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The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence

Yu-zhu Xiang[†], Hui Xiong[†], Zi-lian Cui, Shao-bo Jiang, Qing-hua Xia, Yong Zhao, Guan-bin Li and Xun-bo Jin^{*}

Abstract

Background: Although a previous meta-analysis reported no association between metabolic syndrome (MetS) and prostate cancer risk, a number of studies suggest that MetS may be associated with the aggressiveness and progression of prostate cancer. However, these results have been inconsistent. This systematic review and meta-analysis investigated the nature of this association.

Methods: We systematically searched MEDLINE, EMBASE and bibliographies of retrieved studies up to January 2013 using the keywords "metabolic syndrome" and "prostate cancer". We assessed relative risks (RRs) of the prostate cancer, several parameters of prostate cancer aggressiveness and progression associated with MetS using 95% confidence intervals (95% CIs).

Results: The literature search produced 547 hits from which 19 papers were extracted for the meta-analysis. In cancer-free population with and without MetS, the combined adjusted RR (95% CI) of prostate cancer risk and prostate cancer-specific mortality in longitudinal cohort studies is 0.96 (0.85 ~ 1.09) and 1.12 (1.02 ~ 1.23) respectively. In the prostate cancer patients with and without MetS, the combined unadjusted OR (95% CI) of high grade Gleason prostate cancer is 1.44 (1.20 ~ 1.72), the OR of advanced prostate cancer is 1.37 (1.12 ~ 1.68) and the OR of biochemical recurrence is 2.06 (1.43 ~ 2.96).

Conclusions: The overall analyses revealed no association between MetS and prostate cancer risk, although men with MetS appear more likely to have high-grade prostate cancer and more advanced disease, were at greater risk of progression after radical prostatectomy and were more likely to suffer prostate cancer-specific death. Further primary studies with adjustment for appropriate confounders and larger, prospective, multicenter investigations are required.

Keywords: Gleason score, Recurrence, Clinical stage, Aggressiveness

* Correspondence: jinxunbo@163.com

[†]Equal contributors

Minimally Invasive Urology Center, Provincial Hospital Affiliated to Shandong University, Jinan 250021, China

Background

In men, prostate cancer (PCa) is the most frequently diagnosed malignancy in industrialized countries [1] and it is the second most commonly diagnosed cancer and the sixth leading cause of cancer death worldwide [2]. There is a clear need for a better understanding of the risk factors related to PCa development and progression. Age, race and family history are the only established prostate cancer risk factors and these factors are all non-modifiable. Recently, modifiable lifestyle factors such as physical activity and diet have been investigated. Because a higher incidence of PCa was associated with a higher prevalence of “western” lifestyle, it has been suggested that these lifestyle factors play a significant role in the pathogenesis of PCa [3].

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that includes hypertension, diabetes mellitus, obesity, hypertriglyceridemia, and low high-density lipoprotein cholesterol, with insulin resistance as the underlying hallmark feature [4]. The prevalence of MetS has been increasing worldwide and has become a major public health problem in many western countries. For example, 35%-41% of adults in the USA are reported to exhibit MetS [5]. Recently, increasing evidences suggests that MetS may be involved in the development and progression of certain types of cancer as an independent etiologic factor including breast cancer [6], endometrial cancer [7], colorectal cancer [8], pancreatic cancer [9] and prostate cancer [10]. MetS was firstly observed as a composite factor associated with prostate cancer risk in 2004 [11], and more studies have since reported the association between MetS and prostate cancer. However, the studies investigating the association between MetS and prostate cancer risk have reported inconsistent findings [12-21].

It is crucial to review and evaluate the magnitude to which MetS affects the development and progression of PCa, as proper management of this modifiable lifestyle factor may help improve PCa outcomes.

A recently performed meta-analysis study summarized the association between MetS and the incidence of some common cancer types, including prostate cancer. The results, based on 14 databases, revealed that MetS was not associated with prostate cancer risk [22]. However, a new investigation on MetS and prostate cancer risk was published recently [19], and much increasing evidence in the latest investigations suggests that MetS may be associated with the aggressiveness and progression of PCa; prostate cancer patients with MetS may suffer more aggressive disease and adverse clinical outcomes [19,23-27]. However, inverse results [28] or no significant associations [14,20,29,30] have been reported in other studies. Therefore, to thoroughly investigate the nature of this association, we focused on longitudinal

cohort studies and conducted a new meta-analysis to confirm the association between MetS and prostate cancer risk by searching the latest literature. Subsequently, we performed another meta-analysis to quantitatively summarize several parameters of PCa aggressiveness and progression, including Gleason score, clinical stage, biochemical recurrence and prostate cancer-specific mortality associated with MetS.

