A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma

F. Turati¹,², I. Tramacere¹, C. La Vecchia¹,² & E. Negri*¹

¹Department of Epidemiology, Istituto di Ricerche Farmacologiche ‘Mario Negri’, Milan; ²Department of Clinical Sciences and Public Health, Università degli Studi di Milano, Milan, Italy

Received 22 February 2012; revised 15 June 2012; accepted 18 June 2012

Background: The incidence rates of esophageal and gastric cardia adenocarcinoma (EGCA) have increased over recent years in several countries, and overweight/obesity has been suggested to play a major role in these trends. In fact, higher body mass index (BMI) has been positively associated with EGCA in several studies.

Material and methods: We conducted a meta-analysis of case–control and cohort studies on the BMI and EGCA updated to March 2011. We estimated overall relative risks (RRs) and 95% confidence intervals (CI) for BMI between 25 and 30 and BMI ≥ 30 kg/m², when compared with normo-weight subjects, using random-effects models.

Results: We identified 22 studies, including almost 8000 EGCA cases. The overall RR was 1.71 (95% CI 1.50–1.96) for BMI between 25 and 30, and was 2.34 (95% CI 1.95–2.81) for BMI ≥ 30 kg/m². The continuous RR for an increment of 5 kg/m² of BMI was 1.11 (95% CI 1.09–1.14). The association was stronger for esophageal adenocarcinoma (RR for BMI ≥ 30 kg/m² = 2.73, 95% CI 2.16–3.46) than for gastric cardia adenocarcinoma (RR for BMI ≥ 30 kg/m² = 1.93, 95% CI 1.52–2.45). No substantial differences emerged across strata of sex and geographic areas.

Conclusion: Overweight and obesity are strongly related to EGCA, particularly to esophageal adenocarcinoma.

Key words: body mass index, esophageal and gastric cardia adenocarcinoma, meta-analysis, obesity, overweight

Introduction

The incidence rates of esophageal adenocarcinoma (EA) and gastric cardia adenocarcinoma (GCA) have increased in the last few decades in many developed countries, while esophageal squamous cell carcinoma has shown divergent trends across countries, and gastric non-cardia adenocarcinoma has substantially declined [1–5].

The rise in EA and GCA has been mainly attributed to the increase in the prevalence of obesity worldwide [6], which causes gastroesophageal reflux (GER) and Barrett’s esophagus [7–9]. Obesity is a recognized risk factor for EA [7, 10], and it has been estimated that almost 40% of EA and >20% of GCA cases are attributable to overweight/obesity [11].

In order to provide a more precise quantification of the association between overweight and obesity and esophageal and gastric cardia adenocarcinoma (EGCA) risks, and explore potential differences across anatomical subsites, sex and populations from different areas, we conducted a meta-analysis of all studies on the relation between body mass index (BMI) and EGCA published up to March 2011.

Materials and methods

Identification of studies and data collection

Using PubMed, we carried out a literature search of all case–control and cohort studies published as original articles in English up to March 2011, with the terms ‘body mass index’ or ‘BMI’ or ‘obesity’ and combinations of ‘esophageal neoplasms’ or ‘stomach neoplasms’ and ‘adenocarcinoma’, following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [12]. Two of the authors (EN and IT) retrieved and assessed potentially relevant papers, and reviewed the reference list in the articles to identify additional publications of interest. When multiple reports were published on the same study, we considered only the most informative and/or the recent one. Studies were included if based on cohort or case–control design provided that they (i) investigated the association between the BMI and the risk of EGCA; (ii) reported estimates of the association between exposure and outcome (odds ratio, OR, rate ratio or hazard ratio, HR, as estimators of relative risk, RR, and the corresponding 95% confidence interval, CI, or P value). We excluded studies using patients with Barrett’s esophagus as the comparison group, or reporting only mean or median BMI values, or providing uninterpretable RR estimates.

