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Review Article

Does body mass index correlate with the mortality of prostate cancer? A dose-response meta-analysis of cohort studies

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Abstract: The relationship between body mass index (BMI) and mortality of prostate cancer (PCa) is still controversial. We performed a meta-analysis of cohort studies to evaluate potential linear and non-linear dose-response relationships between BMI and mortality of PCa. Studies were identified by comprehensively searching PubMed, Scopus, and Web of Science databases through June 22, 2016 without language restriction. Linear and non-linear dose-response meta-analyses were conducted to identify the effects of BMI on mortality of PCa. Nine cohort studies were finally included in this meta-analysis. Dose-response analysis indicated that the pooled relative risks (RRs) per 5 kg/m^2 increment of BMI were 1.16 (1.10-1.23) for fatal PCa. There was no evidence of a nonlinear relationship between BMI and fatal PCa (P = 0.908 for nonlinearity). Moderate heterogeneity was observed among included studies (P = 0.027, I^2 = 52.2%). Overall, the findings of this meta-analysis indicate that, based on available information, obesity is associated with a higher risk of fatal PCa.

Keywords: Body mass index, prostate cancer, dose-response, meta-analysis, mortality

Introduction

Prostate cancer (PCa) is the most common cancer in males in the developed countries and the second most common one worldwide after lung cancer [1]. The etiology of PCa is still largely unknown and the greatest known risk factors are those that are inherited and non-modifiable such as age, race, and family history of PCa [2]. However, a high incidence of PCa in the USA and Europe suggests that PCa may be related to a "Western" lifestyle and environmental risk factors [3], in particular the influence of obesity is gaining recognition. In view of recent increase in the worldwide prevalence of obesity [4], understanding the roles of body adiposity in prostate carcinogenesis and tumor progression holds special relevance for clinical medicine and public health.

Body mass index (BMI) is the most widely used measure to diagnose obesity [5]. A number of well-designed longitudinal studies have been conducted on the relationship between BMI and PCa risk with positive, negative, or null associations reported. A large meta-analysis included a total of 27 prospective studies and recorded a non-statistically significant association between BMI and total PCa risk [6]. Furthermore, given the possible PCa subtype-specific differences in this association, the meta-analysis conducted in 2012 examined this relationship separately by PCa tumor characteristics and observed that obesity appeared to increase the risk of advanced PCa but reduce the risk of localized disease [7]. As for fatal prostate cancer, heterogonous results also have been reported in literature but no meta-analysis has addressed this issue up to now.

Dose-response meta-analysis is an ideal solution to the above controversies. Pooling multiple independent but homogeneous studies provides greater statistical power and increases precision of the findings. We therefore performed a random-effects dose-response meta-analysis of all available cohort studies to ex-

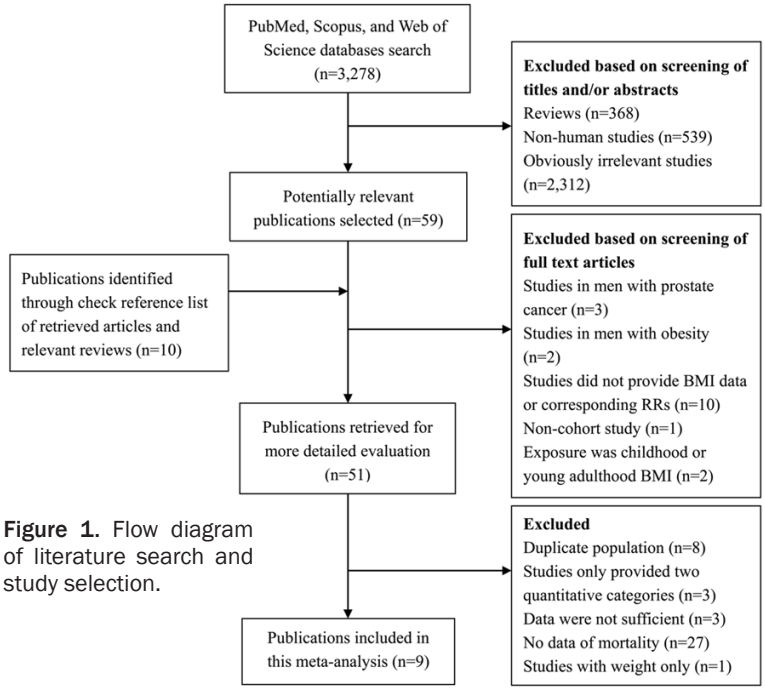

Figure 1. Flow diagram of literature search and study selection.