Methods

Search strategy

We systematically searched MEDLINE, EMBASE through January 2013 for human studies on the association between MetS and PCa with the following medical subject heading terms and/or text words: “metabolic syndrome”, “insulin resistance syndrome”, or “syndrome X”, combined with “prostate cancer”, “prostatic cancer”, “prostate neoplasm”, or “prostatic neoplasm”. We also manually searched relevant journals, bibliographies, and reviews for additional articles. The search had no language restriction.

Inclusion criteria

The eligibility of each study was assessed independently by two investigators (YX and HX). We included only cohort studies of MetS and prostate cancer risk or prostate cancer-specific mortality and clinical studies of MetS and Gleason score or clinical stage at diagnosis or biochemical recurrence after treatment. We included studies that reported standardized forms of relative risk, risk ratio, hazard ratio or odds ratio with estimates of confidence intervals (CIs) or with sufficient data to estimate CIs. We used relative risks (RRs) to represent various effect estimates in a cohort study in this meta-analysis.

Exclusion criteria

We excluded reviews, editorials, meta-analysis and animal studies. Among the 23 studies that underwent full-text reviews, we excluded a study on MetS and prostate cancer risk of re-biopsy [31], a study that did not use a standard definition of MetS [32,33] and one case-control study on MetS and prostate cancer risk [21]. For studies previously published on the same database [34,35], we included only the most recent findings [19,20]. All of the studies on which we focused reported RRs with 95% CIs or sufficient data to estimate them.

Data extraction

The data extracted included publication data (the first author's last name, year of publication, and country of the population studied), study design, population resources, number of cases, risk estimates with their corresponding CIs, and variables controlled for by matching or in the most adjusted model. Abstractions of the data elements

were conducted separately by two authors; discordant results were resolved by consensus.

Statistical analysis

Firstly, we updated the data and attempted to analyze the association of MetS with the prostate cancer risk in longitudinal cohort studies only. Subsequently, we assessed the association between MetS and prostate cancer-specific mortality in cohort studies and between MetS and high grade Gleason PCa and/or advanced PCa or biochemical recurrence in clinical studies. We pooled all of the RRs for MetS and assessed the heterogeneity between the studies by Q and I^2 statistics, which are distributed as χ^2 statistics [36]. A value of $P < 0.10$ was used to indicate lack of homogeneity (heterogeneity) among effects. We used a fixed-effects model if I^2 value significance was < 0.1 ; otherwise, we used a random-effect model. Sensitivity analysis was conducted by omitting one study at a time, generating the pooled estimates and comparing with the original estimates. Funnel plots and both Begg's and Egger's tests were used to evaluate publication bias. All analyses were performed using STATA version 9.0 statistical software (Stata, College Station, Texas, USA). All statistical comparisons were 2-sided, and a p -value < 0.05 was considered statistically significant).

Results

Study characteristics

Nineteen studies met the search inclusion and exclusion criteria. The characteristics of included studies are presented in Tables 1 and 2.

Detailed search steps are described in Figure 1. Briefly, from the initial literature search we identified 547 abstracts. Twenty-three articles were considered of interest and full text of each article was retrieved for detailed evaluation. Eleven studies investigated the association between MetS and prostate cancer [11-21]. Nine of them were longitudinal cohort studies that reported the RRs of PCa in cancer-free population with and without MetS [7-15]. Seven studies evaluated MetS and pathological and clinical stages of PCa, of these studies, 7/7 investigate Gleason score [20,23-26,28,29] and 4/7 investigated clinical stage [20,23,24,29]. Two case-control studies explored biochemical recurrence after primary treatment [23,27], and three longitudinal cohort studies focused on prostate cancer-specific mortality [14,19,30].

Main findings

Prostate cancer risk

Result from a meta-analysis based on nine longitudinal cohort studies revealed that there was no association between MetS and prostate cancer risk (RR = 0.96, 95% CI 0.85-1.09 $n = 9$ studies) (Figure 2).

Prostate cancer aggressiveness

High grade Gleason score The definition of high grade Gleason score is ≥ 7 or > 7 . A trend for a 36% increased risk of a high Gleason score in patients with MetS (OR = 1.36, 95% CI 0.90-2.06 $n = 7$ studies) was identified based on a meta-analysis of seven total relative databases (Figure 3).

Advanced clinical stage Advanced clinical stage was defined as a clinical stage $\geq T3$. Four databases were included in the analysis of the association of MetS with advanced clinical stage. The analysis revealed that MetS was significantly associated with a 37% increased risk of advanced clinical stage (OR = 1.37, 95% CI: 1.12 ~ 1.68; $n = 4$ studies) (Figure 4).

