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The Relationship Between Serum Ghrelin and the Risk of Gastric and Esophagogastric Junctional Adenocarcinomas

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Background Cancers of the upper gastrointestinal tract remain a substantial cause of morbidity and mortality worldwide. Ghrelin is a hormone produced in the oxyntic glands of the stomach, and under conditions of chronic inflammation and atrophy, serum ghrelin concentrations decrease. However, the relationship between ghrelin and the risk of gastric and esophagogastric junctional cancers has not been investigated.

Methods We conducted a nested case-control study within the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study to examine the relationship between serum ghrelin concentration and the risk of gastric non cardia adenocarcinoma (GNCA) and esophagogastric junctional adenocarcinoma (EGJA). Data from 261 GNCA patients, 98 EGJA patients, and 441 control subjects were analyzed. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using logistic regression with adjustment for potential confounders. Lag analysis was also performed to investigate the temporal nature of the associations between baseline serum pepsinogen I and ghrelin in GNCA and EGJA patients. All statistical tests were two-sided.

Results Lower concentrations of serum ghrelin were statistically significantly associated with an increased risk of both GNCA (adjusted OR = 1.75, 95% CI = 1.49 to 2.04; $P < .001$) and EGJA (adjusted OR = 1.56, 95% CI = 1.28 to 1.89, $P < .001$). A multivariable model found that the risk of both GNCA and EGJA were statistically significantly increased for those individuals in the lowest quartile of serum ghrelin levels compared with those in the highest quartile (OR of GNCA = 5.63, 95% CI = 3.16 to 10.03; OR of EGJA = 4.90, 95% CI = 2.11 to 11.35). The statistical significance of these associations remained even after restricting the analysis to those patients who developed cancer more than 10 years after baseline serum ghrelin measurements.

Conclusion Low baseline concentrations of serum ghrelin were associated with a statistically significant increase in the risk of GNCA and EGJA, suggesting a potential role for gastric hormones in carcinogenesis.

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Ghrelin, a hormone produced in the fundic (oxyntic) glands of the stomach, is known to have a variety of metabolic functions that range from stimulation of gastric acid and regulation of gastrointestinal tract motility to regulation of energy balance and control of appetite (1). In contrast to leptin, a satiety hormone, ghrelin plays a role in meal initiation with ghrelin blood levels rising before and falling after eating (1). The physiological actions of ghrelin are increasingly recognized as extending beyond metabolism; experimental data suggest that ghrelin is expressed in human T lymphocytes and monocytes and acts via the growth hormone secretagogue receptor type 1a to inhibit the expression of the pro inflammatory cytokines interleukin 1 β , interleukin 6, and tumor necrosis factor- α (2).

In 2008, there were approximately 989 000 new gastric cancers diagnosed globally and 738 000 deaths. Gastric cancer ranks as the fourth leading incident cancer and the second leading cause of cancer deaths worldwide (3). *Helicobacter pylori* (*H pylori*), a gram-negative

spiral bacterium present in about half of the world's population (4), is a strong risk factor for gastric noncardia adenocarcinoma (GNCA). Chronic *H pylori* infection can result in chronic gastritis that may progress to atrophic gastritis, in which gastric glands are destroyed and may ultimately be replaced by intestinal-type epithelium. In a small proportion of infected individuals, this inflammatory cascade can result in gastric neoplasia (5). In contrast, associations between *H pylori* and esophagogastric junctional adenocarcinoma (EGJA) are unclear (6), but *H pylori* has been shown to reduce the risk of EGJA and esophageal adenocarcinomas in some studies (7).

The gastric mucosa hosts a variety of endocrine cell types and produces a myriad of hormones and peptides (8), including ghrelin. Chronic inflammation and atrophic gastritis in response to *H pylori* infection alter the hormonal milieu of the stomach (9–12). In fact, both chronic inflammation and atrophy have been associated with a decrease in plasma ghrelin, and eradication of *H pylori* is followed by an increase in plasma ghrelin (11,13,14). The

CONTEXT AND CAVEATS

Prior knowledge

Ghrelin is a gastric hormone that plays a role in various metabolic functions and mediates inflammation. Although there is a previous report that ghrelin may promote esophageal carcinoma, there are no previously published prospective epidemiological studies of serum ghrelin in gastric cancer.