plore the potential association between BMI and the mortality of PCa.

Materials and methods

Search strategy

Two authors (WJ and BC) independently searched PubMed, Scopus, and Web of Science databases from its inception to June 22, 2016 with the following search strategy that included both truncated free text and exploded MeSH terms relevant to "overweight", "obesity", "body mass index", "BMI", "body size", "adiposity", "PCa", "prostate cancer", "prostate neoplasm", and their variants. There were no language or date restrictions. We also manually searched the reference lists of included studies and recent reviews for additional articles.

Selection criteria

To identify eligible studies, we used a two-step selection procedure. Two independent reviewers (WJ and BC) undertaken an initial screening of article titles and abstracts and excluded those clearly not relevant articles in the form of reviews, meta-analyses, ecological studies, animal studies, case reports, editorials, and comments. All potentially relevant articles were evaluated based on full text reviews. Reviewers used pre-specified criteria to ensure a consistent and comprehensive approach. Any disagreements between the two reviewers were settled by discussion. Studies were included if they were cohort studies, studied the effects of BMI, and reported mortality rate of PCa as the outcome of interest.

Data extraction and assessment for study quality

Data extraction was conducted with a standardized data collection form. Two reviewers (WJ and BC) independently reviewed full-text versions of eligible studies and recorded the following information: first author's surname, publication year, country, study name or source, the number of cases, sample size, duration of follow-up, adjusted covariates, BMI exposure levels, and corresponding estimates with 95% CIs. The same reviewers completed quality assessment of each included study independently with the Newcastle-Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Discrepancies were resolved by consensus and discussion.

Statistical methods

The outcome we analyzed was the relative risk (RR) with its corresponding 95% confidence interval (CI) of the mortality of PCa. A random-effects model was used for all meta-analyses to account for both within- and between-study heterogeneity. For each of the included studies, we assigned the reported median or mean BMI level of each category to the corresponding RR for each study. When medians and means were not presented, we used the midpoint of the lower and upper bounds of that category. When the highest category was open-ended, we assumed the width of the category to be the same as the closest adjacent category [7]. In the Asia-Pacific Cohort Studies Collaboration [8], we estimated the conventional 95% CIs from a set of 95% CIs calculated by the floating absolute risk method.

Table 1. Main characteristics of studies included in this meta-analysis

Author, year	Country	No. of cases	No. of cohort	Age	Study name or source	Duration of follow-up	Quality score	Adjustment factors
Taghizadeh et al., 2015	Netherland	83	3,718	20-65	Vlagtwedde-Vlaardingen cohort study	40 y	6	Age, smoking, and place of residence
Bassett et al., 2012	Australia	1,374	16,514	68 (47-86)	Melbourne Collaborative Cohort Study	15.0 y	8	Age, country of birth, and education
Häggström et al., 2012	Norway, Sweden, Austria	6,673	289,866	44±11	Metabolic Syndrome and Cancer Project	12 y	7	Age, smoking, and birth year
Discacciati et al., 2011	Sweden	2,084	36,959	45-79	Central Sweden	1998-2008	7	Age, energy intake, physical activity, education, smoking, family history of PCa, diabetes, and BMI at age 30 years
Dehal et al., 2011	USA	44	7,016	47 (25-74)	National Health and Nutrition Examination Survey Epidemiology Follow-Up Study	17 y	7	Age, race/ethnicity, education, family income, marital status, residence area, alcohol, smoking, frequency of eating fruit and vegetables
Stocks et al., 2010	Sweden	10,002	336,159	34.7±13.1	Swedish Construction Workers cohort	22.2 y	6	Age, birth year, smoking, and blood pressure
Parr et al., 2010	Asia-Pacific	278	249,155	48	Asia-Pacific Cohort Studies Collaboration	4 y	6	Age and smoking
Wright et al., 2007	USA	9,986	287,760	50-71	NIH-AARP Diet and Health Study	5 y	6	Age, race, smoking, education, diabetes, and family history of PCa
Rodriguez et al., 2001 (CPS-I)	USA	1,590	381,638	52	Cancer Prevention Study I	1959-1972	8	Age, race, height, education, exercise, smoking, and family history of PCa
Rodriguez et al., 2001 (CPS-II)	USA	3,622	434,630	57	Cancer Prevention Study II	1982-1996	8	Age, race, height, education, exercise, smoking, and family history of PCa