Prostate cancer progression

Biochemical recurrence Only two databases [23,27] focused on the association of MetS which biochemical recurrence. The Individual study results and the overall summary results are presented in Figure 5. The result indicates that MetS was significantly associated with 2-folds of increased risk of biochemical recurrence (OR = 2.06, 95% CI: 1.43-2.96, $n = 2$ studies).

Prostate cancer-specific mortality Three cohort studies [14,19,30] investigated how MetS affected prostate cancer-specific mortality. The meta-analysis revealed that MetS was significantly associated with a higher risk of the prostate cancer-specific death (RR = 1.12, 95% CI: 1.02 ~ 1.23; $n = 3$ studies) (Figure 6).

Sensitivity analysis

We conducted sensitivity analysis by omitting one study at a time, generating the pooled estimates and comparing the pooled estimates with the original estimates. Omitting any one of nine studies concerning MetS and prostate cancer risk or omitting any one of four studies concerning MetS and advanced clinical stage produced no dramatic influence on the original pooled RRs. Omitting Jeon 2012 database [28] in the 7 studies concerning MetS and Gleason score produced a significant OR = 1.44 (95% CI: 1.20 ~ 1.72), whereas none of the remaining seven studies exhibited a significant influence on the original estimates. For biochemical recurrence and prostate cancer-specific mortality, there were too few studies to do a sensitivity analysis.

Publication bias

Visual inspection of the Begg funnel plot for both PCR and Gleason score did not reveal the asymmetry typically associated with publication bias (Figure 7). Evidence of

Table 1 Characteristics of cohort studies of metabolic syndrome and prostate cancer risk

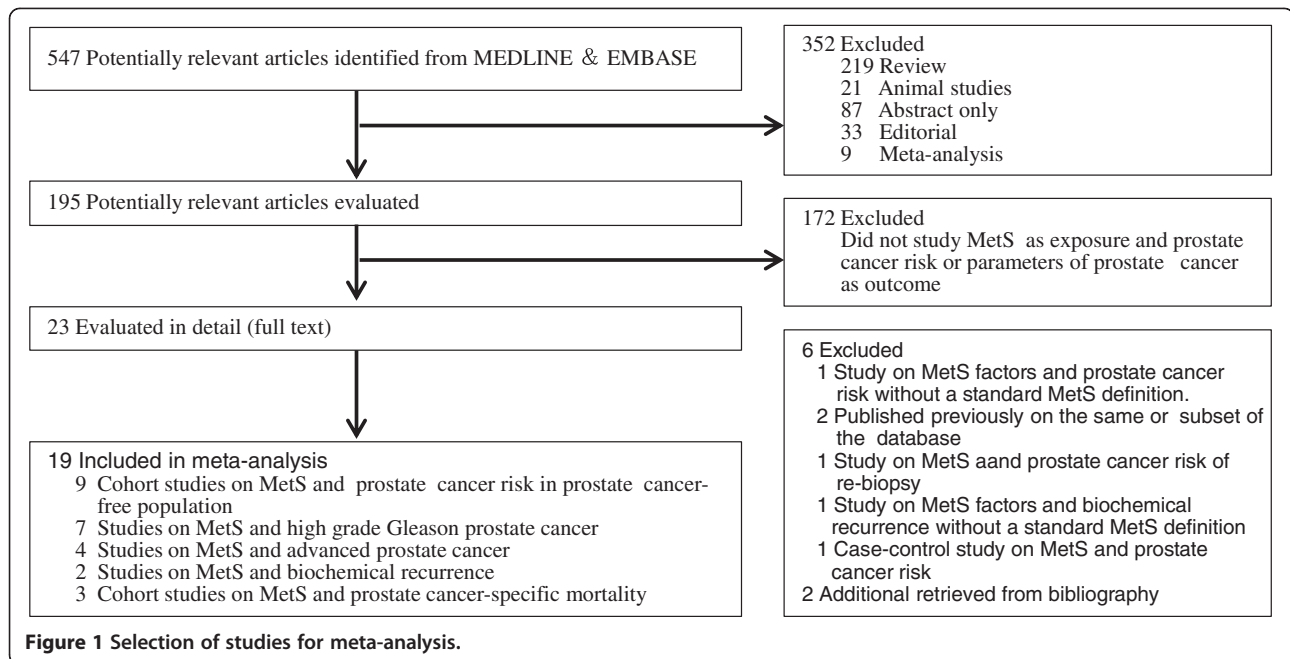
Author yr (ref. no.)	Country	Population	Mean age, yr	Mean FU time, yr	Time period	Cohort size	Definition of MetS	No. of cases	RRs	95% CI	Controlled variables
Laukkanen 2004 [11]	Finland	Kuopio communities	52.6	15	1984-2001	1,880	WHO	56	RR 1.90	1.1-3.5	Age
Tande 2006 [12]	United States	ARIC* (49% white, 51% African American)	45-64	12.1	1987-2000	6,429	NCEP-ATP-III	385	RR 0.77	0.60-0.98	Age, race
Russo 2008 [13]	Italy	A pharmacologically based diagnosis	40	2.7	1999-2005	NA	A pharmacologically based diagnosis	94	RR 0.93	0.75-1.14	Age
Martin 2009 [14]	Norway	HUNT2	48 ± 16.4	9.3	1996-2005	29,364	NCEP-ATP-III	687	RR 0.91	0.77-1.09	Age+
Inoue 2009 [15]	Japan	Japan PHC population	40-69	10.2	1993-2004	9,548	IDF	119	HR 0.76	0.47-1.22	Age+
Grundmark 2010 [16]	Sweden	ULSAM	50	30.3	1970-2003	2,183	NCEP-ATP-III	226	RR 1.29	0.89-1.88	Age
						2,287	IDF	234	RR 1.18	0.81-1.71	
Wallner 2010 [17]	United States	Olmsted County	40-79	15	1990-NA	2,445	WHO	206	HR 0.65	0.37-1.10	Age
Osaki 2011 [18]	Japan	The population-based cancer registry	60.5 ± 10.8	9.3	1992-2007	8,239	NCEP-ATP-III	152	HR 1.37	0.91-2.06	Age
						8,239	IDF	152	HR 1.18	0.74-1.90	
Häggström 2012 [19]	Norway	Me-Can	44	12	NA	289,866	Upper quartile levels ATP-III criteria	6,922	RR 0.96	0.92-1.00	Age+
	Sweden										
	Austria										

