

Abdominal Obesity and the Risk of Esophageal and Gastric Cardia Carcinomas

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Abstract

Background: Esophageal adenocarcinoma is rapidly increasing in incidence. Body mass index (BMI) is a risk factor, but its distribution does not reflect the demographic distribution of the cancer (which is highest among White men). Abdominal obesity patterns may explain this discordance, but no studies exist to date.

Methods: Nested case-control study within 206,974 members of the Kaiser Permanente multiphasic health checkup cohort; subjects received detailed questionnaires, a standardized examination including BMI and anthropometric measurements, and follow-up of esophageal and cardia cancers using registry data.

Results: 101 incident esophageal adenocarcinomas, 105 cardia adenocarcinomas, and 144 esophageal squamous cell carcinomas were detected (BMI data available for all cases; abdominal measurements for a subset). Increasing abdominal diameter was strongly associated with an increased risk of esophageal adenocarcinoma [odds ratio (OR), 3.47; 95% confidence interval (95% CI), 1.29-9.33; abdominal diameter, ≥ 25 versus < 20 cm].

Adjustment for BMI did not diminish this association (BMI-adjusted OR, 4.78; 95% CI, 1.14-20.11). The association was also not diminished by adjustment for gastroesophageal reflux-type symptoms, although reflux-type symptoms were separately associated with both abdominal diameter and cancer risk. Abdominal diameter was not associated with the risk of cardia adenocarcinomas (OR, 1.28; 95% CI, 0.38-4.25; diameter, ≥ 25 versus < 20 cm) or esophageal squamous cell carcinomas (OR, 0.78; 95% CI, 0.32-1.92).

Conclusions: Increasing abdominal diameter was associated with an increased risk of esophageal adenocarcinoma, independent of BMI. Cancer risk was not substantially mediated through gastroesophageal reflux-type symptoms, although symptoms may imperfectly measure reflux severity. Given abdominal obesity is more common among males, these findings suggest that increases in obesity may disproportionately increase the risk of esophageal adenocarcinoma in males. (Cancer Epidemiol Biomarkers Prev 2008;17(2):352-8)

Introduction

The incidence of esophageal adenocarcinoma has risen more rapidly than that of any other malignancy in the United States in the last three decades; obesity has been associated with cancer risk, but its mechanism of action is unknown (1-6). Simple obesity alone is unlikely to explain the sex and ethnic distributions of esophageal adenocarcinoma: the incidence of the cancer is 6-fold higher in men than in women and 5-fold higher in Caucasians than in African Americans (7). In contrast, obesity has been increasing rapidly in most demographic groups, including African Americans and women (8). Another explanation for the rising incidence is that body fat distribution, rather than simple obesity, may be the primary link between a higher body mass index (BMI) and cancer risk. Because the prevalence of abdominal

obesity also varies by sex and ethnicity (9), it is possible that body fat distribution may predict the risk of esophageal adenocarcinoma better than total obesity.

There are several potential mechanisms whereby abdominal obesity may increase cancer risk. Gastroesophageal reflux disease (GERD) is a strong risk factor for esophageal adenocarcinoma, independent of BMI (10), and the prevalence of GERD and its complications, including esophagitis and Barrett's esophagus (a metaplastic change of the esophageal lining that is a strong risk factor for esophageal adenocarcinoma), may also vary substantially by gender and ethnicity (11-13). Abdominal obesity has been associated with the risk of GERD symptoms, and this association appears stronger among Caucasians than among African Americans (11-18). Abdominal obesity is also associated with several hormones, such as insulin-like growth factor and adiponectin, which are known to influence cell division, cell death, and healing; obesity could thus also alter cancer risk through these mechanisms (19, 20).

Because abdominal obesity, independent of BMI, is also more common among men than women (9), an association between abdominal obesity and esophageal adenocarcinoma, if present, would help partially explain the demographic discrepancies in cancer risk, but no large studies have evaluated the association between abdominal

Received 8/13/07; revised 11/19/07; accepted 12/4/07.

Grant support: NIH grants RO1 DK63616 and K08 DK02697 and a Kaiser Permanente Community Benefit Grant.

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doi:10.1158/1055-9965.EPI-07-0748

obesity and this malignancy in a general population in part because of the difficulties of accurately assessing waist circumference before the onset of cancer-induced weight loss and its associated changes in body size.

