REVIEW PAPER

UROLOGICAL ONCOLOGY

Body mass index, obesity and risk of prostate cancer: a systematic review and meta-analysis

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Introduction Prostate cancer (PCa) is one of the most diagnosed cancer in male. Body mass index (BMI) has been linked to the risk of cancer and its mortality. Our objective was to undertake a quantitative analysis elucidating the relationship between BMI and the risk of PCa.

Material and methods A literature search was conducted in PubMed, ProQuest, and EMBASE using relevant keywords and phrases. BMI was classified as underweight (BMI <18.5 kg/m^2), normal (18.5–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2). We used random-effect model to assess relative risk (RR) of PCa incidence and mortality.

Results A total of 13 studies were included in quantitative analysis. Underweight patients exhibited a decreased risk of PCa compared to those with normal weight (RR: 0.44; 95% CI 0.04–5.08; p = 0.51). Higher BMI has been associated with higher risk of PCa among overweight patients (RR: 1.08; 95% CI 1.06–1.11; p <0.00001) and obese patients (RR: 1.12; 95% CI 1.07–1.17; p <0.00001) respectively. The combined analysis of overweight and obese individuals also indicated a heightened risk of PCa (RR: 1.02; 95% CI 1.04–1.11; p <0.0001). Mortality rates were higher in overweight and obese individuals, though not statistically significant (RR 1.15; 95% CI 0.88–1.52; p = 0.31).

Conclusions BMI >25 kg/m^2 was associated with an increased risk of prostate cancer and mortality.

Key Words: body mass index ‹› obesity ‹› mortality ‹› prostate cancer

INTRODUCTION

Prostate cancer is one of the most prevalent malignancies in male, which attributed as the fifth leading cause of death due to cancer. Global report estimated around 1.2 million new cases worldwide with more than 300 000 deaths in 2018 [1]. The incidence and mortality of this malignancy correlates with increasing age, with the disease commonly diagnosed in elder age [2]. The disease usually presents asymptomatic or with minimal symptoms in its early stage, such as difficulty in urination. In advanced stage, patients may complain fatigue, bone pain, or paralysis due to metastasis. There may be renal failure attributed to bilateral ureteral obstruction. Serum prostate-specific agent (PSA) and digital rectal examination (DRE) has been widely used to detect prostate cancer in its early stage. However, despite an increase in early detection of prostate cancer, the mortality remains high [3, 4].

Several factors have been associated with the disease incidence and mortality, including advanced age, ethnicity, and family history of cancer. Obesity has also been linked to cancer. Multiple studies reported that patients with higher body mass index (BMI) were associated with increased lipid signaling, insulin resistance, adipokines, and inflammatory responses, which all aid in development of cancer [5]. Obesity is a significant global health problem, with increasing prevalence worldwide. The Global Burden of Disease Obesity study found that the prevalence of obesity has doubled between 1980 and 2015, while