We identified 22 studies on esophageal (EA) and/or gastric cardia adenocarcinoma (GCA): 12 case–control [9, 13–24] and 10 prospective [25–34] studies (Table 1). For each study, we extracted information on study design, country, sex, cancer site, number of subjects (cases, controls or cohort size), type of controls and period of enrollment for case–control...
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cancer site</th>
<th>Sex</th>
<th>No. of cases</th>
<th>No. of controls/size of cohort</th>
<th>Type of controls</th>
<th>Period of enrollment/duration of follow-up</th>
<th>Variables adjusted for in the regression models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case–control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al. [13]</td>
<td>USA</td>
<td>EA</td>
<td>M</td>
<td>174</td>
<td>750</td>
<td>PB</td>
<td>1986–1989</td>
<td>Age, area, smoking, liquor use, income and calories from food</td>
</tr>
<tr>
<td>Lagergren et al. [16]</td>
<td>Sweden</td>
<td>EA, GCA</td>
<td>M + W</td>
<td>451</td>
<td>820</td>
<td>PB</td>
<td>1995–1997</td>
<td>Sex, age, smoking, alcohol drinking, socioeconomic status, reflux symptoms, energy, fruit and vegetable intake and physical activity</td>
</tr>
<tr>
<td>Cheng et al. [17]</td>
<td>UK</td>
<td>EA</td>
<td>W</td>
<td>74</td>
<td>74</td>
<td>PB</td>
<td>1993–1996</td>
<td>Age, general practice, social class, number of children, fruit consumption and breastfeeding</td>
</tr>
<tr>
<td>Wu et al. [18]</td>
<td>USA</td>
<td>EA, GCA</td>
<td>M + W</td>
<td>499</td>
<td>1356</td>
<td>PB</td>
<td>1992–1997</td>
<td>Sex, age, race, smoking, birthplace and education</td>
</tr>
<tr>
<td>Bollschweiler et al.</td>
<td>Germany</td>
<td>EA</td>
<td>M</td>
<td>47</td>
<td>50</td>
<td>PB</td>
<td>1997–2000</td>
<td>Smoking and vitamin intake</td>
</tr>
<tr>
<td>Chen et al. [20]</td>
<td>Taiwan</td>
<td>GCA</td>
<td>M + W</td>
<td>176</td>
<td>579</td>
<td>HB</td>
<td>1992–1997</td>
<td>Sex, age time of hospitalization, socioeconomic status and years of schooling</td>
</tr>
<tr>
<td>Ryan et al. [21]</td>
<td>Ireland</td>
<td>EA, GCA</td>
<td>M + W, M,W</td>
<td>352</td>
<td>893</td>
<td>PB</td>
<td>1994–2004</td>
<td>Sex, age, smoking and alcohol drinking</td>
</tr>
<tr>
<td>Veugelers et al. [22]</td>
<td>Canada</td>
<td>EA</td>
<td>M + W</td>
<td>57</td>
<td>102</td>
<td>HB</td>
<td>2001–2003</td>
<td>Sex, age, smoking, alcohol drinking, use of multivitamins, intake of energy, calories from dietary fat, fruit, vegetables, fiber and vitamin C</td>
</tr>
<tr>
<td>Anderson et al. [9]</td>
<td>Ireland</td>
<td>EA</td>
<td>M + W</td>
<td>227</td>
<td>260</td>
<td>PB</td>
<td>2002–2004</td>
<td>Sex, age, interview date, smoking, alcohol intake, education and job type</td>
</tr>
<tr>
<td>Lofdahl et al. [23]</td>
<td>Sweden</td>
<td>EGCA</td>
<td>M, W</td>
<td>451</td>
<td>820</td>
<td>PB</td>
<td>1995–1997</td>
<td>Age, education, alcohol drinking, smoking, fruit and vegetable intake and Helicobacter pylori infection</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engeland et al. [28]</td>
<td>Norway</td>
<td>EA</td>
<td>M, W</td>
<td>575</td>
<td>2 001 617 (PR)</td>
<td>45.7 million (PY)</td>
<td>1963–2002 (average 23 years)</td>
<td>Age at measurement and year of birth</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Study Type</td>
<td>Sex</td>
<td>Age</td>
<td>Calendar Year</td>
<td>Follow-up</td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
<td>------------</td>
<td>-----</td>
<td>-----</td>
<td>---------------</td>
<td>-----------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Lindblad et al.</td>
<td>UK</td>
<td>EA, GCA</td>
<td>M + W, M, W</td>
<td>482</td>
<td>10 000 controls selected from a cohort of 4 340 207 PY</td>
<td>1994–2001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tran et al.</td>
<td>China</td>
<td>GCA</td>
<td>M + W</td>
<td>1089</td>
<td>29 584 (PR)</td>
<td>1986–2011</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MacInnis et al.</td>
<td>Australia</td>
<td>GCA</td>
<td>M + W</td>
<td>30</td>
<td>41 295 (PR)</td>
<td>1990/1994–2004 (average 11.3 years)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Merry et al.</td>
<td>Netherlands</td>
<td>EA, GCA</td>
<td>M + W</td>
<td>296</td>
<td>4552 (PR)</td>
<td>1986–1999 (13.3 years of follow-up)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reeves et al.</td>
<td>UK</td>
<td>EA</td>
<td>W</td>
<td>150 (cases), 111 (deaths)</td>
<td>1.2 million (PR)</td>
<td>1996–2001 (average 5.4 years for incidence and 7.0 years for mortality)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Abnet et al.</td>
<td>USA</td>
<td>EA, GCA</td>
<td>M + W</td>
<td>678</td>
<td>480 475 (PR)</td>
<td>1995/1996–2003</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Corley et al.</td>
<td>USA</td>
<td>EA, GCA</td>
<td>M + W</td>
<td>206</td>
<td>1648 controls selected from 206 974 PR</td>
<td>1964/1973–2006</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Steffen et al.</td>
<td>Europe</td>
<td>EA</td>
<td>M + W</td>
<td>88</td>
<td>346 554 (PR)</td>
<td>1992/2000–2007 (average 8.9 years)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

