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Review

Association between obesity and bladder cancer recurrence: A meta-analysis

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ABSTRACT

Background: The association between obesity and bladder cancer prognosis is not well-defined. This meta-analysis was performed to explore whether obesity is related to overall survival (OS) and bladder cancer recurrence.

Methods: Relevant English-language studies were identified by searching PubMed® up to November 1, 2017. We pooled the hazard ratios (HR) and 95% confidence intervals (CIs) using a random effect model. Dose-response relationship, subgroup and sensitivity were also analyzed.

Results: Eleven studies were included. Recurrence rate of bladder cancer was significantly greater in obese (HR = 1.76, 95% CI: 1.36–2.28) vs normal weight patients. Stratification analysis showed that females had higher recurrence risk than males (HR = 1.17, 95% CI: 1.05–1.31). Obesity was not significantly associated with bladder cancer OS (HR = 1.21, 95% CI: 0.97–1.52). Dose-response relationship analysis revealed a linear association between BMI and risk of recurrence. Each one kg/m2 increase in BMI was related to a 1.3% increased risk of bladder cancer recurrence (HR = 1.01, 95% CI = 1.01 to 1.02).

Conclusions: This meta-analysis revealed that obesity may be a risk factor for bladder cancer recurrence.

1. Introduction

Bladder cancer is a common urinary system malignancy with high morbidity and relapse rate. It is the ninth most common and seventh most malignant carcinoma in the world. There are approximately 356,000 new bladder cancer cases and 145,000 bladder cancer deaths annually [1]. Notably, the high incidence of recurrence is a nodus in clinical practice. In accordance with Tumor-Node-Metastasis classification (TNM), tumor grade, and number of primary tumors, 50%–90% of bladder cancer patients will suffer recurrences [2].

Obesity is a public health problem in general and the prevalence of obesity is increasing [3]. As of 2013, the number of overweight and obese individuals reached 2.1 billion worldwide. Of these, the United States accounted for the largest proportion, followed by China and India. Obesity causes a numerous health problems and may impact cancer [4]. In fact, more research has focused on elucidating the relationship between obesity and cancer development. Bhaskaran et al. studied the association between BMI and several cancers and found that high BMI can increase risk of some cancers, like uterine and kidney cancers [5]. Since Kanabrocki et al. first reported the association between obesity and bladder cancer in 1965 [6], numerous studies have tried to identify the effect of obesity on bladder cancer. A meta-analysis by Sun et al. found that obesity increased the risk of bladder cancer and promoted cancer progression [7]. Although several cohort studies have examined the association between obesity and bladder cancer prognosis such as survival and recurrence [8–18], results remain largely inconclusive. For example, an epidemiologic study by Kluth et al. found that obesity was an independent risk factor of bladder urothelial carcinoma recurrence. Patients with BMI > 30 kg/m^2 had worse outcomes than non-obese individuals [12]. A similar positive association between

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; BMI, body mass index

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obesity and increased recurrence rate was also reported by other research teams [9,15,18]. In contrast, a prospective cohort study found that obesity was not an independent risk factor for recurrence [14]. Therefore, we conducted a meta-analysis to summarize the relationship between recurrence, overall survival of bladder cancer and obesity.

2. Materials and methods

2.1. Ethical approval

This article did not contain any studies with human participants or animals performed by any of the authors. Ethics approval was not necessary for this study, as this meta-analysis was based on the published data.

2.2. Search strategy

Literature was identified by searching PubMed through November 1, 2017. The key words were as follows: 'obesity', 'body mass index' ('BMI'), together with 'bladder cancer'. The references of identified literature were screened for potentially relative articles.

2.3. Inclusion criteria

Studies were available for inclusion if they meet the following criteria: (1) to evaluate the relationship between obesity (BMI) and bladder cancer prognosis, including OS and recurrence; (2) to report hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) or offering survival curves to calculate HR; (3) all papers must be written in English.

2.4. Data extraction

The following information was extracted from each study: first author, year of publication, country, sample size, surgery methods, study design, follow-up time, outcome, BMI measure time, HR estimation, quality. For studies that reported HRs using both univariate analyses and multivariate analyses, we selected the latter. For studies that reported HRs using both univariate analyses and multivariate analyses, and BMI in univariate analysis was divided into three groups and in multivariate analysis into two groups, we chose the former.

