, which allowed separate investigations of the association between various upper gastrointestinal tract cancer subsites and physical activity. Also, the prospective study

design minimized the possibility of differential recall of physical activity by participants with and without upper gastrointestinal tract cancer. Subjects with pre-existing cancer at baseline were excluded from the analyses in order to reduce the influence that malignant disease may have had on physical activity levels at study baseline. In secondary analyses, the potential for bias created by pre-existing but undiagnosed cancer was further curtailed by excluding the first 2 follow-up years and excluding participants with poor health status at entry. The substantial size of the cohort yielded sizeable numbers of esophageal and gastric cancer cases and generated ample statistical power and precision in estimating the dose–response relationship with physical activity.

Previous epidemiologic data concerning the relationship between physical activity and esophageal cancer are inconclusive. One cohort study of recreational physical activity[29] showed a relative risk for the combination of oral and total esophageal cancers of 0.46 (95% CI=0.11, 1.90; *p* for trend=0.05). Similarly, in one case–control study,[17] the OR for esophageal adenocarcinoma was 0.67 (95% CI=0.42, 1.09; *p* for trend=0.11) for high versus low levels of occupational physical activity. Another case–control study[20] used a mixed-case group of adenocarcinomas of the esophagus and gastric cardia cancers and showed a nonsignificant inverse relationship with recreational activity, but results were not shown. Further, two cohort studies[30,31] examined total esophageal cancer rates among mail carriers[30] and agricultural workers[31] and presented identical relative risk estimates of 0.5 (95% CI=0.3, 0.8) for subjects with high versus low physical activity levels, but individual-level physical activity data were not assessed.

In contrast, one case–control study[32] showed an apparent adverse effect of occupational physical activity on total esophageal cancer, reporting an OR of 0.7 (95% CI=0.3, 1.4) for low versus high activity level. Another case–control study[18] used a combination of recreational and occupational activity to determine physical activity levels and showed no association with esophageal adenocarcinomas, but the data were not shown.

The association between physical activity and gastric cancer also remains unsettled. Four case–control studies[16,17,32,33] and four cohort studies[19,29,31,34] found a significant[16,17,19,29,31,33] or nonsignificant[32,34] inverse relationship of physical activity to gastric cancer, with relative risk estimates ranging from 0.32 to 0.79. One case-series[35] study reported that people with gastric cardia cancer were less likely to be recreationally physically active than people with esophageal cancer (p=0.031), but it did not show actual risk estimates.

In contrast, two case–control studies[20,36] and four cohort studies[30,37–39] observed no association between physical activity and gastric cancer, and one early retrospective cohort study using occupational mortality data[40] reported a positive relationship between physical activity and gastric cancer but provided no data regarding the statistical significance of the results.

One possible reason for the heterogeneity in findings from previous investigations of physical activity in relation to upper gastrointestinal tract cancers is that analyses were not always carried out according to major histologic type or anatomic location. For example, studies could have missed an inverse association between physical activity and adenocarcinoma of the esophagus if physical activity is truly unrelated to esophageal squamous cell carcinoma but the case definition combined esophageal adenocarcinoma and squamous cell carcinoma. Failure to distinguish between histologic types of esophageal cancer hampers comparisons of risk estimates across studies.

An additional potential explanation for the inconsistencies in findings from previous studies of physical activity in relation to upper gastrointestinal tract cancers is imprecision related to the measurement of physical activity. It appears that investigations using more refined physical

activity instruments tended to uncover inverse relationships of physical activity with gastric cancer, whereas studies using rather crude assessments were less likely to detect an association. For example, four[16,17,19,29] of the five[16,17,19,29,33] studies that detected a significant inverse relationship between physical activity and gastric cancer provided detailed response options regarding the frequency, intensity, and duration of activity.

