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Review

Body mass index and biliary tract disease: A systematic review and meta-analysis of prospective studies

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ABSTRACT

Objective. To evaluate the association between body mass index (BMI, kg/m^2) and incidence of biliary tract disease.

Methods. We performed a systematic review and a meta-analysis of prospective studies by searching the database of PubMed and EMBASE published up to December 31, 2013. Outcome of interest was disease of biliary tract system (gallbladder, extrahepatic bile duct and Ampullar of Vater). We used a random-effects model to combine the study-specific relative risks (RRs) and 95% confidence intervals (95% CIs) from 22 prospective studies. We examined whether BMI was associated with a higher risk of biliary tract disease in a combined analysis.

Results. The positive association was stronger for non-cancer biliary tract disease than biliary tract cancer; combined RRs (95% CIs) comparing the top with bottom categories were 1.40 (1.15–1.65) for biliary tract cancer and 2.75 (2.35–3.15) for non-cancer biliary tract disease (P for difference < 0.001). For non-cancer biliary tract disease, combined RRs (95% CIs) comparing the top with bottom categories were 3.21 (2.48–3.93) for women and 2.01 (1.66–2.37) for men (P for difference = 0.04).

Conclusion. Obesity is associated with higher risks of biliary tract cancer and, to a greater extent, non-cancer biliary tract disease.

Contents

Introduction . . . 14
Methods . . . 14
Search strategy . . . 14
Selection criteria . . . 14
Data extraction and quality assessment . . . 14
Statistical analysis . . . 14
Supplemental analysis . . . 18
Results . . . 18
Study selection . . . 18
Study characteristics . . . 18
Meta-analysis . . . 18
Discussion . . . 20
Study limitations and strengths . . . 21
Conclusions . . . 21
Conflict of interest statement . . . 21
Acknowledgment . . . 21
Appendix A. Supplementary data . . . 21
References . . . 21

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Introduction

Obesity has been increasing worldwide (WHO, 2000) and its relationship with mortality and chronic diseases has been well established (Calle et al., 2003; Chan et al., 1994; Kivipelto et al., 2005; Ogden et al., 2007; Poirier et al., 2006). Biliary tract diseases including gallbladder cancer, extrahepatic bile duct cancer, cancer for Ampullar of Vater, cholelithiasis (presence of gallstones), cholecystitis and cholangitis may be directly linked with body fatness possibly through increases in inflammation, insulin resistance and insulin-like growth factor levels, oxidative stress, cholesterol levels, and adipokine levels. Biliary tract cancer has poor prognosis (Carriaga and Henson, 1995) and a relatively low 5-year survival rate (<20%) (Everhart and Ruhl, 2009; Gatta et al., 2011; Jung et al., 2013). Non-cancer biliary tract disease is common and places economic burden (Everhart and Ruhl, 2009; Kortt et al., 1998; Shaffer, 2006; Wolf and Colditz, 1998) in developed countries. Also, the presences of cholecystitis and gallstones are established risk factors of gallbladder cancer (Wistuba and Gazdar, 2004).

Biliary tract cancer is relatively rare in most parts of Europe and USA (Randi et al., 2006), but highly incident in some populations of Andean area, North American Indians, India, parts of Europe such as Poland, Czech Republic, and Slovakia and East Asia (Lazcano-Ponce et al., 2001). Gallstones, on the other hand, are common in most of Europe and USA and relatively uncommon in African and Asian countries (Yoo and Lee, 2009). This discrepancy may be explained by the dissimilarity in the distribution of risk factors, including obesity, smoking status, alcohol consumption, virus infection, and history of diabetes. Obesity has been shown to increase the risk of gallbladder cancer (Bergstrom et al., 2001; Larsson and Wolk, 2007; Renehan et al., 2008) and some non-cancer biliary tract diseases (Guh et al., 2009; Liu et al., 2008a; Williams, 2008). There was inconsistent longitudinal evidence supporting the hypothesis that obesity plays an important role in the progression of total biliary tract cancer (Ishiguro et al., 2008; Schlesinger et al., 2013). However, the magnitude of the association of biliary tract cancer may differ from that of non-cancer biliary tract disease given the geographic difference in incidence rates. The evidence of gender or ethnicity-difference in the association between BMI and risk of biliary tract disease is not conclusive, partly because of the insufficient sample size in individual studies.

Therefore, to assess quantitatively the association between obesity and diseases of biliary tract system (gallbladder, extrahepatic bile duct and Ampullar of Vater) and to examine how the association may differ according to sex and geographic regions, we systematically reviewed and conducted a meta-analysis of prospective cohort studies which examined the associations between BMI and biliary tract cancer and other biliary tract diseases.