BMI, body mass index; No., number; y, years; PCa, prostate cancer.

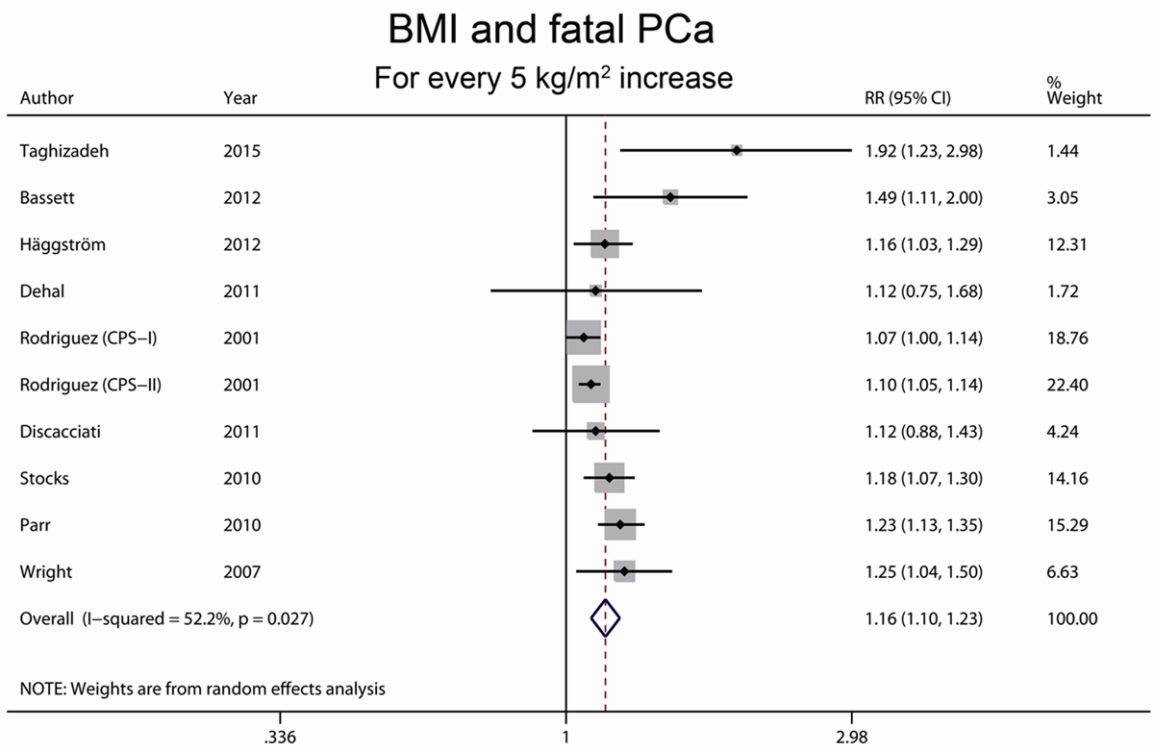

Figure 2. Risk of fatal PCa associated with each 5 kg/m^2 increase in BMI. Weights are from random-effects analysis. RR: relative risk, CI: confidence interval, BMI: body mass index, PCa: prostate cancer.