We thus examined the associations between abdominal obesity, BMI, and the subsequent risk of esophageal adenocarcinomas using a nested case-control study within a large community-based cohort study. We also evaluated the associations between abdominal obesity and two other related cancers: cardia carcinoma (a cancer at the anatomically adjacent gastroesophageal junction, which is of the same histologic type) and esophageal squamous cell carcinoma (an esophageal cancer of different histologic type that is not associated with GERD). Finally, we evaluated whether any association between abdominal obesity and cancer risk was mediated by GERD-type symptoms.

Materials and Methods

Study Design. We did a nested case-control study, within a large cohort, of the associations between abdominal obesity, BMI, and the risks of esophageal adenocarcinoma, cardia carcinoma, and esophageal squamous cell carcinoma.

Study Population. The multiphasic health checkup (MHC) cohort consists of Kaiser Permanente health plan members who underwent a systematic MHC at facilities in San Francisco, CA and Oakland, CA; we used 206,974 cohort members interviewed between 1964 and 1973. Kaiser Permanente is a staff model integrated healthcare delivery system composed of physicians, hospitals, and outpatient medical facilities. Health plan members presenting for a routine health evaluation (for any reason) were asked to complete a detailed questionnaire and standardized physical examination; details have been published previously (21-24). This cohort has been used for numerous risk factor studies, including evaluations of ethnic differences in disease symptoms and outcomes (21, 23-27), and the Kaiser Permanente population resembles the region's underlying census demographics (28, 29).

For each cancer case, we randomly selected eight controls matched for age at the time of examination, gender, and year of health checkup.

Abdominal and BMI Exposure Measurements. Cohort members underwent a standardized physical examination by trained examiners using a written, systematic protocol and standardized instruments. The abdominal diameter was the standing anterior-posterior diameter at the iliac crest during normal breathing. The standing thigh anterior-posterior diameter was the distance from just below the left gluteal fold to the anterior thigh. Height and weight measurements (for the BMI calculations) were done for all years (1964-1973). Abdominal diameter measurements were done from 1965 to 1969 but not in 1964 or from 1970 to 1973. Effectively, this created two cohorts: one from 1964 to 1973 for the BMI analyses and a subcohort of this group from 1965 to 1969 that also had abdominal measurement data. Because controls were matched on the date of interview, cases and controls had comparable data for all analyses.

Outcome Measurements. Cancer outcomes used cancer registry data and individual record review. Kaiser Permanente has reported cancer cases to the National Cancer Institute's Surveillance, Epidemiology, and End Results Northern California cancer registry since 1973. Before this date, Kaiser Permanente maintained a Cancer Incidence File of all recorded cancer cases. Anatomic site and histology definitions used the *International Classification of Disease for Oncology* codes: esophageal carcinoma (C15.0-C15.9), gastric cardia (defined as cardioesophageal junction, esophagogastric junction, and gastroesophageal junction; C16.0), squamous cell carcinoma (8050-8082), and adenocarcinoma (8140-8573; ref. 30). There may also be overlap between the classifications of cardia cancers and the adjacent distal esophageal adenocarcinomas. Given this knowledge and the potential differences in site classification in the Cancer Incidence File, trained data abstractors attempted to retrieve and review the radiology, endoscopy, surgery, and pathology reports for all of the cardia and esophageal adenocarcinomas, all esophageal or cardia carcinomas with an undefined histology, and all cases from the Cancer Incidence File.

An anatomic location and histologic type was assigned for each case; these assignments included subsite assignments for gastroesophageal junction carcinomas (for cancers centered around the gastroesophageal junction) and cardia carcinomas (for cancer locations described as predominantly or exclusively below the gastroesophageal junction). A board certified gastroenterologist (D.A.C.) separately reviewed all reports to confirm the assignments; the few discordant results used the gastroenterologist's assignment. All assignments were completed blinded to BMI or anthropometric risk factor information.