MetS = metabolic syndrome; *PCa* = prostate cancer; *RRs* = Relative risks; *CI* = confidence interval; *Age +* = At least age; *WHO* = World Health Organization; *NCEP-ATP-III* = National Cholesterol Education Program Adult Treatment Panel III; *IDF* = International Diabetes Federation; *HUNT 2* = Nord-Trøndelag Health Study; *ARIC* = Atherosclerosis Risk in Communities; *OR* = odds ratio; *We use White-American data.

Table 2 Characteristics of studies of metabolic syndrome and parameters of prostate cancer

Author yr (ref. no.)	Country	Study design	Population	Mean age,yr	Time period	Definition Vof MetS	No. of cases	Outcomes	RRs	95% CI
B.K 2007 [29]	Korea	Cross-section study	Patients who underwent radical retropubic prostatectomy	64.8 ± 6.2	2004-2006	NCEP-ATP-III	261	Gleason score ≥7(4 + 3) Clinical stage ≥ T3	0.972 0.991	0.637-1.482 0.532-1.846
Beebe-Dimmer 2009 [20]	United States	Case-control study	GECAP	62.3	1999-2004	NCEP-ATP-III	637	Gleason score ≥7(4 + 3) Clinical stage ≥ T3	1.2 1.17	0.64-2.27 0.55-2.51
Castillejos-Molina 2011 [23]	Mexico	Case-control study	Patients with PC who underwent surgical treatment	64.8 ± 6.97	1990-2007	WHO	210	Gleason score >7 Clinical stage ≥ T3	3.346 1.628	1.144-9.791 0.915-2.896
Kheterpal 2012 [24]	United States	Cross-section study	Patients who underwent robot assisted radical prostatectomy	60.7 ± 6.9	2005-2008	IDF	2756	Gleason score ≥7(4 + 3) Clinical stage ≥ T3	1.328 1.416	0.978-1.802 1.109-1.808
De Nunzio 2011 [25]	Italy	Cross-section study	Patients who underwent prostate biopsy for PSA > 4 ng/ml or abnormal DRE	69	2009-2011	NCEP-ATP-III	83	Gleason score ≥7 Clinical stage ≥ T3	3.82 NA	1.33-10.9 NA
Jeon 2012 [28]	Korea	Cross-section study	Patients who underwent prostate biopsy for PSA > 4 ng/ml or abnormal DRE	68.86 ± 8.95	2003-2011	NCEP-ATP-III	90	Gleason score ≥7(4 + 3) Clinical stage ≥ T3	0.101 NA	0.022-0.473 NA
Morote 2012 [26]	Spain	Cross-section study	Patients who underwent prostate biopsy for PSA > 4 ng/ml or abnormal DRE	68(46-79)	2006-2010	NCEP-ATP-III	848	Gleason score >7 Clinical stage ≥ T3	1.75 NA	1.260-2.414 NA
Castillejos-Molina 2011 [23]	Mexico	Case-control study	Patients with PC who underwent surgical treatment	64.8 ± 6.97	1990-2007	WHO	210	Biochemical recurrence	2.73	1.65-4.50
Post 2011 [27]	United States	Case-control study	Patients who underwent radical prostatectomy	60.9	1999- 2004	NCEP-ATP-III	383	Biochemical recurrence	1.5	0.90-2.6
Jaggers 2009 [30]	United States	Cohort study	Aerobics Center Longitudinal Study	20-88	1977-2003	NCEP-ATP-III	185	Mortality	1.32	0.63-2.77
Martin 2009 [14]	Norway	Cohort study	HUNT2	48 ± 16.4	1996-2005	NCEP-ATP-III	107	Mortality	0.81	0.52-1.25
Häggström 2012 [19]	Norway Sweden Austria	Cohort study	Me-Can	44	NA	Upper quartile Levels ATP-III criteria	961	Mortality	1.13	1.03-1.25

