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ALIMENTARY TRACT

Gastroesophageal Reflux Does Not Alter Effects of Body Mass Index on Risk of Esophageal Adenocarcinoma

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BACKGROUND & AIMS: **A history of high body mass index (BMI) is associated strongly with a risk of esophageal adenocarcinoma (EAC). We investigated whether gastroesophageal reflux is involved in this association.**

METHODS: **We analyzed data from a population-based Swedish nationwide study of patients with a new diagnosis of EAC (n = 189) or gastroesophageal junction adenocarcinoma (n = 262), and matched controls (n = 816), from 1995 through 1997. Our analysis included data on BMI 20 years before study inclusion; maximum adult BMI; frequency, severity, and duration of gastroesophageal reflux symptoms; tumor features; and covariates (sex, age, smoking, alcohol, fruit and vegetable intake, and socioeconomic status). We conducted stratified analyses and synergy tests, adjusting for covariates.**

RESULTS: **Odds ratios (ORs) for EAC among subjects with a BMI of 25 or higher 20 years before inclusion, compared with those with a BMI less than 25, did not differ significantly, without or with adjustment for gastroesophageal reflux frequency (OR, 3.1; 95% confidence interval [CI], 2.2–4.4; and OR, 3.3; 95% CI, 2.2–4.8, respectively), severity (OR, 3.3; 95% CI, 2.2–4.8), or duration (OR, 3.2; 95% CI, 2.2–4.7). However, there were interactions between BMI and categories of gastroesophageal reflux. BMI appeared to have the largest effect on gastroesophageal reflux frequency (synergy index, 8.9; 95% CI, 2.3–34.1 for maximum BMI; and gastroesophageal reflux >3 times/wk).**

CONCLUSIONS: **Based on a population-based study, the association between BMI and EAC does not appear to be affected by symptomatic gastroesophageal reflux, although there appears to be synergy between BMI and reflux.**

Keywords: Obesity; Overweight; Cancer Risk; GERD.

Among all obesity-related cancers, esophageal adenocarcinoma (EAC) has the strongest known association with body mass index (BMI),[1,2] and the association is linear.[3–5] There are several potential mechanisms behind the overall increased risk of developing cancer among overweight persons,[6] but the particularly strong association with EAC indicates the involvement of a more organ-specific mechanism. The most obvious explanation would be that overweight, through an increased intra-abdominal pressure caused by visceral adiposity, facilitates gastroesophageal reflux, which in turn causes Barrett's esophagus and EAC.[7] This postulated carcinogenic pathway is supported by the dose-dependent association between BMI and gastroesophageal reflux,[8,9] and by studies showing that abdominal and visceral adiposity, facilitating gastroesophageal reflux, are stronger risk factors for EAC than BMI alone.[10] Existing epidemiologic studies consistently have found that, with mutual control, overweight and gastroesophageal reflux symptoms are independent risk factors for EAC.[2–5,11,12] The degree to which gastroesophageal reflux mediates the body mass–EAC association deserves more in-depth studies.[13] We previously studied the role of both BMI and gastroesophageal reflux in the etiology of EAC and gastroesophageal junctional adenocarcinoma (JAC) in a nationwide Swedish case-control study,[3,7] but we did not conduct any in-depth analyses of how various levels of BMI and gastroesophageal reflux interact in the development of EAC. An Australian study addressed the

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; JAC, gastroesophageal junctional adenocarcinoma; OR, odds ratio; S, synergy.

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combined effects of BMI, gastroesophageal reflux, and tobacco smoking on the risk of EAC and found that adjustment for gastroesophageal reflux only modestly attenuated the association between BMI and EAC.[11] To further explore mechanisms behind the strong association between BMI and EAC, we hypothesized that the effect of BMI is modified by gastroesophageal reflux at certain levels of frequency, severity, or duration.