Among the 206,974 MHC cohort members enrolled between 1964 and 1973, we identified 411 potential incident esophageal or cardia cancers occurring after each subject's interview date through 2006. The manual record reviews targeted the 287 subjects with either esophageal adenocarcinomas, cardia carcinomas, or esophageal cancers of an uncertain histologic type; the remaining esophageal squamous cell carcinomas were not reviewed. Record reviews were completed for 263 (91.6%) of targeted subjects; for 22 of the 24 patients without record review, we assigned location and histology codes using Surveillance, Epidemiology, and End Results data; the other two patients were excluded. We ultimately excluded a total of 61 patients for the following reasons: lacked both record review and Surveillance, Epidemiology, and End Results data; cancer histology was poorly differentiated, not squamous cell or adenocarcinoma, or was not clearly documented; or the cancer location was outside of the target areas or was not clearly specified. This provided 101 incident esophageal adenocarcinomas, 105 cardia adenocarcinomas, and 144 esophageal squamous cell carcinomas for the final analyses.

Measurements of Potential Confounders, Mediating Factors, and Effect Modifiers. Participants completed a comprehensive questionnaire regarding numerous potential confounders, including GERD-type symptoms. The GERD questions evaluated symptoms within the last 6 months, including the presence or absence of "heartburn, indigestion, or pain in your stomach"; the location

of the discomfort; whether food intake or antacid use alleviated the symptom; symptom relation to position (e.g., recumbency or bending over); medication use; and a history of a hiatal hernia diagnosis. For the primary analysis, GERD-type symptoms were defined as a "yes" response to all three of the following components: the presence or absence of "heartburn, indigestion, or pain in your stomach"; a location in the upper abdomen; and relief with antacid use. Detailed gastrointestinal symptom data were available for subjects completing the MHC questionnaire between 1964 and 1968. We also evaluated the following as potential confounders: smoking status (current smoking and ever smoked), recent alcohol use, ethnicity/race, aspirin use (from a question that asked if >6 pills a day), and pain medication use (from a question that asked if subject often used pain medications in the last year). Ethnicity was recorded as skin color and is reported herein as "White," "Black," and "Asian."

Statistical Analysis. Analyses used the Stata statistical package (version 8, Stata) and conditional logistic regression for matched pairs of cases and controls; we evaluated for differences by sex or ethnicity (that is, interaction) using cross-product terms in the logistic regression and stratum-specific ratios (31).

We evaluated the BMI [weight (kg) / height (m)²] as a continuous measure and within categories: "underweight" (<18.5), "normal" (18.5-24.9), "overweight" (25-29.9), and "obese" (≥30; ref. 32). Categories of abdominal diameter were created *a priori* (before analysis); they approximately reflected the quartile distributions within the control population (<20, 20-22.4, 22.5-24.9, and ≥25 cm).

Descriptive data pooled all the controls; individual analyses for each cancer type used individually matched controls. The study and analyses were approved by the institutional review board.

Results

Study Population. Subject characteristics are provided in Table 1. The proportion of males among cases was greater than among controls for all cancer types. The proportion of Whites was higher than Blacks for esophageal adenocarcinoma ($P = <0.01$) and for cardia carcinomas ($P = 0.01$); the proportion of Blacks was higher for esophageal squamous cell carcinoma ($P < 0.01$). BMI measurements were done during all the years studied (1964-1973) and were available for 339 (94%) cases and 2,588 (92%) controls. Abdominal diameter measurements were done from 1965 to 1969 but not in 1964 or from 1970 to 1973; they were available for 181 (52%) cases and 1,320 (47%) controls and availabilities were similar for the different cancer types (esophageal adenocarcinoma, 54%; cardia adenocarcinoma, 51%; and esophageal squamous cell carcinoma, 50%). The numbers of person in each analysis are contained within each table.

Esophageal Adenocarcinoma and Abdominal Diameter. A larger abdominal diameter (not adjusted for BMI) was a risk factor for esophageal adenocarcinoma, and the association strengthened progressively with larger diameters [odds ratio (OR), 3.47; 95% confidence interval (95% CI), 1.29-9.33; diameter, ≥25 versus <20 cm; Table 2]. When evaluated as a continuous variable across the full range of values, there was an ~10% increase in cancer risk for every centimeter increase in abdominal diameter (OR per centimeter, 1.10; 95% CI, 1.03-1.17).

