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Overweight, obesity and gastric cancer risk: Results from a meta-analysis of cohort studies

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ABSTRACT

The relationship between excess body weight and gastric cancer risk has not been well studied to date. We therefore carried out a systematic review and meta-analysis of published cohort studies to evaluate the association between excess body weight and gastric cancer risk. An electronic search of the MEDLINE, PubMed, EMBASE and Academic Search Premier (EBSCO) databases, which contain articles published from 1950 onwards, was conducted in order to select studies for this meta-analysis. Ten studies with a total number of 9492 gastric cancer cases and a studied population of 3,097,794 were identified. Overall, excess body weight [body mass index (BMI) $\geqslant$ 25] was associated with an increased risk of gastric cancer [odds ratio (OR) = 1.22; 95% confidence intervals (CIs) = 1.06–1.41]. Specifically, a stratified analysis showed that excess body weight was associated with an increased risk of cardia gastric cancer [overweight and obese (BMI $\geqslant$ 25), OR = 1.55, 95% CIs = 1.31–1.84] and gastric cancer among non-Asians (overweight and obese, OR = 1.24, 95% CIs = 1.14–1.36); however, the stratified analysis also showed that there was no statistically significant link between excess body weight and gastric cancer in the following subgroups: males (overweight and obese, OR = 1.22, 95% CIs = 0.96–1.55), females (overweight and obese, OR = 1.13, 95% CIs = 0.65–1.94), non-cardia gastric cancer (overweight and obese, OR = 1.18, 95% CIs = 0.96–1.45), and Asians (overweight and obese, OR = 1.17, 95% CIs = 0.88–1.56).

The combined results of this meta-analysis, however, do indicate that overweight and obesity are associated with an increased risk of gastric cancer. The strength of the association also increases with increasing BMI.

1. Introduction

Gastric cancer is a major health concern. With its combination of high incidence and poor survival, it holds the position of fourth most common cancer and second most common cause of cancer death in the world.[1,2] Although gastric cancer incidence is declining in many western countries, it is predicted that the number of gastric cancer cases globally will increase up to the year 2050.[3] Therefore, early intervention on modifiable risk factors of gastric cancer is very important.

Obesity is one of the strongest emerging risk factors for many cancers in many countries[4–8]; however, existing epidemiologic studies of the association between excess body weight and the risk of gastric cancer have conflicting results. While excess body weight has been associated with an increased risk of gastric cancer in some studies,[9–18] other reports have either found no association at all or a negative

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association.[19–22] It is unclear whether these different findings are due to methodologic differences in exposure definitions, outcome definitions, the limited number of studies (especially those with prospective cohort studies), bias introduced by reverse causality with respect to smoking-related cancers, or other aspects of study design or analysis.

To evaluate the association between excess body weight or body mass index (BMI) and the risk of gastric cancer, we carried out a systematic review and meta-analysis of published cohort studies with an emphasis on the creation of more standardised exposure definitions to better compare results between studies.

2. Materials and methods

2.1. Literature search strategy

A search was applied to the following electronic databases: MEDLINE (1966–February 2009), PubMed (1950–February 2009), EMBASE (1950–February 2009), and Academic Search Premier (EBSCO) (1950–February 2009). The following key words or text words were used: gastric OR stomach, carcinoma OR cancer OR tumour OR adenocarcinoma OR neoplasm, obesity OR adiposis OR body mass index OR BMI. The search was done on studies conducted on human subjects, without restriction on language. The reference lists of reviews and retrieved articles were hand searched at the same time. We did not consider abstracts or unpublished reports.

2.2. Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (i) they had to be cohort studies examining exposure to excess body weight or body mass index and the incidence or mortality of gastric cancer and (ii) they had to contain an explicit description of BMI or obesity or overweight, with raw data on each group.

The major reasons for exclusion of studies were (i) no raw data available; (ii) duplicates; and (iii) no usable data reported.

2.3. Data extraction

Data were extracted from each study by two reviewers (Yang P. and Chen B.) independently, according to the pre-specified selection criteria. Any disagreement was resolved by discussion.

2.4. Exposure definition

We defined body mass categories using the following BMI categories [BMI = weight (kg)/height (m^2)]: normal (BMI = 18.5–<25), overweight (BMI = 25–<30), obese (BMI $\geqslant$ 30); these groupings represented the divisions or quartiles most frequently reported in the articles and they differ somewhat from BMI categories in adolescence[33] (normal BMI < 20.3, overweight and obese, BMI $\geqslant$ 22.2). We also created a category that included both overweight and obese (BMI $\geqslant$ 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 most commonly reported.

