Body Mass Index and Adenocarcinomas of the Esophagus or Gastric Cardia: A Systematic Review and Meta-analysis

Ai Kubo[1,2] and Douglas A. Corley[1,3]

[1]Division of Research, Kaiser Permanente Northern California, Oakland, California; [2]Mailman School of Public Health, Columbia University, New York, New York; and [3]Division of Gastroenterology, University of California, San Francisco, San Francisco, California

Abstract

Background: **The incidence of esophageal adenocarcinoma has increased markedly in recent decades in many countries. Obesity is a potential risk factor, although the results of individual studies differ. We did a systematic review and statistical synthesis of studies that evaluated the association between body mass index (BMI) and the risk of esophageal adenocarcinoma or the adjacent gastric cardia adenocarcinoma.**

Methods: **We identified potential studies using Medline, the Web of Science database, a manual review of the literature and expert bibliographies. Studies were included if they reported (*a*) a measure of body mass; (*b*) the occurrence of esophageal or cardia adenocarcinoma diagnosis; and (*c*) a relative risk or odds ratio (OR) with confidence intervals (CI) or provided sufficient data to permit their calculation.**

Results: **We identified 14 studies (2 cohort, 12 case-control; 2,488 esophageal and 2,509 cardia adenocarcinomas). A high BMI (>25) was associated with an increased risk of esophageal adenocarcinoma (males, OR, 2.2; 95% CI, 1.7-2.7; females, OR, 2.0; 95% CI, 1.4-2.9). Higher levels of BMI were associated with increased risk (overweight males, OR, 1.8; 95% CI, 1.5-2.2; obese males, OR, 2.4; 95% CI, 1.9-3.2). The overall associations with cardia cancer were heterogeneous, although stratification by study location provided homogeneous results for populations from the United States or Europe. A high BMI was weakly associated with the risk of cardia adenocarcinoma (OR, 1.5; 95% CI, 1.3-1.8; $P_{heterogeneity} = 0.38$).**

Conclusions: **Pooled results from observational studies support a positive association between high BMI and the risk for esophageal and possibly for cardia adenocarcinoma.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):872–8)

Introduction

The incidence of esophageal adenocarcinoma has been increasing rapidly in several countries, although the reason for the increase is unclear. The incidence of esophageal adenocarcinoma increased ~400% during the past three decades, the most rapid rate of increase of any cancer in the United States (1-4). Similar incidence changes have been seen in several countries (5-7). The proportion of gastric cancers located in the cardia (at the gastroesophageal junction adjacent to the esophagus) has also increased substantially (6). The mortality from these cancers is high and the response to treatments for advanced-stage disease is poor, suggesting that an effective method for mortality reduction may be through early intervention on modifiable risk factors (8).

Obesity is one of the strongest emerging risk factors for many cancers in Western countries (9); however, existing epidemiologic studies of the association between body mass index (BMI) and the risk of esophageal or cardia adenocarcinoma have conflicting results. Higher BMIs were associated with an increased risk of esophageal adenocarcinoma in some studies (10-17), whereas other reports found no association or a negative association (18-20). It is unclear whether these disparate results are due to true differences between the study populations or due to methodologic differences in exposure definitions, outcome definitions, or other aspects of the study design or analysis.

There are several advantages to using a systematic review for the investigation of exposure-disease associations. Data synthesis can help evaluate the influence of different study populations, study designs, etc., on the exposure-disease association. It may also help explore associations that individual studies may lack the power to investigate, such as the influence of gender, levels of BMI, or the presence of confounding factors.

We did a systematic review and meta-analysis of observational studies that evaluated the association between BMI and the risk of esophageal adenocarcinoma or gastric cardia with an emphasis on the creation of more standardized exposure definitions to better compare results between studies and the evaluation of differences in study design and study populations.