In contrast, detailed physical activity information was collected in only two[37,39] of the nine[20,30–32,34,36–39] studies that reported nonsignificant findings for gastric cancer. Of the remaining seven[20,30–32,34,36,38] nonsignificant studies, three studies[30,31,34] lacked an individual-level measure of physical activity because they were based on a comparison of groups of subjects with high versus low occupational activity, an approach that may have lacked precision; two studies[32,36] used cancers potentially related to physical activity as controls (e.g., liver and esophageal cancers), which may have introduced selection bias; one study[38] used college sports as an activity measure, which may not have encompassed the etiologically relevant time period of exposure; and one study[20] cannot be evaluated because it provided no information on the method of physical activity assessment. Inconsistent findings of previous investigations on physical activity and upper gastrointestinal tract cancers are not due to differences in study design (case–control versus cohort studies), sample size (large versus small numbers of cases), or type of physical activity studied (recreational versus occupational activity).

A potential limitation of the present study is related to the physical activity assessment,[41] which was self-reported as opposed to objectively measured, included only one measure at baseline, did not encompass activities of light intensity, and did not include the duration of physical activity. However, the physical activity tool was characterized by a reasonable level of detail because it requested information on the frequency of activities performed each week that reached or exceeded a certain threshold of intensity (i.e., increases in breathing or heart rate or working up a sweat) and activity duration (i.e., 20 minutes). In addition, because the data concerning physical activity were gathered before the diagnosis of cancer, any imprecision or misclassification of physical activity would tend to indicate a weaker rather than a stronger relationship between physical activity and upper gastrointestinal cancer.

The present study lacked data on antacid use (as a surrogate measure of GERD) in the full cohort, but antacid use had virtually no impact on the relationship of physical activity to upper gastrointestinal tract cancer in the subset of participants for whom information on antacid use was available. Residual confounding by GERD remains possible because antacid use represents a weak proxy measure of GERD and antacid use data used here were based on a rather crude binary response variable.

Another limitation of the study is the lack of control for confounding by *H. pylori* infection. Although there is no evidence for an association between physical activity and *H. pylori* infection,[42] physical activity tends to be positively correlated with SES, a variable that is inversely related to *H. pylori* infection. Thus, uncontrolled confounding by *H. pylori* infection could have caused a spurious apparent protective effect of physical activity on risk for gastric cancer in this data, even though estimates were controlled for education level as a surrogate measure of SES.

Increased physical activity may decrease the risk of upper gastrointestinal tract adenocarcinomas by preventing chronic inflammation. For example, endurance-trained athletes and subjects who regularly exercise exhibit decreased resting levels of inflammatory cytokines and C-reactive protein compared with habitually sedentary individuals.[43–46] Chronic inflammation plays a critical role in the etiology of esophageal and gastric

adenocarcinomas,[47–49] and nonsteroidal anti-inflammatory drugs are associated with decreased risk of gastric noncardia adenocarcinoma.[50]

Physical activity improves insulin sensitivity and lowers circulating insulin,[51] thereby enhancing insulin-like growth factor (IGF) binding protein-1, which reduces bioavailable IGF-1.[52,53] IGF-1 stimulates cell proliferation and inhibits apoptosis in gastric cancer,[54,55] and suppressed levels of IGF-1 increase expression of p53, a protein that is involved in DNA repair, cell cycle arrest, and apoptosis.[56] Physical activity may also decrease circulating leptin[57,58] independent of BMI,[59,60] although whether physical activity specifically reduces gastric leptin secretion or its expression in gastric tumor cells is unknown.

In conclusion, these prospective data suggest that increased physical activity plays a role in the prevention of upper gastrointestinal tract adenocarcinomas. No association was seen with esophageal squamous cell carcinoma. Further research is required to evaluate these findings in other populations and to elucidate possible biological mechanisms involved.