PCa = prostate cancer; RRs = Relative risks; CI = confidence interval; WHO = World Health Organization; NCEP-ATP-III = National Cholesterol Education Program Adult Treatment Panel III; IDF = International Diabetes Federation; HUNT 2 = Nord-Trondelag Health Study; NA = Not available; DRE = Digital rectal examination.

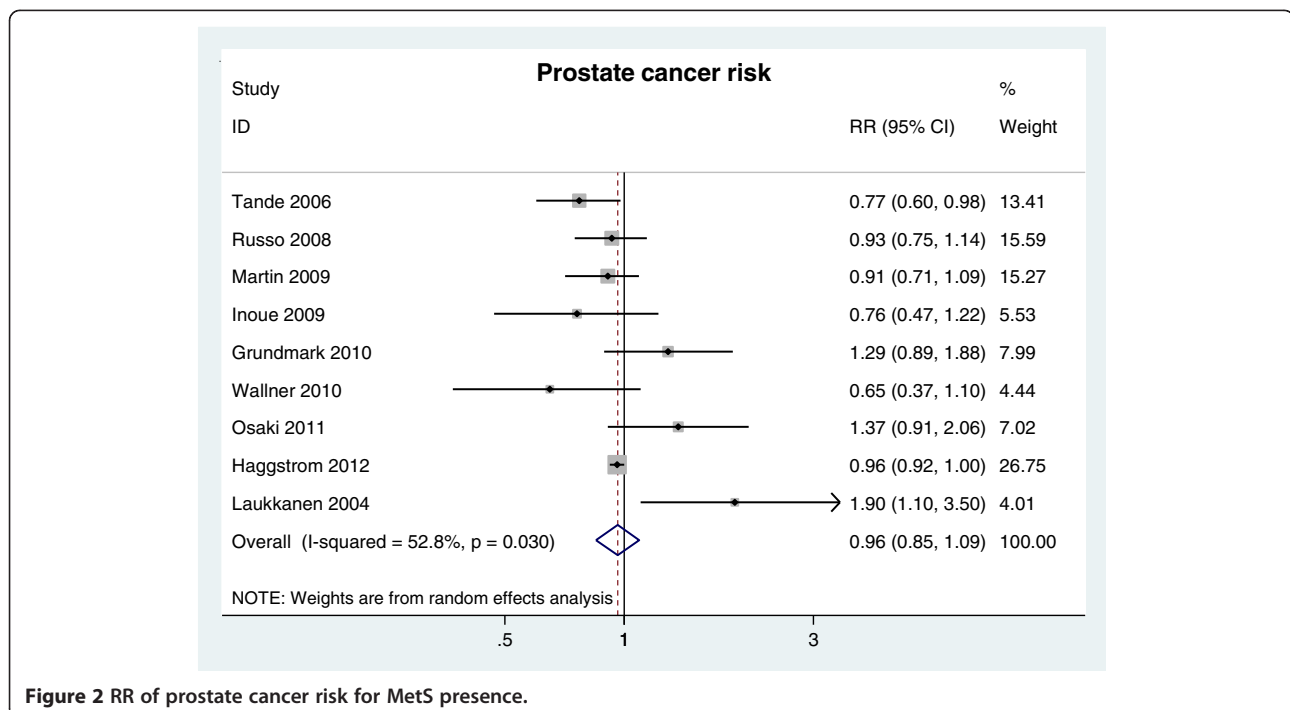


publication bias was also not seen with the Egger or Begg tests (Egger $P = 0.27$ and 0.64 for prostate cancer risk and Gleason score respectively).