Materials and Methods

Search Strategy. We searched for published articles and abstracts that evaluated the associations between BMI and the risk of esophageal or gastric cardia carcinomas. First, we searched Medline (through PubMed, an electronic search engine for published articles) for the years 1966 through July 2005. Medical subject headings or keywords used for the Medline search included [Esophag* AND (adenocarcinoma OR carcinoma OR cancer)] combined with ''body mass index OR BMI OR obesity.'' A similar search was done using the word ''oesophagus,'' a common British spelling for esophagus. Identical searches were done using ''cardia'' AND (adenocarcinoma OR carcinoma OR cancer). Second, we searched the Institute for Scientific Information Web of Science, an international electronic database that includes articles from 8,700 journals and abstracts of meetings from several professional societies (21). Search terms for the Web of Science search were similar to those for Medline. Third, we manually searched the bibliographies of retrieved articles. Fourth, we manually searched expert opinion review articles and reviewed bibliographies from subject experts.

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Requests for reprints: Douglas A. Corley, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612. Phone: 510-891-3811; Fax: 510-891-3606. E-mail: Douglas.Corley@kp.org

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Table 1. Study characteristics

Authors	Year	Design	Location	No. cases	Case population and ascertainment	Comparison population	Confounders adjusted for
Brown (11)	1995	Case-control	United States	n = 174 (AE + CA); n = 750 controls	Cancer registry	Population controls	A, C, E, L, T, S
Chen (12)	2002	Case-control	United States	n = 124 (AE); n = 449 controls	Cancer registry	Population controls	
Cheng (13)	2000	Case-control	United States	n = 74 (AE); n = 74 controls	Cancer registry	United Kingdom health service registries	F, D
Chow (14)	1998	Case-control	United States	n = 292 (AE); n = 201 (CA); n = 695 controls	Cancer registry	Population controls	A, G, L, R, T, X
Engeland (15)	2004	Cohort	Norway	n = 575 (AE); total n = 2 million	General Norwegian population	General Norwegian population	A
Incarbone (19)	2000	Case-control	Italy	n = 262 (AE + CA); n = 262 controls	Single hospital	Hospital controls	
Ji (48)	1997	Case-control	China	n = 185 (CA); n = 1,451 controls	Multiple hospitals in defined area	Shanghai area resident registry	A, T*, E*, S, H
Kabat (18)	1993	Case-control	United States	n = 194 (distal AE + CA); n = 6,772 controls	Multiple hospitals	Hospital controls	A, D, E, L, S, T
Lagergren (16)	1999	Case-control	Sweden	n = 189 (AE, excluding distal); n = 262 (CA); n = 820 controls	Cancer registry	Population registry	A, C, D, E, G, H, P, S, T
Lindblad (10)	2005	Case-control	United Kingdom	n = 287 (AE); n = 10,000 controls	General Practitioner Research database	General Practitioner Research database	A, G, S, E, H
Tran (49)	2004	Cohort	China	n = 1089 (CA); total n = 29,584	Monthly visit by health worker	General population	A, G
Wu (47)	2001	Case-control	United States	n = 222 (AE); n = 277 (CA); n = 1,356 controls	Cancer registry	Population controls	A, G, R, S, T, Y
Zhang (20)	1996	Case-control	United States	n = 95 (AE + CA); n = 132 controls	Single hospital	Hospital controls	A, B, D, E, G, H, K, R, S, T
Zhang (50)	2003	Case-control	China	n = 300 (CA); n = 258 controls	Single hospital	Hospital controls	

Abbreviations: A, age; B, Barrett's esophagus; C, energy intake; D, diet; E, alcohol/ethanol; F, breast-feeding; G, gender; H, history of ulcer, reflux, or gastric disease; J, family history; K, history of hypertension; L, location, area, hospital; M, marital status; P, physical activity; R, race; S, SES, education; T, tobacco; V, vitamin intake; X, proxy or respondent status; Y, birthplace; Z, period, time between interview and disease.
*Adjusted for male only.

Study Selection. Studies were included if they reported all of the following: (*a*) a measure of body mass; (*b*) the diagnosis of esophageal or cardia adenocarcinoma; and (*c*) a relative risk ratio or odds ratio (OR) with confidence intervals (CI) or sufficient data to permit their calculation. The inclusion criteria were not otherwise restricted by study size, publication type, or language of publication. We excluded studies that provided only estimates that combined esophageal adenocarcinoma and esophageal squamous cell carcinoma.