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Table 1

Baseline characteristics according to physical activity (% unless otherwise indicated)

Characteristic[a]	Physical activity (times/week)[b]				
	0	<1	1–2	3–4	≥5
Participants (*n*)	87,222	66,853	106,058	131,852	95,747
Age (years)	62.0	61.1	61.5	62.2	62.4
Gender					
Men	50.6	58.5	61.4	68.9	66.6
Women	49.4	41.5	38.6	37.1	33.4
Race					
White	89.2	91.5	92.3	91.6	92.4
Nonwhite	10.8	8.5	7.7	8.4	7.6
Smoking status					
Current smoker	20.7	17.1	14.2	10.2	9.4
Former smoker	44.8	48.0	49.0	52.5	53.7
Never smoker	34.5	34.9	36.8	37.3	36.9
BMI (kg/m^2)	28.6	27.8	27.2	26.6	26.0
College education	28.1	37.3	40.9	44.5	44.4
Married or living as married	62.1	68.4	70.8	72.5	73.8
Family history of cancer	50.6	51.8	51.4	51.2	50.9
Fruit and vegetable intake (servings/1000 kcal/day)	3.1	3.2	3.4	3.7	3.9
Red meat intake (grams/1000 kcal/day)	37.8	37.2	36.1	32.4	30.6
Alcohol intake (servings/week)	6.8	6.9	6.7	6.6	7.3
NSAID use[c]	49.4	52.4	51.9	52.3	49.3
Antacid use[c]	33.0	31.5	30.3	29.6	27.5

[a] All values (except age) were directly standardized to the age distribution of the cohort.

[b] Physical activity is defined as activity that lasted ≥20 minutes and caused either increases in breathing or heart rate or working up a sweat.

[c] Based on data from the subcohort of study participants for whom we had collected information regarding NSAID and antacid use

NSAID, nonsteroidal anti-inflammatory drug

Table 2

Relative risk (RR) of esophageal and gastric carcinoma by histology and anatomic site according to physical activity (95% CIs)

Variable	Physical activity (times/week)[a]					*p* for trend
	0	<1	1–2	3–4	≥5	
Person-years	616,503	482,118	767,821	957,476	694,566	
Squamous cell esophageal carcinoma (*n*=149)						
Number of cases	34	21	26	35	33	
Age- and gender-adjusted RR[b]	1.0	0.81 (0.47, 1.40)	0.61 (0.36, 1.01)	0.62 (0.39, 0.99)	0.79 (0.49, 1.27)	0.394
Multivariate RR without BMI[b]	1.0	0.95 (0.55, 1.65)	0.79 (0.55, 1.33)	0.91 (0.56, 1.48)	1.16 (0.70, 1.90)	0.484
Multivariate RR with BMI[b,c]	1.0	0.95 (0.55, 1.64)	0.78 (0.46, 1.31)	0.86 (0.53, 1.41)	1.05 (0.64, 1.74)	0.759
Esophageal adenocarcinoma (*n*=374)						
Number of cases	73	43	90	102	66	
Age- and gender–adjusted RR[b]	1.0	0.69 (0.49, 1.05)	0.85 (0.63, 1.16)	0.72 (0.53, 0.97)	0.60 (0.43, 0.84)	0.007
Multivariate RR without BMI[b]	1.0	0.71 (0.49, 1.04)	0.91 (0.66, 1.24)	0.80 (0.59, 1.09)	0.68 (0.48, 0.96)	0.072
Multivariate RR with BMI[b,c]	1.0	0.73 (0.49, 1.06)	0.94 (0.69, 1.29)	0.86 (0.63, 1.17)	0.75 (0.53, 1.06)	0.240
Gastric cardia adenocarcinoma (*n*=313)						
Number of cases	68	50	65	70	60	
Age- and gender-adjusted RR	1.0	0.89 (0.61, 1.28)	0.68 (0.49, 0.96)	0.56 (0.39, 0.78)	0.62 (0.44, 0.88)	0.002
Multivariate RR without BMI[b]	1.0	0.95 (0.66, 1.38)	0.77 (0.54, 1.08)	0.65 (0.46, 0.92)	0.74 (0.52, 1.06)	0.037
Multivariate RR with BMI[b,c]	1.0	0.98 (0.68, 1.42)	0.81 (0.57, 1.15)	0.71 (0.50, 1.00)	0.83 (0.58, 1.19)	0.147
Gastric noncardia adenocarcinoma (*n*=329)						
Number of cases	86	39	64	81	59	
Age- and gender-adjusted RR	1.0	0.59 (0.41, 0.87)	0.58 (0.42, 0.80)	0.55 (0.40, 0.74)	0.53 (0.38, 0.74)	0.001
Multivariate RR without BMI[b]	1.0	0.66 (0.45, 0.96)	0.67 (0.48, 0.93)	0.64 (0.47, 0.87)	0.61 (0.43, 0.86)	0.018
Multivariate RR with BMI[b,c]	1.0	0.67 (0.46, 0.98)	0.68 (0.49, 0.95)	0.65 (0.47, 0.89)	0.62 (0.44, 0.87)	0.024