BMI, body mass index; EA, esophageal adenocarcinoma; EGCA, esophageal and gastric cardia adenocarcinoma; GCA, gastric cardia adenocarcinoma; HB, hospital-based; M, men; M + W, men and women considered together; PR, population-based; PR, persons at risk; PY, person-years; W, women.

aOverlap with Lagergren et al. [16], only sex-specific data were included in the analyses.
bGastroesophageal junction adenocarcinoma.
cNested case–control study.
dSince the upper exposure category of BMI was ≥23 kg/m², we used these data for the dose–response analysis only.
eLower esophagus/gastric cardia.
fCase-cohort study.
studies, duration of follow-up for prospective studies, RR estimates and the corresponding CI, the adjustment variables, and, when available, the number of cases and non-cases or person-years for each category of BMI.

statistical analyses
The measure of interest was the RR, estimated by the OR in case–control and by the HR in prospective studies.

We used the reference category chosen by each article, and we categorized BMI into two levels of exposure: overweight (BMI = 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²). When more than one study category fell in the range considered for categories of BMI, we combined the corresponding estimates using the method proposed by Hamling et al. [35], taking into account the correlation between estimates; otherwise we used fixed-effects models.

We generated forest plots and we also calculated summary RRs of BMI in strata of selected covariates. All the meta-analytic estimates were derived using random-effects models [36]. We assessed the heterogeneity among studies using the $\chi^2$ test [36], defining a significant heterogeneity as the $P < 0.10$, and evaluated the inconsistency using the I² statistic [37].

We estimated the RR per 5 kg/m² increase in BMI by regressing the natural logarithm of the RRs to the corresponding median values of BMI across exposure categories in each study, using the variance-weighted least squares regression. Since the highest and the lowest categories of exposure were open, we considered them of the same amplitude as the previous/successive categories. Then, a summary estimate of the RR was obtained by combining the study-specific linear trends using random-effects models.

We also carried out a dose–risk analysis using a meta-regression model in a non-linear dose–risk relationship framework, choosing the best fitting two-term fractional-polynomial model [38].

To evaluate publication bias, we used Egger’s test for funnel plot asymmetry [39], we provided the trim and fill funnel plots and we calculated the corresponding adjusted estimates [40].

results
The main characteristics of the 22 studies [9, 13–34] included in the meta-analysis are given in Table 1. A total of 7945 EGCA cases were included.

Figure 1 shows the summary RRs of EGCA and for two levels of BMI considered. The overall RR was 1.71 (95% CI 1.50–1.96) for BMI between 25 and 30 (Figure 1A), and 2.34 (95% CI 1.95–2.81) for BMI ≥ 30 kg/m² (Figure 1B). The pooled estimates were higher among case–control than among prospective studies, with a significant heterogeneity for the overweight category ($P = 0.01$), but not for the obese category ($P = 0.29$).

Table 2 shows the linear dose–risk analysis and the association between the BMI and EGCA risk in strata of selected covariates. The overall RR for the increment of 5 kg/m² of BMI was 1.11 (95% CI 1.09–1.14). In all strata, the summary RR was statistically significant, except for that derived from studies from Asia, which was based on three studies only, and for women. No significant differences were found across strata of sex and geographic area, while the association with BMI was stronger for EA than for GCA.

Figure 2 shows the best-fitting dose–risk curve describing the relation between the BMI and EGCA risk (i.e. ln(RR) = dose² + dose³). This function estimated a monotone dose–risk relationship, with RRs of 1.46 (95% CI 1.30–1.65) for a BMI of 25, 2.31 (95% CI 1.95–2.74) for a BMI of 30, and 4.62 (95% CI 3.52–6.07) for a BMI of 35 kg/m².