Data Abstraction. Data abstracted included exposure measurement method (self-report versus measured BMI versus diagnosis of obesity), exposure definitions (e.g., BMI definitions of overweight or obese), outcome definitions (esophageal adenocarcinoma, cardia carcinoma, or a combination of both), total number of persons or person-years in each comparison group, ORs or risk ratios with and without adjustment for potential confounders, potential confounders used for adjustment, study design (cohort versus case control), and the source of the study population. Two investigators (A.K. and D.A.C.) independently abstracted the primary outcome and exposure data; discordant results were resolved by consensus. Data reporting conforms with the Meta-analysis of Observational Studies in Epidemiology study group guidelines (22).

Exposure Definition. We defined body mass categories using the following BMI categories [BMI = weight (kg) / height $(m)^2$]: normal (BMI between 18.5 and 25), overweight (BMI between 25 and 28), and obese (BMI $\geq$28); these groupings represented the divisions or quartiles most frequently reported in the articles and they differ somewhat from BMI categories in common use (overweight, BMI 25-29.9; obese, BMI $\geq$30; ref. 23). We also created a category that included both overweight and obese (BMI $\geq$25). For each study, we selected the BMI-cancer association that most closely approximated each of these categories and the date of BMI determination that was the most commonly reported. We included more than one estimate from some studies (e.g., if a study reported an OR for persons with a BMI 25-28 and an OR for persons with a BMI $\geq$28; both ORs were included in the summary estimate for a BMI $\geq$25). For studies that did not provide estimates for different BMI categories, we calculated estimates for each category using the mean BMI and SD or the OR per unit BMI (12, 19, 20). These calculations assumed that BMI was normally distributed in the populations. We used estimates adjusted for potential confounders whenever they were available; if no adjusted estimates were provided, unadjusted estimates were used or calculated from the data. We assumed that an OR was a valid approximation of a risk ratio.

Outcome Definition. An outcome was defined as any of the following cancer diagnoses (or cancer-related deaths): esophageal adenocarcinoma alone, cardia carcinoma alone (the definition of cardia cancer includes cardioesophageal junction, esophagogastric junction, and gastroesophageal junction carcinomas; ref. 24), or the combined reporting of esophageal adenocarcinoma with cardia carcinoma.

Statistical Analysis. All analyses used the STATA statistical package with the *meta, metainf*, and *metabias* commands (version 8, STATA Corporation, College Station, TX).

Summary OR estimates were calculated using either relative risks (for cohort studies) or ORs (for case-control studies).

Summary OR estimates were calculated based on the assumption of fixed effects and heterogeneity was tested using the Mantel-Haenszel method (25). We also evaluated for heterogeneity by comparing the results between the fixed-effects model and a random-effects model (25); if results were homogeneous, the fixed-effects model was reported. As statistical tests for heterogeneity lack substantial power, heterogeneity was considered present if $P \leq 0.1$ (rather than $P < 0.05$) or if there was a >20% difference in the summary estimates between the fixed effects and random effects models. If these tests suggested heterogeneity, we explored potential causes (see below; refs. 26-29).

Qualitative Assessment/Assessment of Heterogeneity. The use of quality scoring in meta-analyses is controversial. Numerous criteria have been suggested for evaluating study quality; however, different scoring systems may yield substantially different results, raising concerns about validity (26, 30, 31). The adequacy of randomization and blinded allocation to study groups have been shown to influence study outcome in randomized trials, but little information is available for observational studies (32-35).

We assessed study quality and potential heterogeneity using several methods and evaluated the consistency of our results by performing sensitivity analyses. First, we assessed the statistical heterogeneity between trials for the primary summary estimates (see above). Second, to exclude an excessive influence of any single study, we evaluated whether exclusion of any single study substantially altered the magnitude or heterogeneity of the summary estimate, compared with the summary estimate containing all the studies. Third, because different study designs and populations may incorporate different biases, we stratified analyses by several factors (32-38).

Stratified analyses for potential sources of heterogeneity evaluated factors postulated to influence the BMI versus cancer association. Stratifying factors were established *a priori* (i.e., before data analysis) and included level of BMI (see exposure definitions), gender, cancer location (esophageal versus cardia versus studies that combined esophageal with cardia), and study population (country of origin). Studies not providing data for the stratifying factor of interest were excluded from any given analysis (e.g., studies not reporting gender-specific data were excluded from summary estimates stratified by gender).