[a] Physical activity is defined as activity that lasted ≥20 minutes and caused either increases in breathing or heart rate or working up a sweat.

[b] The multivariate model used follow-up person-years as the underlying time metric and included the following covariates: age (continuous); gender (women, men); a combination of smoking status (never, former, current); time since quitting for former smokers (>10 years, 5–9 years; 1–4 years, <1 year); and smoking intensity for former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes/day); race/ethnicity (white, black, Hispanic, other); education (<high school, high school, vocational school or some college, college graduate, postgraduate); marital status (married or living as married, other); family history of cancer (yes, no); intakes of fruits and vegetables combined (quintiles), red meat (quintiles), and alcohol (0, <1, 1–3, >3 servings/day).

[c] Adjustment for BMI included the following categories: <18.5; 18.5–24.9; 25.0–29.9; 30.0–34.9; 35.0–39.9; ≥40.0 kg/m^2.

RR, relative risk

Table 3

Multivariate relative risk of adenocarcinomas of the upper gastrointestinal tract according to physical activity

Variable	Number of cases	Physical activity (times/week)						
		0	<1	1–2	3–4	≥5	*p* for trend	*p* for interaction
All participants	1016	1.0	0.75 (0.60, 0.94)	0.81 (0.66, 0.98)	0.71 (0.58, 0.86)	0.73 (0.59, 0.89)	0.007	
Gender								
Men	865	1.0	0.72 (0.57, 0.91)	0.76 (0.62, 0.94)	0.67 (0.55, 0.81)	0.63 (0.51, 0.78)	<0.001	0.754
Women	151	1.0	0.87 (0.53, 1.44)	0.65 (0.40, 1.05)	0.65 (0.41, 1.07)	0.72 (0.44, 1.19)	0.131	
Smoking status								
Current smoker	191	1.0	0.77 (0.50, 1.19)	0.81 (0.55, 1.20)	0.58 (0.37, 0.90)	0.70 (0.43, 1.14)	0.924	0.368
Former smoker	622	1.0	0.74 (0.55, 0.99)	0.89 (0.69, 1.14)	0.79 (0.63, 1.01)	0.69 (0.53, 0.89)	0.951	
Never smoker	203	1.0	0.94 (0.58, 1.51)	0.64 (0.41, 1.01)	0.72 (0.47, 1.09)	0.89 (0.58, 1.38)	0.985	
Age at baseline (years)								
<65	503	1.0	0.71 (0.52, 0.96)	0.82 (0.63, 1.06)	0.68 (0.52, 0.89)	0.65 (0.48, 0.87)	0.008	0.567
≥65	513	1.0	0.85 (0.62, 1.17)	0.79 (0.60, 1.06)	0.79 (0.62, 1.04)	0.79 (0.59, 1.05)	0.172	
Race/ethnicity								
White	919	1.0	0.81 (0.64, 1.01)	0.82 (0.67, 0.99)	0.73 (0.60, 0.89)	0.74 (0.60, 0.92)	0.010	0.645
Nonwhite	97	1.0	0.57 (0.27, 1.23)	0.81 (0.44, 1.47)	0.82 (0.48, 1.42)	0.59 (0.30, 1.15)	0.316	
Education								
Some college or less	672	1.0	0.73 (0.56, 0.95)	0.85 (0.68, 1.07)	0.75 (0.59, 0.94)	0.75 (0.58, 0.95)	0.041	0.755
College graduate or postgraduate	344	1.0	0.87 (0.59, 1.28)	0.73 (0.51, 1.04)	0.71 (0.51, 0.96)	0.68 (0.47, 0.98)	0.049	
BMI (kg/m^2)								
<25.0	286	1.0	0.79 (0.52, 1.22)	0.71 (0.48, 1.03)	0.65 (0.46, 0.93)	0.69 (0.48, 0.99)	0.074	0.663
25.0–29.9	449	1.0	0.91 (0.65, 1.28)	0.91 (0.68, 1.23)	0.88 (0.66, 1.18)	0.75 (0.54, 1.03)	0.091	
≥30.0	281	1.0	0.64 (0.43, 0.93)	0.81(0.58, 1.12)	0.64 (0.45, 0.91)	0.76 (0.52, 1.13)	0.171	
Fruit and vegetable intakes[a]								
Low	582	1.0	0.79 (0.61, 1.05)	0.89 (0.71, 1.13)	0.79 (0.62, 1.01)	0.66 (0.49, 0.88)	0.008	0.369
High	434	1.0	0.75 (0.52, 1.07)	0.69 (0.51, 0.96)	0.68 (0.51, 0.91)	0.76 (0.56, 1.02)	0.231	
Red meat intake[b]								