The absolute abdominal diameter in centimeters (adjusted for BMI) directly contrasts different levels of abdominal diameter among persons with the same BMI. Abdominal diameter remained an independent risk factor after adjustment for BMI, suggesting that the association between abdominal diameter and cancer risk

Table 1. Subject characteristics

	Esophageal adenocarcinoma	Cardia adenocarcinoma	Esophageal squamous cell	Controls
No. subjects	101	105	144	2,800
Age at exam (y), mean (SD)	44.7 (10.2)	47.8 (11.9)	49.4 (10.4)	47.5 (11.0)
Race, n (%)				
White	92 (91)	90 (86)	90 (63)	2,186 (78)
Black	2 (2)	7 (7)	42 (29)	363 (13)
Asian	4 (4)	1 (1)	7 (5)	123 (4)
Other	3 (3)	7 (7)	5 (3)	120 (4)
Missing	0 (0)	0 (0)	0 (0)	8 (0)
Sex, n (%)				
Male	88 (87)	78 (74)	95 (66)	2,088 (75)
Smoking status, n (%)				
Ever smoked	74 (77)	76 (79)	112 (84)	1,682 (67)
Current smokers	45 (45)	47 (45)	82 (57)	999 (36)
Current alcohol use, n (%)				
None	13 (15)	19 (20)	23 (19)	512 (16)
3+ per day	21 (21)	22 (24)	387 (39)	302 (24)
BMI (kg/m ²), mean (SD)	26.7 (3.5)	26.1 (3.6)	24.4 (3.5)	25.6 (3.8)
Abdominal* diameter (cm), mean (SD)	24.0 (5.1)	22.5 (3.9)	22.5 (4.3)	22.3 (4.1)
Abdominal/thigh ratio,* mean (SD)	1.55 (0.33)	1.52 (0.49)	1.51 (0.31)	1.46 (0.32)
Years between examination and cancer diagnosis, mean (SD)	24.6 (8.6)	22.5 (9.7)	18.5 (0.8)	NA
Reflux-type symptoms,* mean (SD)	23 (46)	14 (22.6)	14 (18.2)	243 (15.4)

NOTE: Percentages and means were calculated using subjects with responses for any given category; percentage and mean calculations did not incorporate subjects with missing values.

*Numbers and proportions are among subjects from 1965 to 1969 when these data were collected.

Table 2. Anterior-posterior abdominal diameter and the risks of esophageal adenocarcinoma, gastric cardia adenocarcinoma, and esophageal squamous cell carcinoma (not adjusted for BMI)

Anterior-posterior diameter (cm)	Cases/controls (<i>n</i>)	Esophageal adenocarcinoma, OR (95% CI)*	Cases/controls (<i>n</i>)	Cardia adenocarcinoma, OR (95% CI)*	Cases/controls (<i>n</i>)	Esophageal squamous cell carcinoma, OR (95% CI)*
<20	8/100	1.00	16/129	1.00	19/131	1.00
20-22.4	13/115	0.92 (0.31-2.74)	12/122	0.69 (0.29-1.60)	24/144	0.91 (0.43-1.94)
22.5-25	12/95	2.35 (0.78-7.12)	12/75	1.17 (0.49-2.84)	14/114	0.89 (0.35-2.24)
≥25	22/80	3.47 (1.29-9.33)	14/87	1.28 (0.38-4.25)	15/128	0.78 (0.32-1.92)
OR per cm increase	55/390	1.10 (1.03-1.17)	54/413	1.03 (0.95-1.11)	72/517	1.00 (0.94-1.06)

*Cases and controls were matched for age, sex, and year of health checkup.

was not solely mediated through a larger BMI increasing the abdominal diameter. For the comparison between the highest and the lowest categories of abdominal diameter, for example, adjustment for BMI did not diminish the strength of the association (unadjusted OR, 3.47; 95% CI, 1.29-9.33 versus BMI-adjusted OR, 4.78; 95% CI, 1.14-20.11; Table 3).

Analyses of the abdominal diameter/thigh ratio (instead of the abdominal diameter alone) showed a significant association for analyses using the ratio as a continuous variable (OR per unit increase in ratio, 3.44; 95% CI, 1.25-9.43), although the trends were weaker for categorical comparisons (e.g., fourth versus first quartiles of the abdominal/thigh ratio OR, 1.58; 95% CI, 0.63-4.00 for ratio ≥1.61 versus <1.28). The significance of the associations did not change substantially after adjustment for BMI (data not shown).