2.5. Statistical analysis

The statistical analysis was performed by RevMan5.0 software, which was provided by Cochrane Collaboration. $P < 0.05$ was considered statistically significant. Meta-analysis was done with either the random effects model or fixed effects model. Heterogeneity was checked by the χ^2 test. If the results of the trials had heterogeneity, the random effects model was used for meta-analysis. To establish the effect of clinical heterogeneity between studies on meta-analysis conclusions, subgroup analyses were conducted on the basis of gender, site of gastric cancer and race – Asian or non-Asian. The results were expressed with odds ratios (ORs) for the categorical variables and 95% confidence intervals (CIs).

3. Results

3.1. Study characteristics

There were 1252 papers relevant to the search words. Via the steps of screening the title, reading the abstract and reading the entire article, 17 cohort studies were identified.[4–9,23–33] Of these, seven were excluded (five did not report raw data for each group or define body mass categories,[4–8] and two did not relate to gastric cancer[23,24]); thus, ten studies,[9,25–33] which included 9492 gastric cancer cases and a total studied population of 3,097,794, were found to match our inclusion criteria. Studies had been carried out in the US, Sweden, the Netherlands, Korea, Japan and the United Kingdom. Characteristics of studies included in the meta-analysis are presented in Tables 1 and 2.

3.2. Quantitative data synthesis

The combined results based on all studies showed that there was a statistically significant link between excess body weight and gastric cancer (overweight and obese, OR = 1.22, 95% CIs = 1.06–1.41; obese, OR = 1.36, 95% CIs = 1.21–1.54; overweight, OR = 1.21, 95% CIs = 1.08–1.36). The strength of the association increased with increasing BMI (Table 3, Fig. 1).

When stratifying for gender, we found that there was not a statistically significant link between excess body weight and gastric cancer for males (overweight and obese, OR = 1.22, 95% CIs = 0.96–1.55; obese, OR = 1.41, 95% CIs = 1.08–1.83; overweight, OR = 1.10, 95% CIs = 1.03–1.18) or females (overweight and obese, OR = 1.13, 95% CIs = 0.65–1.94; obese, OR = 1.16, 95% CIs = 0.89–1.51; overweight, OR = 1.12, 95% CIs = 0.90–1.40) (Table 3).

When stratifying by the location of gastric cancer, we found that there was a statistically significant link between excess body weight and cardia gastric cancer (overweight and obese, OR = 1.55, 95% CIs = 1.31–1.84; obese, OR = 2.06, 95% CIs = 1.63–2.61; overweight, OR = 1.40, 95% CIs = 1.16–1.68), but not non-cardia gastric cancer (overweight and obese, OR = 1.18, 95% CIs =0.96–1.45; obese, OR = 1.26, 95% CIs = 0.89–1.78; overweight, OR = 1.16, 95% CIs = 0.94–1.43) (Table 3).

Table 1 – Characteristics of cohort studies included in this meta-analysis.

Authors (Ref.)	Year	Design	Country	No. of cases	Study population
Abent et al.[25]	2008	Cohort	American	N = 622; total N = 480,475	General population
Jansson et al.[26]	2005	Cohort	Sweden	N = 165; total N = 260,052	Employees within the construction industry
Lukanova et al.[27]	2006	Cohort	Sweden	N = 72; total N = 68,786	Northern Sweden region person register
Merry et al.[9]	2007	Cohort	Netherlands	N = 571; total N = 120,852	General population
Oh et al.[28]	2005	Cohort	Korea	N = 5293; total N = 781,283 (males)	Members of the Korea National Heath Insurance Corporation
Park et al.[29]	2006	Cohort	Korea	N = 1502; total N = 14,578 (males)	Government employees and teachers
Persson et al.[30]	2008	Cohort	Japan	N = 368; total N = 44,453 (females)	Public health centre areas
Reeves et al.[31]	2007	Cohort	UK	N = 521; total N = 1,222,630 (females)	England and Scotland women
Sjodahl et al.[32]	2008	Cohort	Sweden	N = 249; total N = 73,133	General population
Tanaka et al.[33]	2007	Cohort	Japan	N = 129; total N = 31,552	Adolescence population

Table 2 – Exposure and outcome definitions of cohort studies included in this meta-analysis.