Tests for publication bias assess the assumption that studies with statistically significant differences between the intervention groups (i.e., ''positive studies'') are more likely to be published than studies with no significant differences in outcome (i.e., ''negative studies''). The presence of bias (including publication bias) was assessed using quantitative and qualitative methods. First, we calculated a correlation coefficient between the ORs and their SEs (a surrogate for sample size); publication bias was considered present if $P \leq 0.1$ (39). Second, we evaluated for unusual publication patterns by qualitatively assessing funnel plots of the ORs versus their SEs (28).

Results

We identified a total of 146 published articles or meeting abstracts. A manual review of the titles and abstracts provided 22 publications that seemed to meet the inclusion

Table 2. Exposure and outcome definitions

Authors	Exposure (source)	Exposure (definitions)				Outcome (source)	Outcome (definitions)
		BMI reference*	BMI overweight	BMI obese	BMI overweight + obese		
Brown (11)	Self-report BMI 5y before diagnosis	<23.1	26.6-28.9	≥28.9+	≥26.6	Cancer registry and chart review	AE and CA combined
Chen (12)	Self-report BMI 7-9 y before the study	<25 †	25-28	≥28	≥25	Cancer registry and pathology report	AE
Cheng (13)	Self-report BMI at age 20 y	<19.5			≥22.7	Cancer registry and pathology report	AE
Chow (14)	Self-report BMI 1 y before diagnosis	<23			≥27	Cancer registry	AE, CA separated
Engeland (15)	Measured BMI at the enrollment of the study	18.5-25	25-30	≥30	≥25	Cancer registry	AE
Incarbone (19)	Measured BMI at the enrollment of the study	<25 †	25-28	≥28	≥25	Medical record	AE and CA combined
Ji (48)	Self-report BMI 1 y before diagnosis	<19.5			≥22.2	Medical record	CA
Kabat (18)	Self-report BMI 5 y before diagnosis	<22		≥28	≥28	Medical record	AE (distal) and CA combined
Lagergren (16)	Self-report BMI 20 y before diagnosis	<22.3	25-30	≥30	≥25.6	Cancer registry	AE, CA separated
Lindblad (10)	Measured BMI 2 y before diagnosis	20-25	25-30	≥30	≥25	General Practitioner Research database	AE, CA separated
Tran (49)	Measured BMI at the enrollment of the study	<20			≥23	Monthly visit by health workers	CA
Wu (47)	Self-report BMI 1 y before diagnosis	<23		≥28	≥28	Cancer registry	AE, CA separated
Zhang (20)	Self-report BMI at diagnosis	<25 †	25-28	≥28	≥25	Medical record	AE and CA combined
Zhang (50)	Self-report BMI before diagnosis	18.5-24		≥28	≥24	Cancer hospital record	CA

*If different BMI quartiles were provided for each gender, we report only the male values.
†These values were calculated from the mean BMI and BMI distribution.