Study design

Data from a prospective nested case-control study of 261 gastric noncardia adenocarcinoma and 98 esophagogastric junctional adenocarcinoma patients and 441 control subjects were analyzed by logistic regression and lag analysis to investigate the association and temporal relationship between serum ghrelin levels and the risk of gastric and esophagogastric junctional adenocarcinomas.

Contribution

Lower serum ghrelin levels were associated with an increased risk of noncardia adenocarcinoma and esophagogastric junctional adenocarcinoma that was statistically significant even for patients who were diagnosed more than 10 years after their enrollment in the study.

Implication

Serum ghrelin levels may have a role in the development of gastric and esophagogastric junctional adenocarcinomas.

Limitations

The study population included male smokers only, thus the results may not be applicable to a heterogeneous population. Further studies are needed to elucidate the biological mechanism behind the relationship between serum ghrelin levels and gastric cancer risk.

From the Editors

consequences of these alterations in ghrelin levels and their contribution to gastric or esophageal carcinogenesis remain unknown.

Although serum ghrelin has been investigated for its role in adenocarcinoma of the esophagus (15), at present, there are no prospective epidemiological studies investigating the role of serum ghrelin in gastric cancers. We investigated the association between serum ghrelin concentration and subsequent risk of GNCA and EGJA in a case-control study nested in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.

Methods

Subjects in this study were drawn from the ATBC Study, a randomized, double-blind, placebo-controlled primary prevention trial designed to determine whether daily supplementation with α -tocopherol (50 mg/d), β -carotene (20 mg/d), or both, would reduce the incidence of lung cancers in male smokers (16). Between 1985 and 1988, 29 133 eligible Finnish male smokers aged 50–69 years were recruited to the ATBC Study. Although the trial ended in 1993, participants continued to be followed as a cohort. This study was approved by the Institutional Review Boards of both the National Institutes of Health in the United States and the National Public Health Institutes in Finland. All participants provided written informed consent.

All control subjects had incident GNCA or EGJA diagnosed through April 30, 2006. Cancer patients were identified primarily via the Finnish Cancer Registry. Diagnosed gastric cancers were defined according to the *International Classification of Diseases, Ninth Revision* (17). GNCA patients included all patients coded as 151 and 151.1–151.9. We classified EGJA patients according to the World Health Organization classification of tumors of the digestive system (18), which defines EGJAs as: 1) adenocarcinomas that cross the esophagogastric junction; 2) adenocarcinomas located entirely above the esophagogastric junction; and 3) adenocarcinomas located entirely below the esophagogastric junction, considered gastric in origin, often referred to as carcinoma of the gastric cardia. EGJAs included patients coded as 150 and 151.0; all patients had adenocarcinoma (12 patients were coded as esophageal adenocarcinoma and the remaining 86 patients were coded as gastric cardia cancer). For patients diagnosed through April 1999 ($n = 181$ GNCA and $n = 65$ EGJA), two study physicians reviewed medical records for diagnostic confirmation and staging, and one pathologist reviewed histopathologic or cytological specimens when available. Information on gastric cancer patients diagnosed since May 1999 ($n = 80$ GNCA and $n = 33$ EGJA) was derived solely from the Finnish Cancer Registry, which provides almost 100% tumor ascertainment. Control subjects were alive and cancer-free at the time of entry into the trial and were matched to cancer patients by age at random assignment (± 1 year), date of blood collection (± 30 days), and sample availability.

Data Collection

Study participants completed questionnaires at ATBC study entry about general risk factors, medical history, and dietary intake. Dietary intake was assessed by a food-frequency questionnaire, by questions about usual food intake during the previous year including 276 common foods and mixed dishes, and by use of a picture booklet to aid estimation of portion size (19,20). The food-frequency questionnaire was satisfactorily completed by 27 110 of 29 151 participants (93%) at the time of study entry. The weights and heights of all participants were measured by trained study staff. Fasting blood samples were collected from participants at the start of the study (1985–1988), and serum samples were stored at -70°C .