Methods

Design

The organization and design of our Swedish population-based case-control study has been described in detail elsewhere.[7] In brief, the study base consisted of all Swedish-born residents between ages 40 and 80 years in 1995 through 1997. Cases comprised residents newly diagnosed with EAC or JAC during this period. All 195 hospital departments involved in the diagnosis or management of these patients in Sweden collaborated in the recruitment of patients. Controls were selected randomly from the Swedish Register of the Total Population and were frequency matched for age and sex of the EAC case patients. Exposure information was obtained through personal interviews with all study participants. The interviews were conducted by professional interviewers employed by Statistics Sweden (Örebro, Sweden). The interviewers were trained to treat the cases and controls in an equal manner. The tumor classification was rigorous and uniform, which allowed us to distinguish between adenocarcinomas of the esophagus and those of the gastroesophageal junction (tumors within 2 cm above and 3 cm below the junction). All histologic specimens were later re-examined by one experienced pathologist to make the classification more uniform for study purposes.

Exposure Variables and Covariates

Body mass index. BMI was calculated as the weight in kilograms divided by the square of the body height in meters (kg/m^2). Data on weight and height 20 years before the interview as well as the maximum adult weight were collected retrospectively during the interviews. Normal weight was defined as a BMI less than 25, overweight was defined as a BMI of 25 to less than 30, obesity was defined as a BMI of 30 to less than 35, and severe obesity was defined as a BMI of 35 or greater. In some analyses, categories for overweight, obesity, and severe obesity were combined into one category (overweight/obese: BMI $\geq$25).

Gastroesophageal reflux symptoms. Gastroesophageal reflux symptoms were defined as the presence of heartburn or regurgitation at least weekly during at least 6 months, occurring at least 5 years before the interview. This definition is well in line with the current definition of gastroesophageal reflux disease.[14] Information about frequency and duration of reflux was collected through interview questions with open answers and categorized before the initiation of the analyses. We devised a severity score based on the following: (1) symptom characteristics (heartburn only, 1 point; regurgitation only, 1 point; and both heartburn and regurgitation, 1.5 points); (2) nightly reflux symptoms (2 points); and (3) frequency of symptoms (once per week, 0 points; 2–6 times per week, 1 point; 7–15 times per week, 2 points; and $>$15 times per week, 3 points).

Covariates. Six potential confounding variables were evaluated: sex and age, along with tobacco smoking, alcohol consumption, dietary intake of fruit and vegetables, and socioeconomic status. These covariates were selected because they have been found to have confounding effects in previous analyses of our case-control study.[3,7,15–17]

Statistical Analysis

Unconditional logistic regression (frequency matching) was used to calculate odds ratios (ORs) with 95% confidence intervals (95% CIs) for various aspects of body mass and reflux symptoms in relation to EAC and JAC. We fitted separate models of BMI in relation to the cancer outcomes including and not including reflux symptoms as a covariate. Furthermore, evaluation of effect measure modification was performed using stratification to investigate if the association between each single exposure and EAC or JAC varied over strata of a second variable. This was performed both for BMI as the exposure with reflux symptoms as the stratification variable and for reflux symptoms stratified by BMI. The synergy index (S) was used to test the additive interaction of the combined effect of BMI and reflux symptoms.[18] Interaction was present if there was a departure from the additivity scale $S \neq 1$. All models were adjusted for sex (men, women), age (in 5-year classes), tobacco smoking status (never, previous, or current user of any type of tobacco, as assessed 2 years before inclusion), alcohol consumption (0, 1–15, 16–70, or $>$70 g/wk), dietary intake of fruit and vegetables (low, intermediate, or high), and educational level (0–6 y, 7–10 y, or $>$10 y of formal education). Four controls of 820 were excluded because of missing values on the BMI variables. All data management and analysis was performed using SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Participants

Included were 189 patients with EAC and 262 patients with JAC, constituting 87% and 83%, respectively, of all eligible incident cases that occurred within the study base. The 816 control subjects constituted 75% of all subjects who had been originally selected. Some characteristics of the participants are presented in Table 1. The presence of overweight and reflux was highest in cases of EAC, followed by cases of JAC, and