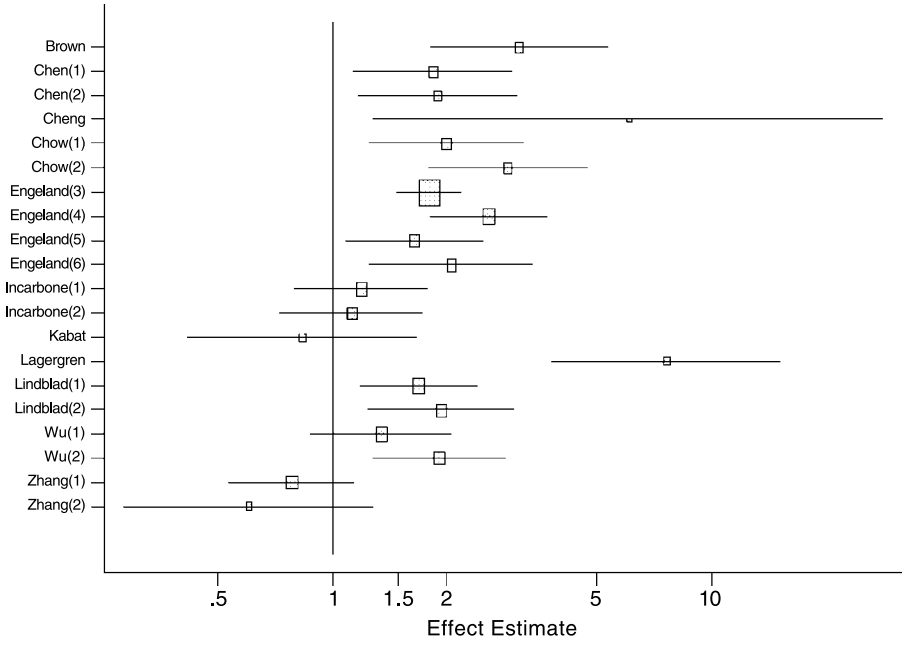

Figure 1. Esophageal adenocarcinoma versus high BMI (overweight + obese) for all studies. Individual study estimates (including estimates that combined esophageal adenocarcinoma with cardia adenocarcinoma), male and female. No summary estimate is provided given heterogeneous results. *1,* overweight (male + female); *2,* obese (male + female); *3,* overweight males; *4,* obese males; *5,* overweight females; *6,* obese females.

criteria. The excluded studies consisted of review articles, animal experiments, case series that lacked a comparison group, or studies that did not report on the subject of interest. The 22 publications underwent a complete data abstraction; eight additional studies were excluded after data abstraction because the results included only estimates that combined both esophageal squamous cell and adenocarcinoma (9, 40-43) or they lacked data that would permit calculation of relative risk estimates (44). For studies that had more than one publication, only the most recent or most complete results were included (45, 46).

The remaining 14 studies were included in the primary analyses (Tables 1 and 2). The studies reported results in three ways: esophageal adenocarcinoma alone (10, 12-16, 47), cardia carcinoma alone (10, 14, 16, 47-50), or estimates that combined esophageal adenocarcinoma with cardia carcinoma (11, 18-20). The studies included 2,488 cases of esophageal adenocarcinoma (including those studies that combined esophageal and cardia carcinomas) and 2,509 cases of gastric cardia adenocarcinoma (excluding those studies that combined esophageal and cardia carcinoma; refs. 10-20, 48-50).

Esophageal Adenocarcinoma. An evaluation of increased BMI (overweight or obese) versus cancer for all esophageal adenocarcinoma studies (including studies that combined esophageal and cardia carcinomas) provided heterogeneous results (OR, 1.7; 95% CI, 1.6-1.9; test for homogeneity $P < 0.01$; Fig. 1; Table 3).

Stratification by cancer location and BMI category showed a homogeneous positive association between increased BMI (overweight or obese) and esophageal adenocarcinoma alone (excluding studies that combined esophageal and cardia carcinomas) for both males and females (Fig. 2). The strength of the association increased with increasing BMI (Table 3). The risk for overweight males (OR, 1.8; 95% CI, 1.5-2.2; $P = 0.93$) increased further for obese males (OR, 2.4; 95% CI, 1.9-3.2; $P = 0.35$). Similar results were seen in females (overweight OR, 1.5; 95% CI, 1.1-2.2; $P = 0.57$ versus obese OR, 2.1; 95% CI, 1.4-3.2; $P = 0.94$).

Cardia Adenocarcinoma. An evaluation of increased BMI (overweight or obese) versus cardia adenocarcinoma provided heterogeneous results (OR, 1.2; 95% CI, 1.1-1.3; $P < 0.01$). The heterogeneity was not improved after stratification by BMI category or gender (results not shown). Stratification by geographic location (United States or Europe versus other) or source population (hospital versus population-based) provided more homogeneous results for the United States and Europe (male and female, overweight + obese OR, 1.5; 95% CI, 1.3-1.8; $P = 0.38$; Fig. 3; Table 4). The stratified results for studies from China included too few studies to be informative. An evaluation of potential sources for this heterogeneity is provided below.