2.5. Quality assessment

The quality of literature was assessed using the Newcastle-Ottawa Scale [19] for nonrandomized studies, which has a highest score of nine points to each cohort study (four points for quality of selection, two for comparability, and three for quality of outcome). Studies with scores of less than seven were considered as low-quality studies, and those with scores great than or equal to 7 were high-quality studies as corresponding [20].

2.6. Statistical analysis

Pooled HRs and corresponding 95%CIs were derived by random-effect model. The heterogeneity among studies was assessed by Q and I^2-statistics tests (heterogeneity was thought as statistically significant if $P < 0.10$ or $I^2 > 70\%$). We assessed the publication bias using Begg's rank correlation test and Egger regression analysis. HR > 1 meant higher risk of recurrence and worse OS. HR was extracted from survival curves by software plot-digitizer if studies did not provide HR, and was pooled and analyzed by Stata software (v11.0). All two-sided tests used a significance level of 0.05. Not each study used the same BMI category standard to define obesity because of different regions. In Europe and the United States, obesity is defined as BMI of 30 kg/m^2 or greater, while in Asia is of 25 kg/m^2 or greater. A study performed in China by Xu et al. defined patients obese if their BMI ≥ 28 kg/m^2. We considered each HR as separate reports in the meta-analysis if results were stratified by operative methods [21].

Subgroup analyses were conducted to assess the influence of potential confounders, such as gender (e.g. male and female). We also conducted a sensitivity analysis to assess the potential effect of individual study [7,22,23]. In addition, to find out whether risks increased along with the growth of BMI, we evaluated the dose-response relationship analysis between obesity and bladder cancer prognosis if the data were available to seek potential curve linear association. As the exposure values were translated from BMI categories, studies included in the analysis should involve at least three BMI categories. Medians of each BMI categories were calculated as dose values. If the extreme BMI categories were open-ended, critical values added or deducted 1 (0.5 if category did not contain critical value) were considered as dose values [24,25]. Besides, death or recurrence numbers were respectively taken as response values. If some study did not provide death or recurrence number, we extracted it from survival curve. All dose-response analyses were performed with Stata 11.

3. Results

3.1. Study characteristics

We identified 387 articles from PubMed prior to November 1, 2017. A total of eleven articles were included in final meta-analysis [8–18]. Four studies conducted in North America [8,10,16,17], five in Europe [9,12–14,18] and two in Asia [11,15]. A total of 726 patients were recruited in study by Wyszynski et al., and only data from 338 patients were available for BMI analysis [14]. Study by Maurer et al. recruited a total of 390 patients with clinical data, and patients were divided into different groups according to different surgical methods [13]. Thus, survival data of 341 patients was collected for Kaplan-Meier analysis. Ultimately this meta-analysis consisted of 7193 bladder cancer cases for OS analysis and 6452 for recurrence. And as mentioned above, Bachir et al. [8] and Maurer et al. [13] classified patients into two types according to surgery methods, we regarded them as two separated reports. Among these eleven articles, most studies measured BMI values at the time before surgery, except one study by Wyszynski et al. which calculated BMI at diagnosis and two by Kluth et al. and Ahmadi et al., which has not provided relevant information [12,14,17]. Three studies were included in dose-response analysis [9,15,18]. Characteristics of each included study were shown in Table 1.

3.2. Qualitative assessment

The scores of study quality assessed by Newcastle–Ottawa quality assessment scale ranged from 7 to 9 (with a mean of 7.72), which indicates acceptable methodology. Scores of each study was presented in Table 1.

3.3. Association between obesity and recurrence

Five articles were included in the analysis. As shown in Table 2 and Fig. 1, obesity was an independent predictor of bladder cancer recurrence (pooled HR = 1.76, 95% CI: 1.36–2.28). The patients with higher BMI were found to have an increased risk of recurrence as compared with individuals of normal weight. No statistically significant association was found between overweight and recurrence (pooled HR = 1.16, 95% CI: 0.90–1.50). There was high heterogeneity existing in both analyses (each $I^2 > 60\%$, $P < 0.010$, Fig. 1).

3.4. Association between obesity and OS

We did not observe a different in the rate of cancer overall survival associated with obesity. But obese patients were prone to shorter