Discussion

In 2007, Hsing et al. summarized five studies on MetS and prostate cancer risk and concluded that the epidemiologic evidence was insufficient to suggest a link between MetS

and PCa [37]. In 2012, Esposito et al. performed a systematical review and meta-analysis on the association of MetS and cancer risk including prostate cancer. The authors also concluded that MetS was not associated with prostate cancer risk too [22]. In the present study, we updated the data and used the current evidence to analyze whether MetS is associated with prostate cancer risk. We observed the same result as previous meta-analysis; no



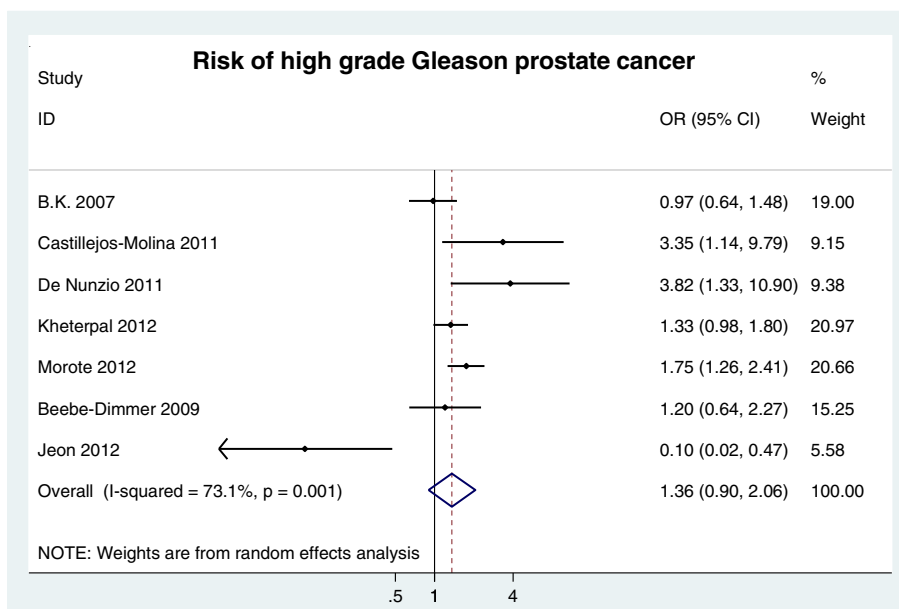


Figure 3 RR of high grade Gleason prostate cancer risk for MetS presence.

association could be detected between Mets and prostate cancer.

We believe the result is reliable for two reasons. Firstly, only longitudinal cohort studies were included in this analysis, imparting strong evidence for our conclusions. In addition, the association between MetS and prostate cancer may be affected by several factors, including heterogeneity among the individual studies. The heterogeneity may arise from differences in age, race, the definition of MetS [22], and geographic factors [26]. Further, MetS is a syndrome

composed of at least 3 components, and the individual component may exert antagonistic functions on one another. Thus the syndrome may represent an integrated outcome that combines neutralizing positive and negative functions. For example, a meta-analysis revealed that diabetes mellitus was significantly negatively associated with prostate cancer risk in population-based studies (RR = 0.72, 95% CI: 0.64-0.81) and cohort studies conducted in the USA (RR = 0.79, 95% CI: 0.73, 0.86) [38]. Furthermore, several genome-wide association

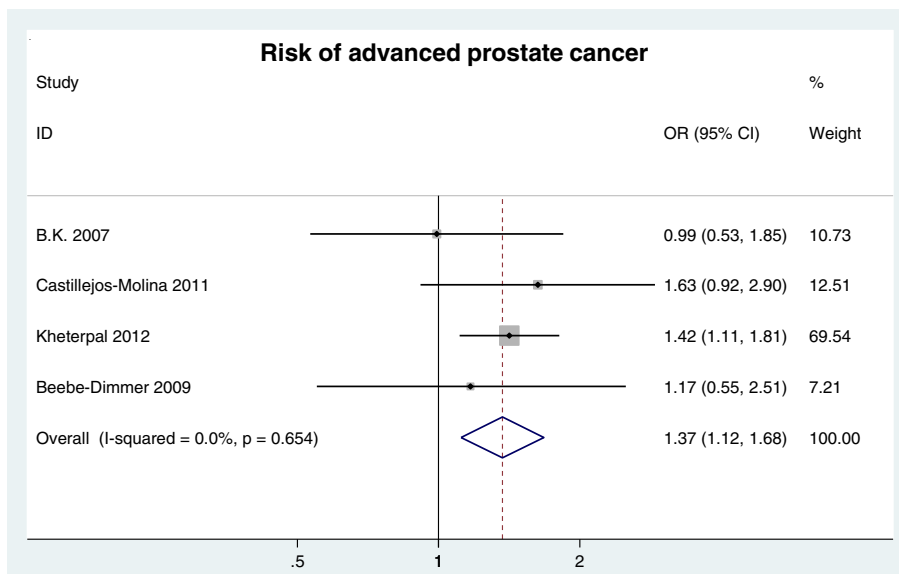


Figure 4 RR of advanced clinical stage for MetS presence.