Cardia Adenocarcinoma and Abdominal Diameter. A larger abdominal diameter (not adjusted for BMI) was not a substantial risk factor for cardia carcinomas (OR, 1.28; 95% CI, 0.38-4.25; diameter, ≥25 versus <20 cm; Table 2). This association did not change after adjustment for BMI (OR, 1.27; 95% CI, 0.25-6.51; Table 3).

There was also no significant association between the abdominal/thigh ratio and the risk of cardia carcinoma, whether the ratio was evaluated as a continuous variable (OR per unit increase in ratio, 1.38; 95% CI, 0.64-2.99) or as a categorical comparison between the fourth and the first quartiles of the abdominal/thigh ratio (OR, 0.82; 95% CI, 0.31-2.16 for ratio ≥1.61 versus <1.28).

Esophageal Squamous Cell Carcinoma and Abdominal Diameter. A larger abdominal diameter (not adjusted for BMI) was also not a substantial risk factor for esophageal squamous cell carcinomas (OR, 0.78; 95% CI, 0.32-1.92; diameter, ≥25 versus <20 cm; Table 2). This

association did not change after adjustment for BMI (OR, 1.29; 95% CI, 0.25-6.51).

There was no significant association between the abdominal/thigh ratio and the risk of esophageal squamous cell carcinoma whether the ratio was evaluated as a continuous variable (OR per unit increase in ratio, 1.52; 95% CI, 0.70-3.32) or as a categorical comparison between the fourth and the first quartiles of the abdominal/thigh ratio (OR, 0.85; 95% CI, 0.31-2.34 for ratio ≥1.61 versus <1.28).

Mediation by GERD Symptoms. A large abdominal size has been associated with an increased risk of GERD-type symptoms possibly through mechanical means of increased intra-abdominal pressure (11, 14). Because GERD is strongly associated with the risk of esophageal adenocarcinoma, any association between abdominal size and esophageal adenocarcinoma may be at least partially mediated by larger abdominal sizes increasing the risk of GERD (10). If GERD is in the causal pathway between abdominal size and esophageal adenocarcinoma, then "adjusting" for GERD symptoms in the logistic model should diminish or eliminate any association between abdominal size and esophageal adenocarcinoma.

Adjustment for GERD-type symptoms did not decrease the strength of the association between abdominal diameter and esophageal adenocarcinoma (OR, 3.90; 95% CI, 1.31-11.60 without GERD in the model versus OR, 3.91; 95% CI, 1.26-12.02 with GERD in the model for the comparison of an abdominal diameter ≥25 versus <20 cm); this was despite a strong association between the presence of GERD-type symptoms and the odds of esophageal adenocarcinoma (OR, 4.36; 95% CI, 2.37-8.00).

BMI and Cancer Risk. BMI was positively correlated with the risk of esophageal adenocarcinoma, less

Table 3. Anterior-posterior abdominal diameter and the risks of esophageal adenocarcinoma, gastric cardia adenocarcinoma, and esophageal squamous cell carcinoma (adjusted for BMI)

Anterior-posterior diameter (cm)	Esophageal adenocarcinoma/control (<i>n</i>)	Esophageal adenocarcinoma, OR (95% CI)*	Cardia adenocarcinoma/control (<i>n</i>)	Cardia adenocarcinoma, OR (95% CI)*	Esophageal squamous cell carcinoma/control (<i>n</i>)	Esophageal squamous cell carcinoma, OR (95% CI)*
<20	8/100	1.00	16/129	1.00	19/131	1.00
20-22.4	13/115	0.81 (0.24-2.67)	12/122	0.75 (0.30-1.86)	24/144	1.77 (0.74-4.26)
22.5-25	12/95	1.17 (0.28-4.98)	12/75	1.27 (0.44-3.65)	14/114	1.54 (0.50-4.74)
≥25	22/80	4.78 (1.14-20.11)	14/87	1.27 (0.25-6.52)	15/128	1.29 (0.32-5.20)

*Cases and controls were matched for age, sex, and year of health checkup.

strongly correlated with the risk of cardia adenocarcinoma, and inversely correlated with the risk of esophageal squamous cell carcinoma (Table 4). Adjusting for abdominal diameter slightly decreased the association between BMI and esophageal adenocarcinoma from OR per unit BMI of 1.10 (95% CI, 1.04-1.17) to 1.09 (95% CI, 0.98-1.21).

