Body Mass Index and the Risk of Gallbladder Cancer: An Updated Meta-analysis of Epidemiologic Studies

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May 29, 2015, June 30, 2015, July 06, 2015

To provide a quantitative assessment of the association between excess bodyweight, expressed as increased body-mass index (BMI), and the risk of gallbladder cancer (GBC), we conducted an updated meta-analysis of epidemiologic studies.

We searched the MEDLINE and EMBASE databases form1966 to February 2013, and the reference lists of retrieved articles. A random-effects model was used to combine study-specific results. A total of 12 cohort studies (involving 5,101 cases) and 8 case-control studies (1,013 cases and 43,591 controls) were included in the meta-analysis.

Overall, compared with normal weight, the summary relative risks of GBC were 1.14 (95% CI,

pred ict-

of retrieved articles to search for additional studies. No language restrictions were imposed.

Study selection criteria

A published article was included according to the following criteria: (1) cohort or case-control study in which GBC incidence or mortality was an outcome; (2) the exposure of interest was overweight or obesity defined by BMI; (3) estimates of relative risk (rate ratio, odds ratio, or standardized incidence ratio) with corresponding 95% confidence intervals (or information to calculate them) of GBC associated with BMI or obesity. When there were multiple published reports from the same study population, only the one with the largest sample size was included in the meta-analysis. We excluded studies that did not provide risk estimates, only provided an RR with corresponding 95% CI per unit increase in BMI.

Data extraction

Three authors (C.C.F, B.Z, and J.Z.) independently evaluated all of the studies retrieved according to the pre-specified selection criteria. Discrepancies between the three reviewers were solved by discussion. The following information from each included study was extracted: the first author's name, country of origin, publication year, sample size, study population, study design, sex and age of participants, duration of follow-up (cohort studies), BMI categories, method of assessment of weight and height (measured versus self-reported), and point estimates [relative risk (RR), odds ratio (OR), or standardized incidence ratio (SIR)] and corresponding 95% CI. When several risk estimates were presented, we used the ones adjusted for the largest number of potential confounders. We used the Newcastle-Ottawa scale to assess the quality of included studies [10].

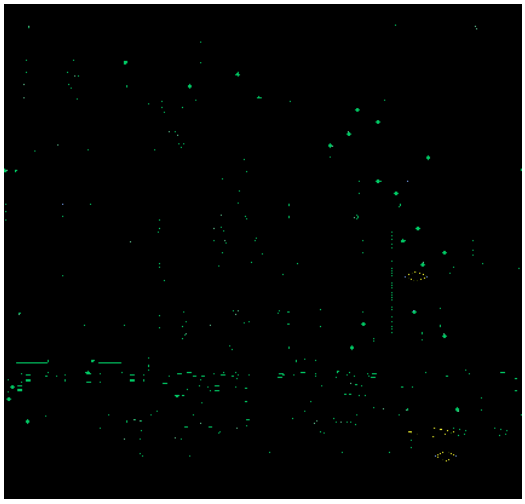
Statistical analysis

The present systematic review and meta-analysis was conducted in accordance with the methodology recommended by the Cochrane Collaboration. Three authors (C.C.F, B.Z, and J.Z.) performed data analysis. To examine associations of overweight and obesity with the risk of GBC, we combined the log-RRs from each study for the category representing overweight (BMI 25-30 kg/m^2) or obesity (BMI >30 kg/m^2 or a discharge diagnosis of obesity) versus the reference category (BMI 18.5-24.9 kg/m^2). If studies reported results separately

Quantitative data synthesis

As shown in Figures 2A and 2B, the overall analysis of all studies revealed a statistically significant positive association between BMI and GBC risk (overweight: RR=1.14, 95% CI=1.04-1.25, I2=24.9%; obesity: RR=1.56, 95% CI=1.41-1.73, I2=15.4%) compared to normal weight. We then conducted subgroup meta-analyses by study design, sex, geographic region, ascertainment of exposure and confounders, as shown in Table 1.