Laboratory Analysis

Adequate serum samples for ghrelin analysis were collected from 261 incident GNCA patients, 98 EGJA patients, and 441 control subjects. Total ghrelin was measured by radioimmunoassay using reagents obtained from Millipore Linco Research (St Charles, MO). The radioimmunoassay uses a rabbit anti-ghrelin polyclonal antibody and requires 0.1 mL of serum for a 2-day disequilibrium assay. Using 98 blinded quality control samples from a single serum pool from the ATBC Study, the coefficient of variation for these assays was calculated as 11.6% and the intraclass correlation was 89%.

H pylori (whole cell) seropositivity was measured by enzyme-linked immunosorbent assays (Biohit Diagnostics, Helsinki, Finland) according to the manufacturer's instructions. Each assay included two quality control samples provided by the manufacturer and three blinded quality control samples from a single serum pool

from the ATBC Study. All samples were assayed in duplicate. A cut point was used to determine *H pylori* positivity. Concordance of *H pylori* positivity among quality control samples was 100%.

Serum pepsinogen I measurements were performed in two laboratories. Samples were assayed at the University of California (Los Angeles, CA) between 1989 and 1991. After the facility was damaged by an earthquake in 1991, the remaining serum samples were assayed at the University of Helsinki (Helsinki, Finland), from 1992 to 1993 (21–23). The results of the serum pepsinogen I measurements from both laboratories were correlated and standardized. A low serum pepsinogen I level was defined as 25 µg/L or less. Using quality control samples (~10%) from the ATBC Study, the coefficients of variation for these assays were between 10% and 13% (23).

Statistical Analysis

Statistical analyses were performed using STATA version 10.1 (Stata Corp, College Station, TX), and all *P* values were two-sided. A *P* value of less than .05 was considered statistically significant. The distributions of baseline characteristics across GNCA and EGJA relative to control subjects were compared using Student *t* tests for continuous variables and Pearson χ^2 tests for categorical variables. The associations between baseline characteristics and serum ghrelin quartiles were determined using the Jonckheere–Terpstra test for trend for continuous variables and the Mantel–Haenszel trend test for categorical variables (SAS, version 9.1.3; SAS Institute Inc, Cary, NC). Both tests were two-sided.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between serum ghrelin concentration and the risk of GNCA and EGJA were calculated by unconditional logistic regression models. When we modeled ghrelin as a continuous variable, the odds ratios were scaled to 181 pg/mL (half of the interquartile range observed in control subjects, [Q3 – Q1]/2). Multivariable models of risk were adjusted for: age at randomization, total years of smoking and total cigarettes per day, alcohol (g/d), body mass index (kg/m²), fruit intake (g/d), vegetable intake (g/d), post-primary school education (yes or no), *H pylori* (positive or negative), low pepsinogen I (≤ 25 µg/L), and ATBC Study treatment group assignment. Lag analysis was also performed: GNCA

and EGJA patients were classified according to whether they occurred within 5 years of baseline, between 5 and 10 years of baseline, or more than 10 years after baseline. Estimates derived from conditional and unconditional logistic regression models were similar, and as such, only the results of the unconditional models, which offered more precise risk estimates, are reported.

Results

Baseline characteristics of the patients and control subjects are shown in Table 1. Incident cancers included 261 GNCA and 98 EGJA patients. Cigarette smoking (cigarettes per day) was higher in EGJA patients than in control subjects, GNCA patients were more likely to be *H pylori* seropositive, and both EGJA and GNCA patients were more likely to have low baseline levels of serum pepsinogen I.

Among control subjects, serum ghrelin was positively associated with the number of cigarettes smoked per day and education whereas levels were inversely associated with body mass index, *H pylori* seropositivity, and low serum pepsinogen I. In addition, there were no associations between age, mean years of smoking, alcohol intake, fruit intake and vegetable intake with serum ghrelin levels in these subjects (Table 2). In a multivariable linear regression model for predictors of serum ghrelin, only the inverse associations with body mass index and *H pylori* seropositivity remained statistically significant (data not shown).

Baseline serum ghrelin (as a continuous variable, scaled to half the interquartile range of serum ghrelin in the control subjects, [Q3 – Q1]/2) was statistically significantly inversely associated with the risk of GNCA (OR = 1.89, 95% CI = 1.61 to 2.17) and EGJA (OR = 1.52, 95% CI = 1.25 to 1.82) in an age-adjusted model (Table 3). These associations remained statistically significant for both cancer sites following multivariable adjustment (OR of GNCA = 1.75, 95% CI = 1.49 to 2.04; OR of EGJA = 1.56, 95% CI = 1.28 to 1.89).