Supplemental Analyses. There was no evidence of confounding by current smoking status, recent alcohol use patterns, daily heavy aspirin use, pain medication use, or race/ethnicity. The OR for a saturated model containing abdominal diameter as a categorical variable and all of these confounders (OR, 1.57; 95% CI, 1.17-2.12) was similar to the OR for only the bivariate association between abdominal diameter and esophageal adenocarcinoma (OR, 1.49; 95% CI, 1.13-1.97). Similar results were found with cardia adenocarcinoma and squamous cell carcinoma (data not shown). Similarly, there was no evidence of statistical or qualitative evidence of interaction, for example, between ethnicity, abdominal diameter categories, and cancer risk. Given the absence of evidence for confounding, and because the cases and controls were exactly matched for age at MHC examination, sex, and year of MHC, each logistic model contained only the exposure and outcome variables.

Two subjects developed their cancers (one esophageal adenocarcinoma and one squamous cell carcinoma) within the first year after their interview date; exclusion of these subjects did not influence the estimates shown.

Discussion

This is the first cohort study, to our knowledge, which has evaluated the association between abdominal obesity and the risk of esophageal and cardia adenocarcinomas. There were several findings: (a) there was an independent association between increasing abdominal diameter and esophageal adenocarcinoma, (b) this association was independent of BMI, (c) this association was not substantially mediated by GERD-type symptoms despite the presence of an association between GERD-type symptoms and esophageal adenocarcinoma, and (d) there was no association between abdominal diameter and the risks of cardia carcinoma or esophageal squamous cell carcinoma.

This study extends the findings of previous analyses of esophageal and cardia carcinomas, although almost no

data exist on the association between abdominal obesity and these cancers (5). A prior study of 30 patients with a mixture of cardia or distal esophageal cancers showed an increased hazard ratio of 1.46 (95% CI, 1.05-2.04) per 10 cm increase in the waist circumference, although that study did not stratify by cancer location (33). Similarly, persons with an abdominal obesity pattern have recently been shown to be at increased risk for Barrett's esophagus, a metaplastic condition of the esophagus that increases the risk of esophageal adenocarcinoma (34, 35). A cross-sectional study of patients with Barrett's esophagus suggested that abdominal obesity may also increase the risk of neoplastic progression from Barrett's esophagus to esophageal adenocarcinoma, although this study did not have population controls (36).

These findings, if causal, suggest that abdominal obesity increases the risk of esophageal adenocarcinoma, independent of BMI. There are several potential mechanisms whereby this might occur. First, abdominal fat may directly cause GERD, a strong risk factor for esophageal adenocarcinoma. A recent study within the MHC cohort suggested that abdominal obesity was independently associated with GERD-type symptoms, that this association was stronger among Whites than among African Americans, and that men were more likely to have abdominal obesity than women (11). The abdominal obesity-GERD association may be through a direct increase in intra-abdominal pressure, thereby causing increased reflux, or through other mechanisms (11, 14-16, 18, 37).

The current study, however, does not provide general support for this mechanism, as adjusting for GERD-type symptoms did not markedly diminish or eliminate the association between abdominal diameter and cancer risk. Second, fat is metabolically active; it produces numerous compounds that circulate throughout the body and the metabolic activity of intra-abdominal fat differs from peripheral fat (38). Some of these metabolic products, such as insulin-like growth factor and leptin, have been associated with malignancies possibly through the induction of pro-growth changes in the cell cycle, decreased cell death, and similar pro-neoplastic changes at the cellular level (20, 39). These compounds may directly influence cancer development or may modify the risk after injury from other factors (such as GERD). We did not find, however, a difference in the magnitude of the association between abdominal diameter and cancer risk between patients with and patients without GERD-type symptoms (data not shown).