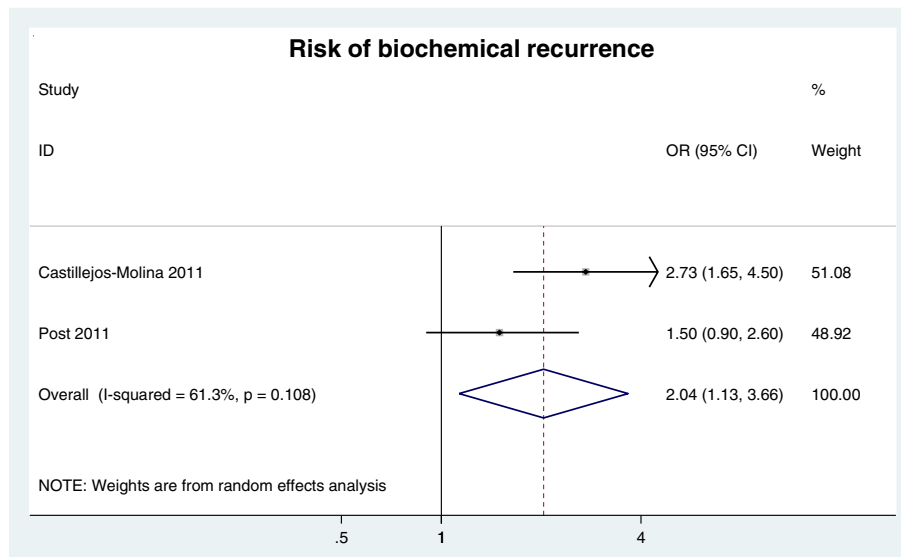


Figure 5 RR of biochemical recurrence for MetS presence.

studies suggest that diabetes mellitus and prostate cancer share certain genetic factors, including the *HNF1β* and *JAZF1* genes, and a previous study suggested that *JAZF1* might represent a potential target against diabetes and obesity [39]. Although hypertension was found to be positively associated with prostate cancer risk [33,40-42], Obesity is negatively with localized prostate cancer (0.94, 95% CI, 0.91-0.97) and positively associated with advanced prostate cancer risk (1.07, 95% CI 1.01-1.13) [43].

However, after analyses of several parameters of PCa aggressiveness and progression, we found MetS to be significantly associated with an increased risk of prostate cancer with a high-Gleason score or advanced clinical stage, with biochemical recurrence after primary treatment and with prostate cancer-specific mortality. If confirmed by more investigations, this finding may open a new research field on PCa development and progression, potentially leading to new strategies or methods for PCa treatment. MetS is a major public health problem

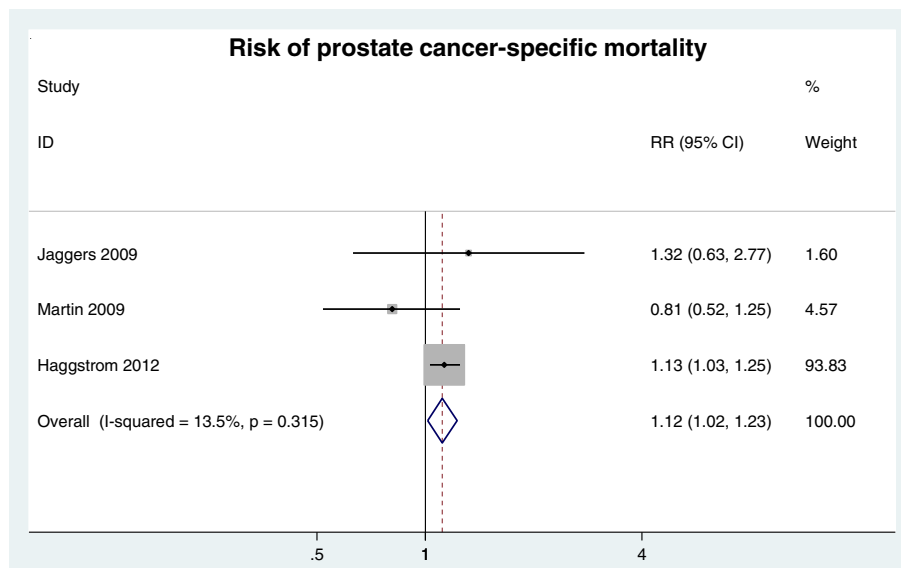


Figure 6 RR of prostate cancer-specific mortality for MetS presence.