When divided into ghrelin serum quartiles on the basis of the distribution of the control subjects, the risk of GNCA and EGJA increased statistically significantly and monotonically from the highest to the lowest quartile of baseline serum ghrelin ($P_{\text{trend}} < .001$ for

Table 1. Descriptive characteristics of gastric noncardia adenocarcinoma (GNCA) and esophagogastric junctional adenocarcinoma (EGJA) patients and control subjects from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study*

Variable	Control subjects	GNCA patients	<i>P</i>	EGJA patients	<i>P</i>
Total No. of participants	441	261	NA	98	NA
Mean age at baseline, y (SD)	58.3 (4.9)	58.2 (5.0)	.79	57.9 (4.9)	.20†
Years of smoking, mean (SD)	36.5 (8.3)	36.8 (9.4)	.62	37.4 (7.4)	.29†
Mean No. of cigarettes per day (SD)	18.9 (8.5)	20.2 (8.9)	.06	21.3 (9.3)	.01†
Mean alcohol intake, g/d (SD)	16.0 (17.6)	16.6 (19.4)	.67	14.5 (15.7)	.45†
Post-primary school education, No. (%)	40 (23.0)	26 (14.9)	.06	20 (20.4)	.35‡
Mean body mass index, kg/m ² (SD)	26.4 (3.9)	26.2 (3.9)	.52	26.8 (4.0)	.37†
Mean fruit intake, g/d (SD)	224.6 (207.0)	200.7 (156.8)	.12	213.5 (170.3)	.64†
Mean vegetable intake, g/d (SD)	301.4 (111.5)	284.5 (105.5)	.06	289.9 (109.4)	.38†
<i>Helicobacter pylori</i> positive, No. (%)	253 (72.9)	238 (91.5)	<.001	64 (74.4)	.77‡
Pepsinogen I (≤ 25 µg/L), No. (%)	17 (4.2)	17 (8.5)	.03	9 (12.3)	.005‡

* NA = not applicable, SD = standard deviation.

† *P* values were calculated by a two-sided Student *t* test.

‡ *P* values were calculated by a two-sided Pearson χ^2 test.

Table 2. Baseline characteristics by quartiles of serum ghrelin concentration in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study control subjects (n = 441)

Control subject characteristic	Quartile				P _{trend}
	Q1 (<549 pg/mL)	Q2 (549–703 pg/mL)	Q3 (703–911 pg/mL)	Q4 (>911 pg/mL)	
Mean age at baseline	59	59	58	58	.13†
Mean No. of years of smoking, y	36.6	36.0	36.3	36.9	.66†
Mean No. of cigarettes per day	19.0	17.5	19.1	20.3	.05†
Mean alcohol intake, g/d	15.9	16.3	15.0	17.1	.35†
Post-primary school education, No. (%)	21 (19.1)	18 (16.5)	28 (25.5)	32 (29.4)	.03*
Body mass index, kg/m ²	27.0	26.5	26.8	25.3	.01†
Mean fruit intake, g/d	227.3	226.8	246.9	195.5	.19†
Mean vegetable intake, g/d	306.8	282.3	300.3	311.7	.24†
<i>Helicobacter pylori</i> positive, No. (%)	91 (82.7)	85 (79.4)	83 (75.5)	61 (56.5)	<.001*
Pepsinogen I ≤ 25 µg/L, No. (%)	10 (10.4)	2 (2.0)	4 (3.9)	1 (1.0)	.01*

* A two-sided Mantel-Haenszel trend test for categorical variables was used to calculate *P* values.

† Jonckheere-Terpstra test for trend for continuous variables was used to calculate *P* values. This statistical test was two-sided.

GNCA and EGJA) (Table 3). Following adjustment, those in the lowest quartile of serum ghrelin had a statistically significant increased risk of both GNCA (OR = 5.63, 95% CI = 3.16 to 10.03) and EGJA (OR = 4.90, 95% CI = 2.11 to 11.35). Models were stratified according to whether tumors were intestinal or diffuse and if the association did not differ between tumor types (data not shown).