For dose-response meta-analysis, we first estimated the dose-response trend for each study using the method proposed by Greenland and Longnecker [9], which takes into account the correlation of the RRs within each study. These dose-response trends were then pooled with random-effects meta-analysis. Next, we explored potential non-linear dose-response relationship in each study by using restricted cubic regression splines with three knots at the 25th, 50th, and 75th percentiles of the distribution, and results from each study were then combined using random-effects multivariate meta-analysis [10].

Potential small study bias was evaluated by Begg's test [11] and Egger's test [12]. If publication bias was indicated, we performed a trim and fill analysis to evaluate whether this had affected the results. Heterogeneity was evaluated by I^2 and Cochran's Q (significance level at $P < 0.10$) [13]. Galbraith plot was used to detect the studies that led to heterogeneity.

For sensitivity analysis, we first removed one study at a time and recalculated the pooled estimates for the remainder of the studies to determine whether the results could have been influenced greatly by a single study. Secondly, we repeated the analysis after excluding studies that contributed to heterogeneity. Lastly, we conducted meta-analysis based on studies that adjusted for physical activity or personal history of diabetes to examine whether these variables would confound the relationship between BMI and PCa. Except where otherwise specified, a 5% significance level and a two sided test were adopted throughout this study. All statistical analyses were performed with Stata version 11 (StataCorp, College Station, TX).

Results

Literature search and study characteristics

We identified 3,278 articles for review of title and abstract (**Figure 1**). After the initial screening, full articles of potentially eligible studies were retrieved for detailed assessment. Nine eligible studies [8, 14-21] were eventually included in this meta-analysis. The cohort size

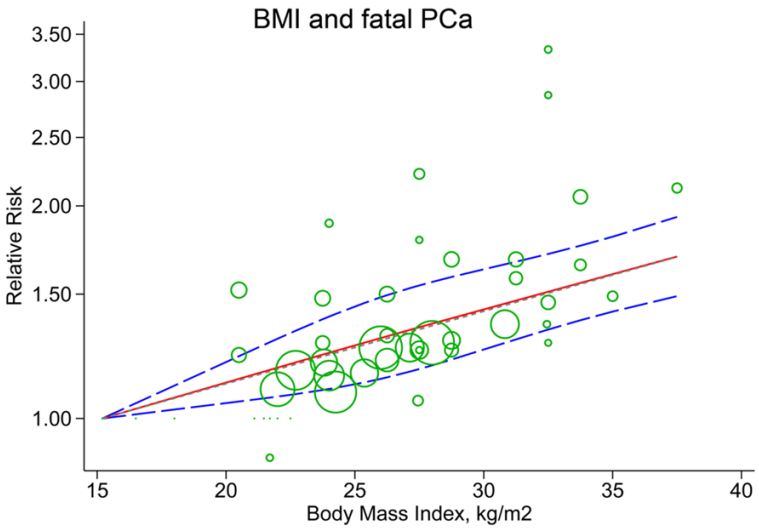

Figure 3. Non-linear dose-response meta-analysis for fatal PCa. Weights are from random-effects analysis. Red solid line and blue dash lines represent point estimates and 95% confidence intervals for non-linear analysis; Grey dash line represents point estimates for linear analysis. Green circles present the dose-specific relative risk estimates reported in each study; size of bubble is proportional to precision (inverse of variance) of relative risk. RR: relative risk, CI: confidence interval, BMI: body mass index, PCa: prostate cancer.