Table 3. Meta-analysis results: BMI versus esophageal adenocarcinoma

	BMI category (versus normal weight)	OR (95% CI)	$P_{homogeneity}$	No. studies
Overall				
Both gender	Overweight + obese	1.7 (1.6-1.9)	<0.01	11
Males	Overweight + obese	2.2 (1.7-2.7)	0.01	6
Females	Overweight + obese	2.0 (1.4-2.9)	0.20	5
Esophageal adenocarcinoma only				
Both genders	Overweight	1.9 (1.5-2.4)	0.02	6
	Obese	2.4 (2.0-2.8)	<0.01	6
	Overweight + obese	2.1 (1.7-2.4)	0.01	7
Males	Overweight	1.8 (1.5-2.2)	0.93	3
	Obese	2.4 (1.9-3.2)	0.35	3
	Overweight + obese	2.2 (1.8-2.7)	0.11	4
Females	Overweight	1.5 (1.1-2.2)	0.57	3
	Obese	2.1 (1.4-3.2)	0.94	3
	Overweight + obese	1.9 (1.5-2.5)	0.20	5

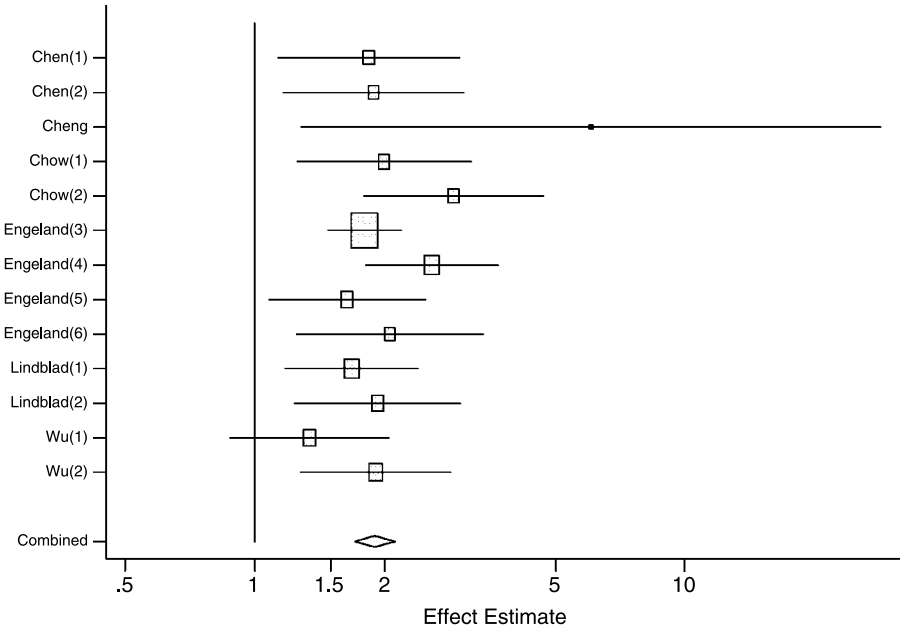

Figure 2. Esophageal adenocarcinoma versus high BMI (overweight + obese), male and female. This estimate excludes studies that combined esophageal adenocarcinoma with cardia adenocarcinoma and excludes the study by Lagergren et al. (see heterogeneity analysis). Square size indicates weight each study contributed to the summary estimate. *1,* overweight (male + female); *2,* obese (male + female); *3,* overweight males; *4,* obese males; *5,* overweight females; *6,* obese females.

Evaluation of Heterogeneity. The initial summary estimates for esophageal adenocarcinoma and cardia carcinoma were heterogeneous, as described above. Stratification by BMI category diminished but did not substantially resolve the heterogeneity; however, additional stratification by gender provided more homogeneous results for esophageal adenocarcinoma (Table 3). Similarly, stratification by country of origin provided more homogeneous estimates for cardia carcinoma. Stratification of the entire population by exposure measurement (e.g., self-report versus measured), study design (case control versus cohort), and adjustment for confounders (including only studies with estimates adjusted for potential confounders versus including all studies) did not substantially influence the initial heterogeneity.