Variable	Number of cases	Physical activity (times/week)						
		0	<1	1–2	3–4	≥5	*p* for trend	*p* for interaction
Low	447	1.0	0.67 (0.47, 0.96)	0.70 (0.52, 0.95)	0.70 (0.53, 0.93)	0.69 (0.52, 0.93)	0.099	0.651
High	569	1.0	0.85 (0.65, 1.12)	0.89 (0.70, 1.15)	0.76 (0.59, 0.98)	0.74 (0.56, 0.98)	0.023	
Alcohol use								
No	234	1.0	0.72 (0.46, 1.12)	0.81 (0.56, 1.18)	0.64 (0.44, 0.94)	0.67 (0.45, 0.99)	0.044	0.919
Yes	782	1.0	0.81 (0.63, 1.03)	0.82 (0.66, 1.03)	0.78 (0.63, 0.96)	0.75 (0.59, 0.95)	0.004	
NSAID use[c]								
No	294	1.0	0.75 (0.50, 1.12)	0.72 (0.51, 1.03)	0.57 (0.40, 0.81)	0.66 (0.46, 0.95)	0.022	0.880
Yes	210	1.0	0.87 (0.54, 1.39)	0.87 (0.57, 1.34)	0.91 (0.59, 1.38)	0.83 (0.52, 1.32)	0.600	
Antacid use[c]								
No	340	1.0	0.87 (0.59, 1.26)	0.76 (0.54, 1.07)	0.71 (0.51, 0.98)	0.76 (0.54, 1.08)	0.129	0.905
Yes	225	1.0	0.79 (0.49, 1.24)	0.86 (0.58, 1.27)	0.63 (0.43, 0.94)	0.66 (0.43, 1.02)	0.036	

Note: The multivariate model used follow-up person-years as the underlying time metric and included the following covariates: age (continuous); gender (women, men); a combination of smoking status (never, former; current), time since quitting for former smokers (≥10 years, 5–9 years, 1–4 years, <1 year), and smoking intensity for former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes/day); race/ethnicity (white, black, Hispanic, other); education (less than high school, high school, vocational school or some college, college graduate, postgraduate); marital status (married or living as married, other); family history of cancer (yes, no); intakes of fruits and vegetables combined (quintiles), red meat (quintiles), alcohol (0, <1, 1–3, >3 servings/day); and BMI (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m^2).

[a] The strata of low and high fruit and vegetable intakes were defined based on the cutoff point representing the median value of 3.2 servings/1000 kcal/day.

[b] The strata of low and high red meat intakes were defined based on the cutoff point representing the median value of 31.4 grams/1000 kcal/day.

[c] The analyses that were stratified by NSAID and antacid use were conducted using data from the subcohort of study participants for whom we had collected information regarding NSAID and antacid use.

NSAID, nonsteroidal anti-inflammatory drug