	Studies, n									
Cohort studies	12	1.15 (1.02-1.29)	0.04	22.03	45.5	12	1.62 (1.45-1.81)	0.28	19.98	14.9
Case-control studies	8	1.16 (0.96-1.41)	0.68	5.75	0	8	1.37 (1.10-1.71)	0.39	9.52	5.5
>10 years	6	1.12 (1.00-1.27)	0.04	17.78	49.4	9	1.65 (1.49-1.83)	0.4	13.58	4.3
<10 years	2	1.52 (1.06-2.19)	0.54	1.22	0	3	1.69 (0.91-3.17)	0.1	6.32	52.5
Hospital	3	1.14 (0.61-2.03)	0.3	2.39	16.4	4	1.07 (0.66-1.74)	0.57	2.03	0
Population	4	1.18 (0.96-1.46)	0.67	3.19	0	4	1.43 (1.09-1.89)	0.3	6.12	18.3
Men	9	1.06 (0.94-1.20)	0.24	10.33	22.5	11	1.42 (1.21-1.66)	0.85	5.63	0
Women	8	1.26 (1.13-1.40)	0.45	6.84	0	10	1.67 (1.38-2.02)	0.06	16.38	45
Asia	6	1.19 (0.98-1.45)	0.06	15	46.7	7	1.48 (1.26-1.74)	0.43	8.07	0.9
202) 1.8643	Non-Asia	9	1.14 (1.05-1.25)	0.43	1<8					



and vascular alterations [36]. Further more, obese and metabolic syndrome are risk factors for gallstone disease [37], which may indirectly increase the risk for GBC [38]. In addition, female sex hormones adversely influence hepatic bile secretion and gallbladder function [39]. Estrogens increase cholesterol secretion and diminish bile salt secretion, while progestins act by reducing bile salt secretion and impairing gallbladder emptying leading to stasis [40]. These may partially explain the stronger association observed with overweight or obesity in women than in men.

To our knowledge, the strengths of this study include as follows: (1) this study was based on 20 epidemiologic studies, which might minimize the possibility of selection bias. (2) The large number of studies of different geographic region expands prior observational studies by permitting additional evaluation of subgroups, which may lend us to more precisely evaluate. (3) The association between BMI and GBC risk of each study were derived from regression after adjustment at least for age, and most adjusted for potential confounders for GBC, such as smoking and alcohol use.

As with any meta-analysis of observational studies, our study also has limitations. First, inadequate control for confounders may bias the results, leading to exaggeration or underestimation of risk estimates. Thus, when interpreting the link between excess body weight and GBC risk, possible unmeasured or residual confounding should be considered. Gallstone is closely in related to GBC risk [41]. Meanwhile, obesity tends to be accompanied with DM, which is also associated with increased GBC risk [6,42]. However, most studies did not adjust for these risk factors. This could have led to an overestimation of the true association between obesity and risk of GBC. Second, several studies in this meta-analysis relied on self-reported weight and height measures, which may attenuate the relative risk estimates. However, the summary RR estimates for the studies that had measured weight and height were similar to those on self-reported. Finally, as in any meta-analysis, there was some suggestion of publication bias, because a few studies with null results tend not to be published. However, the results obtained from this study did not provide evidence for such bias.

There was no heterogeneity observed across studies about overweight and GBC risk, and obesity and GBC risk. We analyzed this review in both fixed effects and random effects, and found that they had no significant differences. Thus, the more conservative one, random effects, was chosen finally. Next, when we tried to carry out subgroup analysis to investigate sources of heterogeneity, statistical heterogeneity was lower in analysis of case-control studies, population based studies, Non-Asia studies and BMI ascertainment by self-reported, indicating that these might account for heterogeneity observed in studies about overweight and GBC risk.

In summary, findings of this meta-analysis provide evidence that obesity may increase GBC risk. Further studies that meet epidemiologic criteria on this subject are needed to strengthen the link between BMI and GBC risk, especially those adjusting potential confounding factors such as gallstones and DM.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (No. 81401996), and the Medical Research Foundation of Guangdong province (No. A2014228).

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