Figure 3 provides the trim and fill funnel plots of studies on the association between EGCA risk and BMI. A significant publication bias was evident for the BMI category between 25 and 30 ($P$ for Egger’s test <0.01) (Figure 3A), and a borderline significance of publication bias emerged for a BMI over 30 kg/m² ($P$ for Egger’s test = 0.07) (Figure 3A). The adjusted RRs for missing estimates using the trim and fill method were 1.44 (95% CI 1.24–1.66) for overweight, and 2.15 (95% CI 1.75–2.64) for obese categories, thus lower but still significant compared with the estimates not adjusted for publication bias.

discussion
This meta-analysis based on 22 studies and almost 8000 EGCA cases found that a BMI between 25 and 30 increases EGCA risk of ~70%, and that a BMI over 30 kg/m² is associated with a more than two-fold risk of EGCA, when compared with normo-weight subjects. Results were consistent across strata of sex and geographic area. The association with BMI was stronger for EA than for GCA.

EGCA has a multifactorial etiology, and tobacco use, GER and Barrett’s esophagus are well recognized risk factors. Other factors, like diet, colecistectomy, lower esophageal sphincter relaxing and asthma medications, aspirin or nonsteroidal anti-inflammatory drugs’ use and family history of EGCA, may also affect EGCA risk [7]. The possible correlations of these factors with obesity must be considered in interpreting the results.

The BMI is the most commonly used measure of overweight and obesity. Our results are in broad agreement with those of studies examining abdominal obesity in relation to EA and/or GCA, which showed in general positive associations, mainly restricted to (or stronger for) EA [27, 30, 34, 41, 42]. We were not able to carry out a meta-analysis on the waist-to-hip ratio (WHR) and EGCA risk since we found only three studies on the issue [30, 34, 41]. The National Institutes of Health-American Association of Retired Persons’ Diet and Health Study found increased risks of EA with increasing levels of waist circumference (WC) and WHR; however, no relation with WHR emerged for GCA [41]. Similar results were observed in the European Prospective Investigation into Cancer and Nutrition cohort, with significant RRs of EA around 3 and 2 for the highest quintiles of WC and WHR, respectively [34]. In the Melbourne collaborative cohort study, the WC was positively associated with adenocarcinomas of the lower esophagus and GCA [30], with a HR of 2.9 (95% CI 1.2–6.9) for the highest tertile, compared with the lowest one. A non-significant increased risk also emerged for WHR. A nested case–control study carried out within 206 974 members of the Kaiser Permanente multiphasic health checkup cohort found that increasing abdominal diameter was associated with an increased risk of EA, with a HR of 1.46 (95% CI 1.05–2.04) per 10 cm increase in the WC. The association was independent from BMI [27]. No relation between the abdominal diameter and the risks of GCA was found in that study [27]. Moreover, a case–control study assessing the abdominal fat area using computed tomography (CT) found that patients with esophageal/junctional adenocarcinoma had higher levels of...
visceral adiposity compared with subjects admitted to hospital for investigation of abdominal pain and whose CT was normal, patients with gastric adenocarcinoma or with esophageal squamous cell carcinoma \[42\].

Overweight and obesity promote GER and its transition to Barrett’s esophagus (a precursor lesion for EA) and EA \[43–46\], through increasing intra-abdominal pressure on the lower esophageal sphincter \[47–49\]. Abdominal pressure in obese may also be favored by the sitting position and the constraining influence of tight belts \[49\]. Other mechanisms may, however, also be involved, since the relation between obesity and EGCA usually persists even after accounting for GER disease—though incomplete allowance is likely \[14, 16, 24, 26\]. Accumulation of adipose tissue increases the

---

**Figure 1.** Summary relative risk (RRs) of EGCA for BMI between 25 and 30 (A), and BMI over 30 kg/m² (B). BMI, body mass index; CI, confidence interval; EA, esophageal adenocarcinoma; EGCA, esophageal and gastric cardia adenocarcinoma; GCA, gastric cardia adenocarcinoma; M, men; W, women; M + W, men and women considered together; PY, person-years; RR, relative risk.
concentrations of endogenous hormones, including sex steroids, insulin and insulin growth factor-1, increasing cell proliferation and impairing apoptosis, and consequently favoring preneoplastic and neoplastic cell growth [50, 51]. Furthermore, obesity is a recognized proinflammatory state by increasing the release of inflammatory mediators that promote tumor growth [52]. It has been suggested that obese subjects have a prolonged esophageal transit time [53] and that a longer contact time between esophageal mucosa and food (containing potentially carcinogenic components) may promote the development of cancer [54].

Reflux mechanisms are more closely related to Barrett’s esophagus and subsequent EA than to GCA [15], and this may explain the stronger association of BMI with EA risk.