Methods

Search strategy

We identified prospective studies examining the association between BMI and biliary tract diseases by searching the database of PubMed and EMBASE (including MEDLINE records) published through December 31, 2013. Two authors (M. Park and D. Y. Song) performed the literature search. We used Medical Subject Heading (MeSH) terms in PubMed and Excerpta Medica Tree (Emtree) in EMBASE. Search terms used included: (1) For PubMed: "obesity, overweight, body mass index, biliary tract neoplasms, bile duct neoplasms, gallbladder neoplasms, and cholangiocarcinoma" for biliary tract cancer; and "obesity, overweight, body mass index, cholelithiasis, choledocholithiasis, gallstones, cholecystitis gallbladder diseases and biliary tract diseases" for non-cancer biliary tract disease; and (2) For EMBASE: "obesity, body mass, gallbladder tumor, biliary tract tumor, and bile duct tumor" for biliary tract cancer; and "obesity, body mass, gallbladder disease, biliary tract disease, cholelithiasis, bile duct stone, gallstone, and biliary tract inflammation" for non-cancer biliary tract disease.

The search was restricted to human studies published as full-text manuscript in English-language. In EMBASE, we additionally restricted the study type to prospective study. We also searched the bibliographies of retrieved papers. This meta-analysis was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). We excluded intrahepatic bile duct cancer from biliary tract cancer, because it can be classified as primary liver cancer on the basis of the ICD-10 criteria (WHO, 2010).

Selection criteria

Eligibility criteria were assessed as follows by two authors (M. Park and J. E. Lee) and selected manuscripts were checked by an independent author (Y. Je); (1) prospective design, published as full-text manuscripts; (2) the main exposure of interest was BMI; (3) the endpoints of interest were biliary tract cancer (cancers of gallbladder, extrahepatic bile duct and Ampullar of Vater) and non-cancer biliary tract disease defined as one of the following conditions — cholelithiasis (gallstones), bile duct stone, choledocholithiasis, and cholecystitis; and (4) relative risks (RRs) with 95% confidence intervals (CIs) for every category of BMI or per unit increase in BMI were reported. When there were multiple publications that covered the same study population (Ko et al., 2000, 2005; Misciagna et al., 1999, 2000; Oh et al., 2005; Robsahm and Tretli, 1999; Song et al., 2008; Stampfer et al., 1992; Syngal et al., 1999), we only included the study with a larger sample size.

Data extraction and quality assessment

We abstracted from each publication the data (Tables 1A, 1B). Two authors (M. Park and Y. Je) independently assessed the quality of each study using the Newcastle–Ottawa Scale (Wells et al., 2011). Disagreements of more than 1 score by both authors were resolved by consensus.

Statistical analysis

We used a random-effects model to combine RRs and 95% CIs reported in each study (DerSimonian and Laird, 1986). We also extracted the RRs and 95% CIs for BMI categories or per unit change in BMI. When there were one or more RR values for the same exposure within a manuscript, we selected the most adjusted RRs for potential confounders or estimates from more segmented categories. When 95% CIs were not reported, but there were numbers of cases and person-time for BMI categories, we calculated the standard error and 95% CIs using the number of sample and reported relative risk and unified unit of BMI in kg/m^2 (Layde et al., 1982). We estimated the RR per 5 kg/m^2 increase in BMI by regressing the natural log RRs using the method described by (Greenland and Longnecker (1992)_) and Orsini (Orsini et al., 2012) to assess the dose–response relationship between BMI and biliary tract disease. For this analysis, we assigned the midpoint of the upper and lower levels in each category to a corresponding relative risk estimate. When the lowest or highest category was open-ended, we considered it at the same amplitude as the neighborhood categories. Studies that reported RRs for three or more categories of BMI were included in the dose–response analysis.

We performed subgroup analyses and meta-regression analyses to assess potential sources of heterogeneity by gender (men or women), type of endpoint (biliary tract cancer or non-cancer biliary tract disease), follow-up duration (≥10 years or <10 years), site of cancer (only gallbladder or gallbladder and other biliary tract), geographic location (Western or Asian population), assessment type of weight and height [self-report or others (direct measurement or data linkage)], ascertainment method of outcomes [self-report or others (data review, data linkage or physician diagnosis)], adjustment for covariates (alcohol consumption, cigarette smoking or parity for women) and the Newcastle–Ottawa Scale (≤5 scores or >5 scores). For subgroup analysis by site of cancer, we calculated summary RRs and 95% CIs comparing top category with bottom category of BMI. If only continuous estimate was available (Schlesinger et al., 2013), we estimated the relevant interval by subtracting the median value in the bottom category from the median value in the top category. We also conducted stratified analysis according to the cutoff for the highest BMI category in non-cancer biliary tract disease because the top category of BMI varied across the studies. The statistical significance of heterogeneity among studies was tested by using the I^2 statistic (Higgins et al., 2003).

We performed sensitivity analyses to examine the influence of individual studies by creating a sensitivity plot using *metaninf* command, which sequentially omitted one study at a time. We investigated whether there was any individual study that produced heterogeneity in a meta-analysis using meta-regression, such as a study of pregnant women in nested case–control study