The temporal nature of the associations between baseline serum pepsinogen I and ghrelin was explored by performing a lag analysis (Table 4). Overall, low serum pepsinogen I at baseline was associated with an increased risk of GNCA (OR = 1.77, 95% CI = 0.85 to 3.71) and EGJA (OR = 3.00, 95% CI = 1.18 to 7.59); however, the statistically significant increase in the risk of cancer noted for those with low baseline serum pepsinogen I was confined to the first 5 years after baseline for GNCA (OR = 6.82, 95% CI = 2.86 to 16.26) and EGJA (OR = 23.21, 95% CI = 4.55 to 118.36). By contrast, the statistically significant inverse association between baseline serum ghrelin and risk of GNCA and EGJA was observed across all periods, although the magnitude of the association was attenuated over time.

We also mutually adjusted for pepsinogen I and ghrelin, and risk estimates for serum pepsinogen I for those cancers diagnosed within the first 5 years were only modestly attenuated when adjustment

included serum ghrelin. However, for all other time intervals, risk estimates for low serum pepsinogen I were non-statistically significant for either GNCA and EGJA using these models, although risk estimates for ghrelin remained statistically significant but slightly attenuated across all periods (Table 4).

Discussion

This case-control study nested within the ATBC Study cohort provides evidence, for the first time to our knowledge, of a statistically significant increase in the risk of both GNCA and EGJA for individuals with lower baseline serum ghrelin concentrations. This statistically significant increased risk of gastric cancer was independent of the baseline pepsinogen I concentration and *H pylori* infection and was present even for patients diagnosed more than 10 years after baseline. In contrast, the increased risk of GNCA and EGJA noted for those with low serum pepsinogen I was confined to cancers developing less than 5 years after baseline.

Although to the best of our knowledge, no previous studies have reported the relationship between serum ghrelin concentration and the risk of gastric cancer, one study nested in a multi-phasic health checkup cohort in the Kaiser Permanente Medical Care Program (California) analyzed serum ghrelin concentrations

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for serum ghrelin concentration and the risk of gastric noncardia adenocarcinoma (GNCA) or esophagogastric junctional adenocarcinoma (EGJA) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

Type of gastric cancer	Continuous*		Quartile				P _{trend}
	OR (95% CI)	P	Q1	Q2	Q3	Q4	
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
GNCA							
Age adjusted	1.89 (1.61 to 2.17)	<.001	7.53 (4.35 to 13.03)	3.77 (2.13 to 6.69)	1.21 (0.62 to 2.35)	1.0 (referent)	<.001
Adjusted†	1.75 (1.49 to 2.04)	<.001	5.63 (3.16 to 10.03)	2.73 (1.49 to 5.04)	0.96 (0.48 to 1.92)	1.0 (referent)	<.001
EGJA							
Age adjusted	1.52 (1.25 to 1.82)	<.001	4.10 (1.96 to 8.59)	3.23 (1.52 to 6.90)	1.26 (0.53 to 3.00)	1.0 (referent)	<.001
Adjusted†	1.56 (1.28 to 1.89)	<.001	4.90 (2.11 to 11.35)	4.27 (1.80 to 10.17)	1.59 (0.62 to 4.08)	1.0 (referent)	<.001

* Continuous odds ratios are scaled to 181 pg/mL, which is one half of the interquartile range in the control subjects ((Q3 – Q1)/2).

† Adjusted odds ratios and 95% confidence intervals were calculated by logistic regression models adjusted for age at randomization, total years of smoking, total cigarettes per day, alcohol (g/d), body mass index (kg/m²), fruit intake (g/d), vegetable intake (g/d), post-primary school education (yes or no), *Helicobacter pylori* (positive or negative), low serum pepsinogen I (≤25 µg/L), and Alpha-Tocopherol, Beta-Carotene Cancer Prevention treatment group. *P* values for trend were calculated by two-sided linear trend tests.