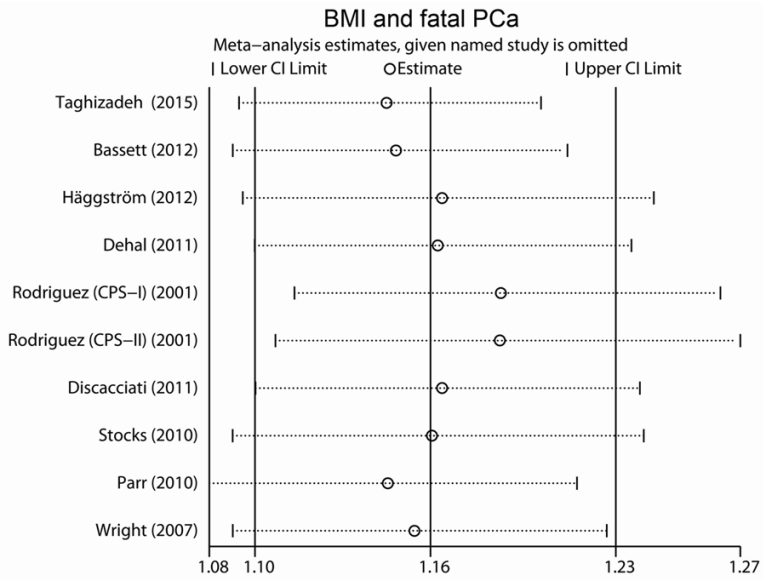

Figure 4. Sensitivity analysis for the effect of body mass index on fatal prostate cancer. The analysis was conducted by omitting each study in turn. Meta-analysis random-effects estimates were used. The two ends of the dotted lines represent the 95% CI. BMI, body mass index; PCa, prostate cancer.

ranged from 3,718 to 434,630. Three studies were conducted in United States, four in Europe, one in Australia, and one in multiple Asia-Pacific countries. Studies were published between 2001 and 2015. All of the nine studies provided RR estimates adjusted for age. Assessment of study quality yielded an average score of 6.8. Detailed characteristics of the included studies are presented in **Table 1**.

Dose-response meta-analysis

Figure 2 displays the study-specific linear trend estimates of the relationship between BMI and mortality of PCa and the combined estimate from a random-effects meta-analysis model. The pooled RR per 5 kg/m^2 increase in BMI is 1.16 (95% CI 1.10-1.23) for fatal PCa, with some evidence of heterogeneity among included studies (P = 0.027, I^2 = 52.2%). **Figure 3** shows the results of non-linear dose-response meta-analysis. There was no evidence of a non-linear relationship for fatal PCa (P = 0.908 for nonlinearity).

Sensitivity analysis

To evaluate the robustness of the significant associations between BMI and fatal PCa, several sensitivity analyses were performed. We first removed one study at a time and repeated the meta-analysis. All the results were not influenced greatly by a single study (**Figure 4**). Secondly, we used Galbraith plot to detect the studies that contributed to heterogeneity. The study performed by Taghizadeh et al. (**Figure 5**) was the major source of heterogeneity for fatal PCa. After excluding this outlying study, no significant heterogeneities were observed across the remaining studies (P = 0.104, I^2 = 39.6%) and the corresponding pooled RRs was not materially altered (RR = 1.15, 95% CI 1.10-1.20).

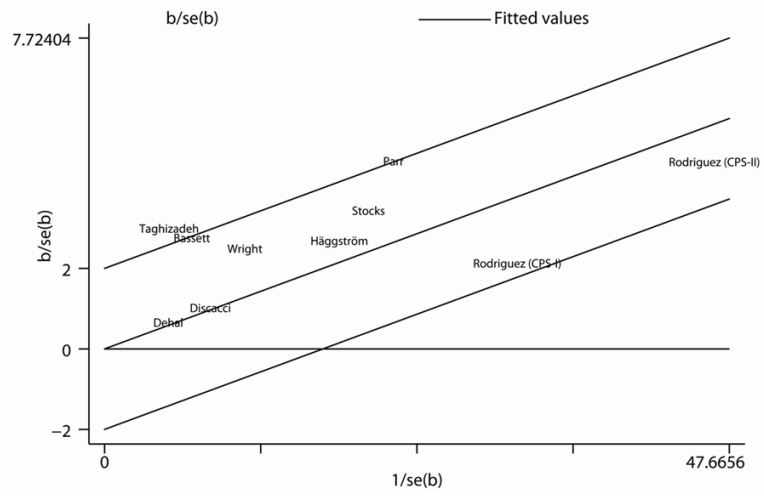

Figure 5. Galbraith plot analysis was used to assess heterogeneity. It indicated that Taghizadeh et al., study was the potential source of heterogeneity.