We evaluated the possibility that a single, dominant study influenced the main results by systematically excluding each study, and evaluating its influence on the magnitude and heterogeneity of the main summary estimates. The evaluation for influential studies of the esophageal adenocarcinoma analyses showed a single such study (16); exclusion of this study provided homogeneous results for both genders combined (BMI > 25; OR, 1.9; 95% CI, 1.7-2.1; $P = 0.45$). This study by Lagergren et al. (16) showed a much stronger association between increased BMI and esophageal adenocarcinoma (OR, 7.6; 95% CI, 3.8-15.2) than was found in the other studies (Figs. 1 and 2). This study also differed from the other studies in that its outcome definition excluded distal esophageal cancers (all distal esophageal cancers within 2 cm of the gastroesophageal junction unless they also showed Barrett's esophagus). In contrast, a study that included only distal esophageal adenocarcinomas and cardia cancers found no significant association between cancer and increased BMI (18); see the discussion for a potential interpretation of this finding.

The evaluation for influential studies of the cardia adenocarcinoma analyses did not show any single influential study, although one study found an inverse association between BMI and the risk of cardia adenocarcinoma (50). The reason for this inverse association is unknown. In contrast, the other studies in the United States, Europe, and China showed a positive association or no association.

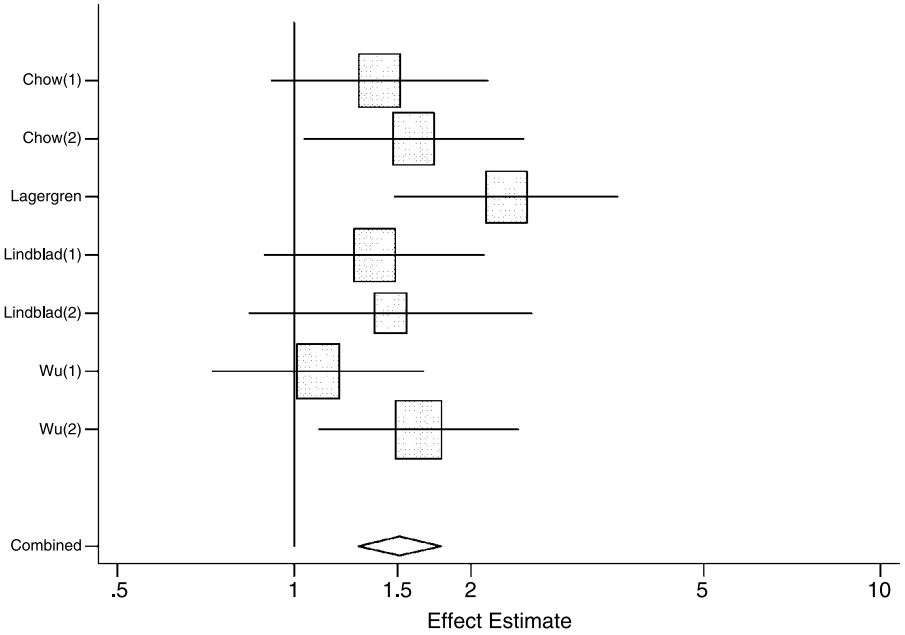

Figure 3. High BMI (overweight + obese) versus cardia adenocarcinoma. United States and European studies only, male and female. Square size indicates weight each study contributed to the summary estimate. *1,* Overweight; *2,* obese.

Table 4. Meta-analysis results: BMI versus gastric cardia adenocarcinoma (males and females)

Gastric cardia	BMI category (versus normal weight)	OR (95% CI)	$P_{homogeneity}$	No. studies
Overall	Overweight	1.2 (1.0-1.5)	<0.01	5
	Obese	1.5 (1.2-1.9)	<0.01	5
	Overweight + obese	1.2 (1.1-1.3)	<0.01	7
United States + European studies only	Overweight	1.5 (1.1-1.8)	0.16	4
	Obese	1.9 (1.3-2.7)	0.08	4
	Overweight + obese	1.5 (1.3-1.8)	0.38	4
Chinese studies only	Overweight	0.6 (0.4-0.9)	0.41	1
	Obese	0.5 (0.2-1.3)	0.18	1
	Overweight + obese	1.0 (0.8-1.1)	<0.01	3

Publication Bias. The rank correlation test did not suggest the presence of publication bias for the main summary estimates for either esophageal adenocarcinoma ($P = 0.52$) or cardia carcinoma ($P = 0.53$). A review of funnel plots also did not show patterns suggestive of publication bias.