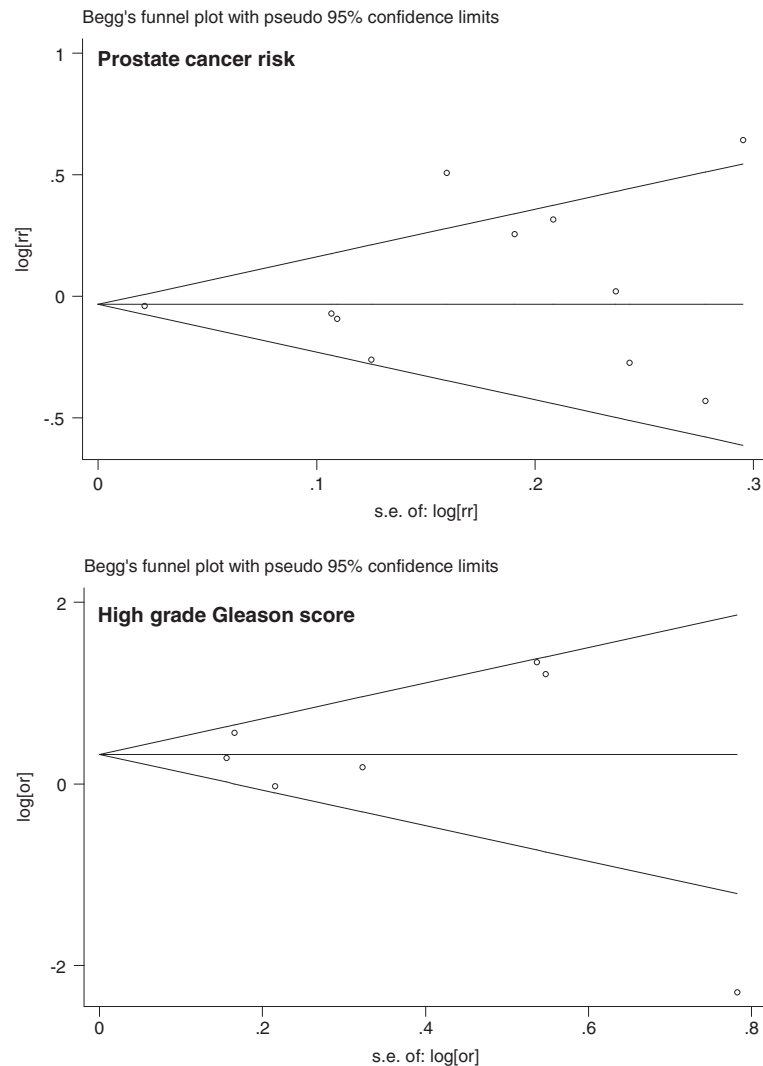


Figure 7 Funnel plot with pseudo 95% confidence limits.

and prostate cancer is the most prevalent solid organ tumor, accounts for 29% of all cancer cases and the second most common cause of death by cancer among men in the USA [44]. Therefore we believe that there is a compelling need to investigate this association between MetS and prostate cancer although the association is not strong.

Nevertheless, the reliability of these results is limited. First, Gleason score and clinical stage data were extracted from cross-sectional studies not longitudinal cohort studies. Second, there exists a small difference among studies on the definition of high-grade Gleason PCa, some authors defined a high Gleason score ≥ 7 whereas others defined a high score as >7 . Third, the pathological stage data in some studies were from biopsy not radical prostatectomy specimens. Last but not least, to date there remains limited studies focusing

on this association, although many of the available studies are well designed case-control or longitudinal cohort studies.

In addition to the limitations listed above, another limitation for the analyses of the association between MetS and prostate cancer risk or prostate cancer parameters is that we did not perform a meta-regression to attempt to explain the heterogeneity of the study because of the varying adjustments in the individual studies. The result of a recent meta-analysis on 9 cross-sectional studies of metabolic syndrome in adult cancer survivors increases the weight of this suspicion, as it revealed that no significant association was found for non-hematologic malignancies, including testicular tumor, prostate cancer, sarcoma, and epithelial ovarian [45]. Therefore, there is an urgent future need to confirm this association and to find potential mechanisms to explain

how metabolic factors affect the development or progression of PCa.

Conclusions

Based on the current findings, MetS is not associated with prostate cancer risk, but preliminary evidences demonstrates that men with MetS more frequently suffer high-grade prostate cancer, more advanced disease and are at greater risk of progression after radical prostatectomy and prostate cancer-specific death. Together, these findings indicate that MetS may be associated with the progression of prostate cancer and adverse clinical outcomes. Further studies with adjustment for appropriate confounders and larger, prospective, multicenter investigations are required in the future.

Abbreviations

PCa: Prostate cancer; MetS: Metabolic syndrome; RR: Relative risk; OR: Odd ratio; HR: Hazard ratio; CIs: Confidence intervals.

Competing interests

No potential conflicts of interest were disclosed.

Authors' contributions

This study was designed and supervised by XJ. Literature search, selection and data extraction was by YX and HX, and data analyses were performed by YX, HX, ZC, SJ, QX, YZ and GL. Data interpretation and manuscript writing received contributions from all authors. All authors read and approved the final manuscript.

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