Table 4. BMI and the risks of esophageal adenocarcinoma, gastric cardia adenocarcinoma, and esophageal squamous cell carcinoma

BMI (kg/m ²)	Esophageal adenocarcinoma/controls (n)	Esophageal adenocarcinoma, OR (95% CI)*	Cardia carcinoma/controls (n)	Cardia adenocarcinoma, OR (95% CI)*	Esophageal squamous cell carcinoma/control (n)	Esophageal squamous cell carcinoma, OR (95% CI)*
<18.5	1/8	1.36 (0.12-15.52)	0/11	Not calculable	3/18	0.91 (0.19-4.29)
18.5-24.9	28/345	1.00	43/359	1.00	78/480	1.00
25-29.9	51/307	2.20 (1.31-3.67)	40/338	0.91 (0.55-1.53)	46/436	0.66 (0.44-1.00)
≥30	14/75	3.17 (1.43-7.04)	16/83	2.04 (0.99-4.21)	9/128	0.30 (0.13-0.72)
OR per unit BMI increase		1.10 (1.04-1.17)		1.04 (0.98-1.09)		0.89 (0.84-0.94)

*Cases and controls were matched for age, sex, and year of health checkup. BMI results were also adjusted for ethnicity (White versus non-White given small numbers).

There are several strengths of this analysis. First, the population consisted of a diverse patient group from a broad geographic base; thus, the results can likely be generalized to similar large populations. Second, the data were of high quality. The measurements were obtained using a systematic protocol, follow-up cases were identified using high-quality cancer registries, and the data from this cohort have been validated and used in numerous studies. Third, the cohort design permits the evaluation of abdominal size before the weight loss that often accompanies gastrointestinal malignancies; a large cohort thus offers one of the few opportunities for evaluating the association of abdominal size and cancer risk. Fourth, the number of cancers detected is fairly large for a cohort study of an uncommon cancer. Finally, the availability of comprehensive questionnaires permitted the analysis of several potential confounders.

There are several potential limitations of this analysis. First, observational studies cannot establish cause and effect, because other associated factors may act as confounders (40). However, if the main risk was from a large abdominal diameter causing GERD (which in turn increased the risk of esophageal adenocarcinoma), we might expect the GERD to lead to weight reduction; under these circumstances, the abdominal diameter-cancer associations would only become weaker. Similarly, additional analyses that adjusted for physical activity, smoking, gender, age, aspirin use, and alcohol use suggested that there was little evidence of confounding by these factors; however, we cannot exclude confounding by unmeasured factors (such as differences in diet) or incomplete control of confounding by measured factors.

Second, for the evaluation of mediation by reflux-type symptoms, the symptom measure likely misclassified some patients with non-reflux dyspepsia as having "reflux-type" symptoms. However, a prior large analysis of several thousand subjects with GERD-type symptoms in the same cohort found that the incorporation of several qualifying questions that are more specific for GERD (including relation to recumbency or bending over) did not substantially change the associations between abdominal diameter and GERD-type symptoms (38). Nevertheless, there is likely some residual misclassification of GERD based on symptoms alone.

Third, it is unknown whether the primary association of importance is total abdominal fat/size or only intra-abdominal fat. Abdominal diameter is an indirect and imperfect measure of intra-abdominal fat; although correlated, the associations between the two may differ (41). We had available a single measure of body mass and abdominal size; abdominal circumference was not available in this data set.

Fourth, the abdominal measurements and GERD-type symptoms were assessed at a single point in time; although body weight and abdominal size typically do not typically decrease with age, we were not able to evaluate long-term patterns of anthropometrics.

Fifth, the total number of cancers is relatively small, which decreases the precision of the estimates, particularly for subgroup analyses.

Sixth, some of the controls may have left the membership and developed a target cancer as a nonmember of the health plan (and thus been misclassified as nondiseased); however, the relative rarity of the cancer makes such misclassification unlikely.

In summary, this is the first evaluation of abdominal size as an independent risk factor for esophageal and cardia carcinomas in a large population. The results suggest that abdominal diameter, independent of BMI, is a risk factor for the subsequent development of esophageal adenocarcinoma but not for cardia carcinoma or for esophageal squamous cell carcinoma. Given that abdominal obesity is more common among males, these findings suggest that recent increases in obesity may disproportionately increase the risk of esophageal adenocarcinoma in males more than in females. Further research is needed to evaluate whether modifications of abdominal obesity, presumably through weight reduction, can influence the risks of esophageal adenocarcinomas.

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Cancer Epidemiol Biomarkers Prev 2008;17:352-358.

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