Discussion

Our pooled results of observational studies support a positive association between increased BMI and the risk of esophageal adenocarcinoma. The strength of the association increased with increasing BMI and there was a trend towards a stronger association in men compared with women. The results of the gastric cardia analyses were mixed; we observed a weaker association between increased BMI and cardia cancer in studies from the United States and Europe and no clear association in studies from China, with one study showing a negative association (50).

These results extend prior observational studies by permitting additional evaluation of subgroups (e.g., by gender and cancer site), the ability to more precisely evaluate risk with increasing BMI, and by providing more stable estimates of the BMI versus cancer associations. Examined singly, several existing observational studies did not show a consistent association between BMI and cancer: The differences in exposure definitions made comparisons between studies difficult and many studies lacked the power to make meaningful subgroup analyses. The stratification by site in this study suggested that BMI was not a clear risk factor in the studies that combined esophageal and cardia cancers together; however, a clearer association was shown when analyses were limited to studies of esophageal adenocarcinoma alone. This finding of a stronger association of BMI with more proximal esophageal adenocarcinomas was strengthened by the analysis of heterogeneity. This analysis showed that the BMI-cancer association was strongest in the study that primarily included only esophageal adenocarcinomas that were >2 cm from the gastroesophageal junction (16). Cumulatively, these findings suggest that the association between BMI and adenocarcinoma is weakest in the gastric cardia and increases with increasing distance from the gastroesophageal junction.

The association between increased BMI and esophageal and gastric cardia adenocarcinoma is consistent with a similar association seen with other cancers, although the biological mechanism remains unclear (9). One proposed pathway is that increased BMI may increase the risk of gastroesophageal reflux, which has been associated with Barrett's esophagus (a potentially precancerous condition) and esophageal adenocarcinoma; however, no study has investigated this entire pathway within a single population and some studies have not found a consistent relationship between BMI and reflux (14, 16, 51). Alternative mechanisms for the BMI-cancer association include potential alterations in endogenous hormone metabolism, such as insulin-like growth factor, estrogen, glucocorticoids, and insulin (16). More research is needed to better understand the mechanism through which obesity may cause esophageal adenocarcinoma to develop effective intervention programs.

Strengths of this analysis include the consistency of a positive BMI-esophageal adenocarcinoma association across different patient populations and between studies with different designs, the demonstration of an increased association with increasing BMI, the creation of more comparable BMI categories for each study (making risk estimates more comparable), the ability to stratify by cancer site, and the ability to assess the influence of including only estimates adjusted for potential confounders.

There are potential limitations of this analysis. First, only observational studies were available. The results of observational studies may be influenced by unmeasured confounders. Some factors, such as physical activity and dietary composition, may be related to BMI and were not routinely adjusted for in all studies; however, studies that included estimates with and without adjustment for these variables did not show a substantial influence of these factors on the risk estimates (16). In addition, an analysis we did that stratified by estimates adjusted versus not adjusted for potential confounders provided similar risk estimates (data not shown). Another limitation of observational studies is their inability to definitively establish when the putative risk factor may exert its influence and whether there is a minimum threshold level or duration of the risk factor required.

Our results support feasibility studies for whether reduction of BMI may decrease the risk of esophageal adenocarcinoma in high-risk populations. Patients with long-standing, frequent gastroesophageal reflux symptoms or Barrett's esophagus, for example, have an ~40-fold increased risk of esophageal adenocarcinoma (52).

In conclusion, a synthesis of existing studies supports a positive association between increasing BMI and esophageal adenocarcinoma and between BMI and cardia carcinoma in certain populations. The stratification of data suggests that the cancer risk associated with increased BMI may increase with increasing distance from the gastroesophageal junction. The high fatality rates for esophageal and cardia adenocarcinoma, combined with the other adverse effects of high BMI, support current efforts at risk factor modification in the population in general, and the study of risk factor modification in populations at high risk of developing esophageal carcinoma in particular. More research is needed to understand the mechanism through which obesity may cause these cancers and whether interventions to lower BMI can decrease cancer risk.

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