Table 4. Lag analysis of the association between low serum pepsinogen I or ghrelin concentrations by time to diagnosis since baseline and the risk of gastric noncardia adenocarcinoma (GNCA) or esophagogastric junctional adenocarcinoma (EGJA)*

Time to diagnosis relative to baseline	No. of patients (%)	Pepsinogen I†		Pepsinogen I‡		Ghrelin†		Ghrelin§	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
GNCA									
Total No. of patients	261	1.77 (0.85 to 3.71)	.13	1.09 (0.50 to 2.40)	.83	1.75 (1.49 to 2.04)	<.001	1.79 (1.52 to 2.13)	<.001
<5 y	70 (27)	6.82 (2.86 to 16.26)	<.001	3.27 (1.24 to 8.65)	.02	2.56 (1.89 to 3.57)	<.001	2.56 (1.72 to 3.85)	<.001
5–10 y	95 (36)	0.47 (0.10 to 2.12)	.32	0.36 (0.08 to 1.67)	.19	1.67 (1.35 to 2.08)	<.001	1.70 (1.32 to 2.17)	<.001
>10 y	96 (37)	0.54 (0.12 to 2.45)	.43	0.38 (0.08 to 1.78)	.22	1.61 (1.30 to 2.00)	<.001	1.72 (1.35 to 2.22)	<.001
EGJA									
Total No. of patients	98	3.00 (1.18 to 7.59)	.02	2.11 (0.81 to 5.50)	.13	1.56 (1.28 to 1.89)	<.001	1.67 (1.33 to 2.13)	<.001
<5 y	23 (24)	23.21 (4.55 to 118.36)	<.001	17.60 (3.24 to 95.67)	.001	2.04 (1.30 to 3.23)	.002	2.33 (1.27 to 4.35)	.007
5–10 y	31 (32)	1.04 (0.13 to 8.55)	.97	0.73 (0.09 to 6.21)	.77	1.79 (1.25 to 2.56)	.002	1.82 (1.18 to 2.78)	.007
>10 y	44 (45)	2.24 (0.59 to 8.50)	.24	1.63 (0.42 to 6.38)	.48	1.32 (1.03 to 1.69)	.03	1.47 (1.10 to 1.96)	.009

* CI = confidence interval, OR = odds ratio.

† Adjusted odds ratios and 95% confidence intervals were calculated by models adjusted for age at randomization, total years of smoking and total cigarettes per day, alcohol (g/d), body mass index (kg/m²), fruit intake (g/d), vegetable intake (g/d), post-primary school education, *Helicobacter pylori* (positive or negative), and Alpha-Tocopherol, Beta-Carotene Cancer Prevention treatment group.

‡ Model was adjusted for age at randomization, total years of smoking and total cigarettes per day, alcohol (g/d), body mass index (kg/m²), fruit intake (g/d), vegetable intake (g/d), post-primary school education (yes or no), *Helicobacter pylori* (positive or negative), Alpha-Tocopherol, Beta-Carotene Cancer Prevention treatment group, and ghrelin (continuous, scaled to one half of the interquartile range, [Q3 – Q1]/2).

§ Model was adjusted for age at randomization, total years of smoking and total cigarettes per day, alcohol (g/d), body mass index (kg/m²), fruit intake (g/d), vegetable intake (g/d), post-primary school education (yes or no), *Helicobacter pylori* (positive or negative), Alpha-Tocopherol, Beta-Carotene Cancer Prevention treatment group, and low serum pepsinogen I (≤25 µg/L).

in 31 esophageal adenocarcinoma patients and 79 matched control subjects (15). Similar to our results in EGJA cancers, the authors found an adverse relationship between lower serum ghrelin and esophageal adenocarcinoma for those in the lowest quartile of serum ghrelin concentration (OR = 5.55, 95% CI = 1.28 to 25.0). This association with esophageal adenocarcinoma, like the EGJA association that we report here, was found to be independent of *H pylori*.

In a previous analysis from the ATBC Study cohort, we reported that *H pylori* infection was statistically significantly inversely associated with adenocarcinomas of the esophagogastric junction (referred to as gastric cardia adenocarcinomas in that report) (OR = 0.31, 95% CI = 0.11 to 0.89) and was a statistically significant risk factor for GNCA (OR = 7.9, 95% CI = 3.0 to 20.9) (6). In contrast to this striking difference in *H pylori* association, in the current analysis, both low serum pepsinogen I and low serum ghrelin were statistically significantly associated with increased risk of adenocarcinoma at both sites, suggesting that the carcinogenic effect of *H pylori* may not always be mediated by gastric fundic atrophy, at least in the esophagogastric junctional region.