Lastly, physical activity and personal history of diabetes may confound the relationship between BMI and PCa. We thus performed meta-analysis of studies that adjusted for diabetes or physical activity and obtained statistically significant risk estimates for fatal PCa (RR = 1.25, 95% CI 1.04-1.50; RR = 1.09, 95% CI 1.05-1.13).

Publication bias

There was no significant publication bias detected by Egger's test (P = 0.053) or Begg's Test (P = 0.210).

Discussion

The present study indicated that BMI was significantly associated with the mortality of PCa by summarizing the results of all available cohort studies. Overall, the dose-response analysis showed that each 5 kg/m^2 increment of BMI corresponded to a 16% increase in the risk of fatal PCa. There was no evidence of a nonlinear relationship for fatal PCa (P = 0.908 for nonlinearity).

Several potential mechanisms could explain the positive association between BMI and risk of fatal PCa. Obese men have lower serum testosterone concentrations [22]. Testosterone may contribute to the growth and development of PCa [23]. Furthermore, a genome-wide association study and Metabochip meta-analysis of BMI identified 97 BMI-associated loci, of which many have significant effects on metabolic phenotypes [24]. Accordingly, obese men were characterized with high circulating concentrations of insulin, leptin and insulin-like growth factor-I (IGF-I) and low levels of adiponectin, all of which have been proposed to stimulate PCa growth and spread and underlie the higher risk of advanced and fatal PCa [25]. Tumor microenvironment may also play a role in this link. A recent study detected an altered expression of genes encoding molecules involved in adipogenesis, cell proliferation, and immunological responses in the periprostatic adipose tissue of obesity/overweight participants [26].

Several limitations of this meta-analysis should be acknowledged. Firstly, errors in measurement of BMI are inevitable. A large portion of the studies included in this meta-analysis estimated the BMI based on self-reported weight and height, which were less accurate than anthropometric data obtained directly by trained investigators. However, many studies have shown that self-reported anthropometric data correlate highly with measured data [27, 28]. Secondly, during the long follow-up, participants may have changed their BMI. All exposures were defined according to information collected at the time of their entry into the cohort. Weight may have changed over the follow-up period, which may have resulted in some underestimation of the true associations since it has been reported that the prevalence of obesity increases with increasing age, which is gender-equivalent and independently of socioeconomic status [29]. Thirdly, although we extracted data from the fully adjusted models, a meta-analysis is not able to solve the problems of confounding variables that could be inherent in the original studies. Residual or unmeasured confounding may bias the results in either an exaggeration or an underestimation of a risk estimate. Fourthly, moderate heterogeneity across studies was observed among included studies, which would throw some doubt on the reliability of the combined esti-

mates for these relationships. However, the significant associations persisted after we removed the studies that contributed to heterogeneity in the sensitivity analyses. Lastly, this meta-analysis was performed relied on aggregate data instead of individual data. Access to individual participant data (IPD) would allow a more precise delineation of the exposure-response relationship and adjustment for potential confounding factors.

This meta-analysis also has some strengths. The present study collected all eligible cohort studies from various countries and populations. The large sample size of included studies increased the statistical power. The estimates from models adjusting for most established risk factors in each study were used in our analyses to minimize potential confounding. Linear and non-linear dose-response analyses were performed to quantify the potential associations and examine the shape of the dose-response curve. Various sensitivity analyses were performed to evaluate the robustness and stability of the results.

In summary, results from our meta-analysis indicate higher BMI level is associated with a higher risk of fatal PCa. Future research is warranted to investigate the potential mechanisms underlying these associations.

Disclosure of conflict of interest

None.

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