### Table 2. Summary RRs of EGCA and BMI between 25 and 30, and BMI over 30 kg/m², in strata of selected covariates. Summary RRs of EGCA for the increment of 5 kg/m² of BMI

<table>
<thead>
<tr>
<th>Subsite</th>
<th>BMI 25–30</th>
<th>BMI 30+</th>
<th>Increment of 5 kg/m² of BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>RR (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>1.71 (1.50–1.96)</td>
<td>12</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10</td>
<td>2.13 (1.63–2.78)</td>
<td>5</td>
</tr>
<tr>
<td>Women</td>
<td>8</td>
<td>1.59 (1.20–2.09)</td>
<td>5</td>
</tr>
<tr>
<td>P heterogeneity</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographical area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>6</td>
<td>1.51 (1.34–1.70)</td>
<td>3</td>
</tr>
<tr>
<td>Europe</td>
<td>12</td>
<td>1.74 (1.43–2.11)</td>
<td>8</td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>2.44 (1.01–5.88)</td>
<td>1</td>
</tr>
<tr>
<td>P heterogeneity</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; EA, esophageal adenocarcinoma; EGCA, esophageal and gastric cardia adenocarcinoma; GCA, gastric cardia adenocarcinoma; RR, relative risk.

*P for heterogeneity between strata.

bIncluding Australia.
Mislackification of the tumor site may, however, have occurred in some studies. If some non-cardia gastric cancers were incorrectly considered as cardia tumors, the association between BMI and GCA could have been diluted [15]. The declined prevalence of *Helicobacter pylori* infection has also been related to increased obesity [55] and also to increased risk of EGCA, due to acid reflux and consequent lesions on esophageal and cardial epithelia [56].

A major concern of this analysis is the publication bias, which may have led to an overestimation of the true association. However, the results corrected for publication bias were not substantially different from those from the main analysis.

Anthropometric measures were self-reported and thus subject to information bias [9, 13–26, 32, 33]. In particular, weight tends to be systematically underestimated, more so by heavier subjects, and height is typically overestimated, especially by shorter subjects [57–60]. The association with BMI was found in cohort studies as well, albeit weaker than for case–control studies, suggesting that differential reporting in case–control studies may not totally explain it. Moreover, high correlations were observed between self-reported and measured weight and height, indicating that self-reported data are acceptable for the purpose of epidemiological studies [57, 58, 61–63]. Further, when we included in the analysis exclusively the studies in which weight and height were directly measured [27, 28, 30, 31, 34], the results did not materially change (the pooled RR for BMI between 25 and 30 was 1.55, 95% CI 1.32–1.82, and the pooled RR for BMI over 30 kg/m² was 2.17, 95% CI 1.71–2.82).

A potential insidious bias in studying the association between BMI and EGCA is reverse causation, particularly in case–control studies in which patients were asked about their weight close to cancer diagnosis, since weight loss is one of the symptoms of EGCA, and it is not clear how long before diagnosis this weight loss becomes noticeable. This would, however, have led to an underestimation of the association with BMI. On the other hand, inaccuracies in recall of past weight may have occurred in retrospective studies in which exposure in the distant past was recorded. However, past body weights over a long period were found to be recalled with good accuracy in some studies [64–66].

Smoking is a possible confounder of the association between BMI and EGCA, since it has been positively related to EGCA [7, 67] and inversely related to BMI [68–71]. An interaction between smoking and BMI in EA risk was also suggested, with a stronger association between BMI and EGCA in non-smokers [15]. Only a few studies included in our meta-analysis did not account for smoking habits [17, 20, 25, 27–30]. However, when these studies were excluded from the analysis, we obtained similar risk estimates (the pooled RR for BMI between 25 and 30 was 1.81, 95% CI 1.51–2.17, and the pooled RR for BMI over 30 kg/m² was 2.23, 95% CI 1.71–2.91). A pooled analysis of 12 case–control studies investigating the separate effects of exposure rate (cigarettes per day) and the duration of smoking on the risk of EA and esophagogastric junctional adenocarcinoma found that BMI did not modify the smoking and drinking ORs [72].

A strength of our analysis is the effort to include all the studies investigating the association between the BMI and EGCA, for a total of almost 8000 cases. This allowed the definition of comparable exposure categories and the investigation of the association of interest in different subgroups.

In conclusion, this meta-analysis provides more definite and quantitative evidence than previously available that overweight and obesity increase the risk of EGCA, particularly of EA.

**acknowledgements**

The authors thank Ms I. Garimoldi for editorial assistance.

**funding**

This work was supported by the Italian Association for Cancer Research (AIRC) [grant number 10068].

**disclosure**

The authors have declared no conflicts of interest.

**references**