Like ghrelin, the proenzyme pepsinogen I, is also produced in the gastric fundic mucosa. Pepsinogen I is commonly used to serologically indicate the presence of gastric fundic atrophy, the destruction of the fundic glands and frequent sequelae of chronic inflammation, and it has been investigated as a possible early detection marker for gastric cancer (24,25). Gastric fundic atrophy also results in destruction of the ghrelin-producing cells in the fundic mucosa (1), so ghrelin may be a marker worth investigating for its potential in identifying early gastric cancer.

Our analysis suggests, however, that ghrelin and pepsinogen may act differently in the context of upper gastrointestinal carcinogenesis.

When risk was calculated by time from baseline to the development of cancer, the increase in risk of GNCA and EGJA associated with low baseline serum pepsinogen I was confined to those cancers occurring within 5 years of baseline, indicating that serum pepsinogen I may be altered only in the latter stages of carcinogenesis. Similar temporal associations between serum pepsinogen I and gastric cancer have been previously noted (26–28). In contrast, the increase in risk of GNCA and EGJA associated with low baseline serum ghrelin remained statistically significant for cancers occurring long after baseline, indicating that changes in serum ghrelin may occur early in the carcinogenic process, long before the development of the tumor, and that ghrelin may be involved in the etiology of these upper gastrointestinal cancers.

The potential role of ghrelin in carcinogenesis is not yet known; however, data regarding ghrelin's relevance to both inflammation and carcinogenesis have been reported. The relationship between ghrelin and inflammation preceding atrophy is likely complex: Whereas most studies report that ghrelin has predominantly anti-inflammatory associations (2), there are also data to suggest that ghrelin may be associated with increased inflammation in some situations (2,29,30). In a study of plasma ghrelin levels across various gastrointestinal disorders, the lowest ghrelin levels were associated with chronic gastritis, whereas the highest levels of ghrelin were seen in patients with acute gastritis and patients with gastric cancer (31,32). Higher circulating ghrelin levels among cancer patients may be the result of a compensatory response, possibly involving secretion of ghrelin from auxiliary ghrelin-producing organs (such as the small and large intestines, the kidney, or the lung); however, the mechanism and function of such a response, if it occurs, are unknown (13,33).

The relationship between ghrelin and carcinogenesis appears similarly complicated. Colorectal carcinoma cells are reported to secrete excessive ghrelin *in vitro*, and in these cells, ghrelin appears to act in both an autocrine and a paracrine manner to promote the proliferative and invasive nature of the cells (34). An increase in proliferation in response to secreted ghrelin has also been observed in human pancreatic and hepatoma cell lines (35,36). However, studies of human thyroid, breast, and prostate cancer cell lines have shown that ghrelin induces both proliferative and antiproliferative effects, which are often dependent on the histological cell type and the dose and timing of ghrelin administration (30,37–39). Further studies are needed to characterize the interaction between ghrelin, inflammation, and carcinogenesis in different organs.

The prospective design of our study is one of its major strengths because baseline prediagnostic serum for analysis of ghrelin, *H pylori* infection, and pepsinogen I was collected for analyses. The ATBC Study also includes substantial covariable information that allowed for adjustment for potential confounders.

The ATBC Study includes only male smokers, and as such, the generalizability of our findings may be limited. Unfortunately, data regarding serum pepsinogen II serostatus was unavailable in this analysis, thus preventing the use of both low pepsinogen I levels and low pepsinogen I/II ratio as indicators of gastric atrophy. *H pylori* CagA serostatus, a marker of *H pylori* infection virulence, was also unavailable, although the data indicate that *H pylori* infection did not substantially modulate the risk associated with low ghrelin. As with all epidemiological studies, the possibility of residual confounding cannot be excluded.

In conclusion, in this large prospective study, we found that individuals with lower baseline serum concentrations of ghrelin had a statistically significant increase in the risk of both GNCA and EGJA. Serum ghrelin levels may be a useful marker of gastric fundic atrophy and may also have a role in the etiology of gastric and esophagogastric junctional cancers. The gastrointestinal tract can be thought of as an endocrine organ, and further studies investigating the effects of alterations in the hormonal *milieu* of the stomach in response to *H pylori* infection and subsequent atrophy that could drive gastric carcinogenesis are needed.

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