Authors (Ref.)	Exposure	BMI reference[a]	BMI overweight	BMI obese	BMI overweight and obese	Case diagnosis method
Abent et al.[25]	Self-report BMI between 1995 and 1996	18.5–25	25–30	⩾30	⩾25	Cancer registry
Jansson et al.[26]	Measured BMI at the enrollment of the study	22–24.9	25–29.9	⩾30	⩾25	Cancer registry
Lukanova et al.[27]	Self -report BMI 10 y before the study	18.5–24.9	25–29.9	⩾30	⩾25	Northern Sweden region person registry
Merry et al.[9]	Measured BMI at the age 20 y	20–24.9	25–29.9	⩾30	⩾25	Cancer registry
Oh et al.[28]	Measured BMI at the enrollment of the database	18.5–22.9	25–29	⩾30	⩾25	Cancer registry
Park et al.[29]	Measured BMI at the enrollment of the study	<23			⩾25	Cancer registry
Persson et al.[30]	Self-report BMI at the enrollment of the study	<19.9			⩾25	Cancer registry
Reeves et al.[31]	Measured BMI at the enrollment of the study	22.5–24.9	25–29.9	⩾30	⩾25	Cancer registry
Sjodahl et al.[32]	Measured BMI at the age 20 y	18.5–24.9	25–29.9	⩾30	⩾25	Cancer registry
Tanaka et al.[33]	Measured BMI at age 20	<20.3			⩾22.2	National Vital Statistics office

a If different BMI quartiles were provided for each gender, we report only the males values.

When stratifying for race, there was a statistically significant link between excess body weight and gastric cancer among non-Asians (overweight and obese, OR = 1.24, 95% CIs = 1.14–1.36), but not among Asians (overweight and obese, OR = 1.17, 95% CIs = 0.88–1.56) (Table 3).

Statistically significant heterogeneity was observed among the included studies ($\chi^2 = 47.25$, $P < 0.00001$, $I^2 = 81\%$) (Fig. 1). In addition, we did obtain evidence of publication bias as shown by the funnel plot (Fig. 2). However, the fail-safe number ($N_{fs0.01} = 80$) is large, suggesting that publication bias probably has little effect on summary estimates.

4. Discussion

Previous studies have shown that adiposity is associated with an increasing risk of cancers of the endometrium,[34–37] the breast (especially in postmenopausal women),[37,38] the ovaries,[39,40] the oesophagus,[6,8,9,11–13,15,16,18,25,37] and the colon (particularly in males),[37,41–43] and so on. Our pooled results of published cohort studies also support a positive association between excess body weight and the risk of gastric cancer. The strength of association increases with increasing BMI. However, a previous study found no such association with gastric cancer.[37]

In this meta-analysis, we also found an association between obesity and site-specific gastric cancer. This pattern is consistent with prior studies.[5,12,25,44] Cardia gastric cancer is different from non-cardia gastric cancer in both clinical and pathological features,[45,46] and the incidence of cardia gastric cancer has been increasing in several countries (especially in western countries).[47–49] Therefore, it would not be surprising if the effect of excess body weight on gastric cancer differed with respect to site.

In a subgroup analysis stratified on the basis of Asians and non-Asians, we found that excess body weight was associated with a statistically significant increase in the risk of gastric cancer among non-Asians, but not among Asians. The prevalence of obesity and incidence of gastric cancer was different between Asians and non-Asians (especially in the western world).[1,2,50–53] This may partly explain the difference between Asians and non-Asians.

These results extend prior observational studies by permitting additional evaluation of subgroups, the ability to more precisely evaluate risk with increasing body weight,

Table 3 – Statistical results of cohort studies included in the meta-analysis by Revman 5.0.

Groups	No. of studies	OR (95% CIs)	Statistical method	P
All studies				
Overweight and obese	10	1.22 [1.06–1.41]	Random	0.007
Obese	6	1.36 [1.21–1.54]	Fixed	<0.00001
Overweight	7	1.21 [1.08–1.36]	Random	0.001
Males				
Overweight and obese	4	1.22 [0.96–1.55]	Random	0.10
Obese	1	1.41 [1.08–1.83]	Fixed	0.01
Overweight	2	1.10 [1.03–1.18]	Fixed	0.005
Females				
Overweight and obese	4	1.13 [0.65–1.94]	Random	0.67
Obese	1	1.16 [0.89–1.51]	Fixed	0.28
Overweight	2	1.12 [0.90–1.40]	Fixed	0.31
Cardia gastric cancer				
Overweight and obese	3	1.55 [1.31–1.84]	Fixed	<0.00001
Obese	3	2.06 [1.63–2.61]	Fixed	<0.00001
Overweight	3	1.40 [1.16–1.68]	Fixed	0.0003
Non-cardia gastric cancer				
Overweight and obese	4	1.18 [0.96–1.45]	Random	0.13
Obese	4	1.26 [0.89–1.78]	Random	0.20
Overweight	4	1.16 [0.94–1.43]	Random	0.16
Asians				
Overweight and obese	4	1.17 [0.88–1.56]	Random	0.29
Non-Asians				
Overweight and obese	6	1.24 [1.14–1.36]	Fixed	<0.00001

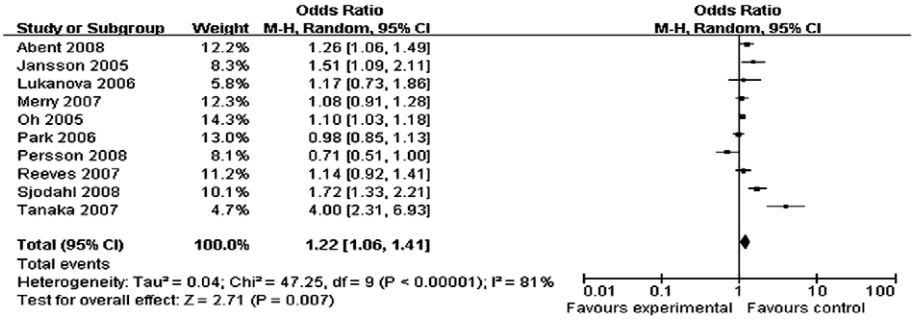

Fig. 1 – Forest plot for the association between excess body weight and gastric cancer risk. Summary odds ratios come from random effects models by Revman 5.0.

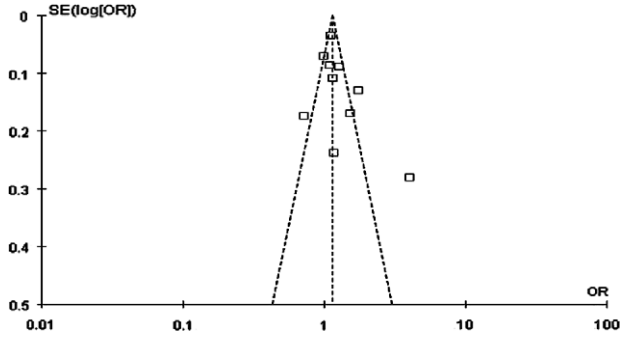

Fig. 2 – Funnel plot for all studies included in this meta-analysis of excess body weight and gastric cancer by Revman 5.0.

and by providing more stable estimates of excess body weight versus gastric cancer associations.

The association between excess body weight and gastric cancer is consistent with similar associations seen with other cancers, although the biological mechanism is unclear. Because the adenocarcinomas of the distal oesophagus and gastric cardia have been regarded as one clinical entity,[54,55] one proposed pathway is that increased body weight may increase the risk of gastro-oesophageal reflux,[16,56,57] which has been associated with adenocarcinomas of the gastro-oesophageal junction; however, some studies have not found a consistent relationship between BMI and reflux.[21,58] Other possibly mechanisms include: (i) insulin resistance,[59] (ii) levels of adiponectin and leptin,[60,61] (iii) insulin-like growth factors,[59,62] (iv) sex steroids and glucocorticoids,[59,63] (v)

obesity-related inflammatory markers,[64] (vi) the nuclear factor kappa beta (NF-kappaβ) system,[65] and (vii) oxidative stresses.[66]

To our knowledge, the strengths of this study include the consistency of positive association between excess body weight and gastric cancer across high-quality studies with different patient populations, the demonstration of an increased association with increasing body mass, the creation of more comparable BMI categories for each study, the ability to stratify by cancer site and race, and the ability to assess the influence of including only estimates adjusted for potential confounders.

However, there are several limitations to this meta-analysis: (i) as in most meta-analyses, these results should be interpreted with caution because of the observational studies included. Although this meta-analysis includes ten high-quality cohort studies, the results of observational studies may be influenced by unmeasured confounders such as physical activity and dietary composition; these may be related to BMI and not routinely adjusted for all studies, (ii) an analysis we did that stratified by estimates adjusted versus not adjusted for potential confounders provided similar risk estimates (raw data not obtained), (iii) 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, (iv) various biases of observational studies (e.g. recall bias, selection bias) may distort the results, and (v) as shown in Fig. 2, there was also a publication bias. Because of resource limitations, we did not attempt to search for unpublished studies on the association between excess body weight and gastric cancer.

In conclusion, the results of this meta-analysis indicate that, overall, overweight and obesity are associated with an increased risk of gastric cancer. The strength of the association also increases with increasing BMI. Specifically, excess body weight was associated with an increased risk of cardia gastric cancer, but not non-cardia gastric cancer. There was also a positive association between excess body weight and gastric cancer among non-Asians, but not among Asians. However, more research is needed to understand the mechanisms involved and whether interventions to a lower body weight can decrease gastric cancer.

Conflict of interest statement

None declared.

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