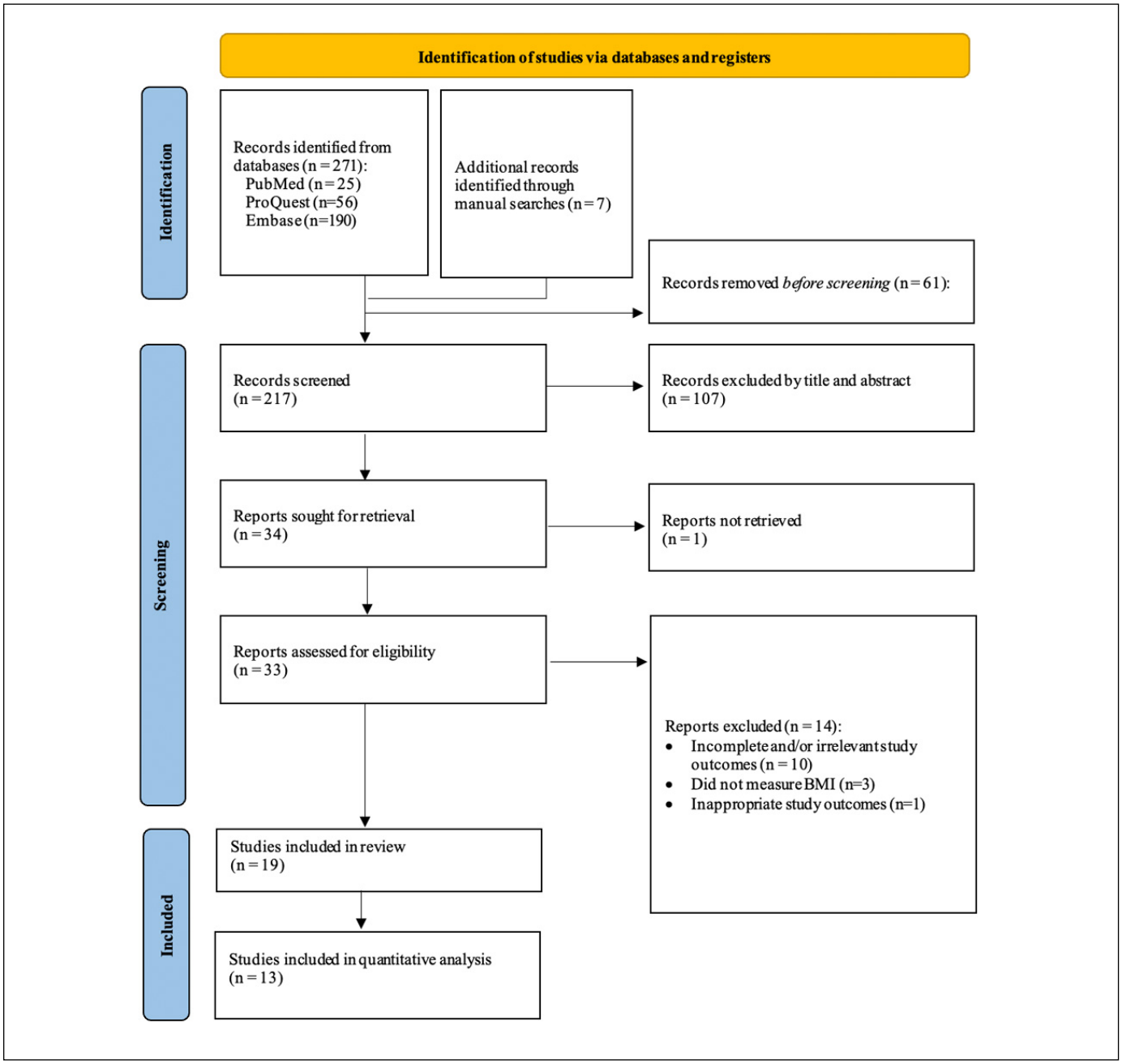

Figure 1. *Flow diagram.*

Table 1. *Search strategy*

Database	Search strategy	Hits
PubMed	('prostatic neoplasms' [MeSH Terms] OR prostate cancer [Text Word]) AND ('Body Mass Index' [Majr] OR BMI OR underweight OR obese OR overweight) AND ('incidence' [MeSH Terms] OR incidence [Text Word] OR 'mortality' [MeSH Terms] OR mortality [Text Word])	25
ProQuest	('prostatic neoplasms' [MeSH Terms] OR prostate cancer [Text Word]) AND ('Body Mass Index' [Majr] OR BMI OR underweight OR obese OR overweight) AND ('incidence' [MeSH Terms] OR incidence [Text Word] OR 'mortality' [MeSH Terms] OR mortality [Text Word])	56
Embase	prostate AND (tumor OR neoplasm OR cancer) AND (body AND mass AND index OR bmi OR overweight OR underweightOR obesity) AND ((incidence OR mortality) AND rate OR death) AND rate AND 'prostate cancer'/dm AND 'human'/de AND [male]/lim AND 'article'/it	190

the Noncommunicable Disease Risk Factor collaborations study found that prevalence of obesity has increased from 3.2% to 10.8% in men [6]. As obesity is a common and a potential modifiable risk factor, it is becoming increasingly important to consider in the trajectory of cancer development, progression, and subsequently its treatment. Understanding the role of obesity in prostate cancer could aid in targeted screening and prevention strategies, therefore improving patients' overall outcome and well-being [7]. However, the association between BMI and risk of prostate cancer has been inconsistent, while existing review has been qualitative in nature. Therefore, we conducted a systematic review and meta-analysis to quantitatively evaluate the association between body mass index (BMI) and risk of prostate cancer, including the mortality.

MATERIAL AND METHODS

Search strategy and eligibility criteria

This study was conducted according to the Cochrane Handbook 6.2 and the Preferred Reporting Items for Systematic Review and Meta-Analysis [8]. A literature search was conducted in three journal databases, such as PubMed, ProQuest, and EMBASE using relevant keywords and phrases as shown in Table 1. We included studies that report the association of body mass index (BMI) and prostate cancer. BMI was classified as underweight (BMI <18.5 kg/m^2), normal (18.5–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2). Outcomes include risk of cancer and mortality. Studies that evaluated outcomes other than prostate cancer and its risk of mortality, different categorization of BMI, irrelevant article types (presented abstract, commentaries, reviews, and letter to editors), and unavailable full-text articles were excluded.

Data extraction and statistical analysis

Following data were obtained: number of participants, BMI, PSA, incidence of prostate cancer, mortality cases, and other risk factors. Meta-analysis was then carried out using Review Manager v5.4 software. Random-effect model was used to obtain pooled estimates using risk ratio (RR) and mean difference (MD), which were presented using forest plot using 95% confidence interval (CI). I^2 statistic was used to measure studies heterogeneity, with >50% defined as significant heterogeneity. Sensitivity analysis was then performed to identify the source of heterogeneity. Statistical significance was defined as $p < 0.05$. Furthermore, visual inspection of funnel plot symmetry was used to analyze possible publication bias. Asymmetry in the funnel plot indicate the presence of publication bias.

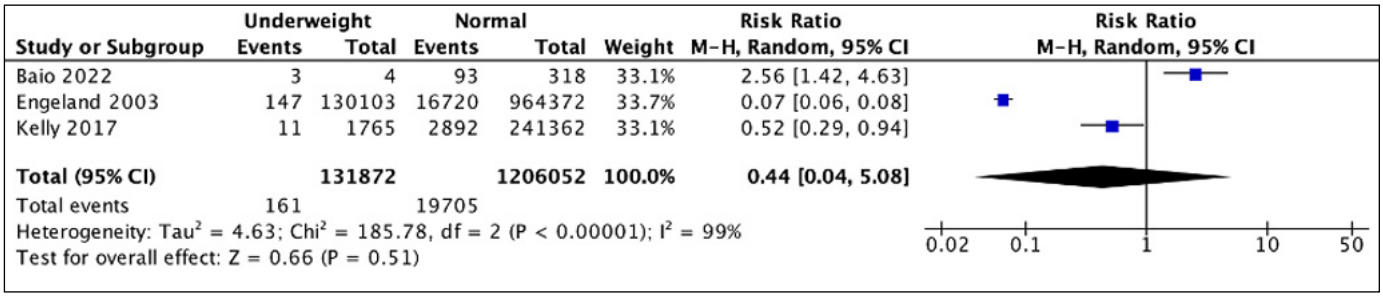

Figure 2. *Forest plot showing prostate cancer risk in underweight vs normal weight patients.*

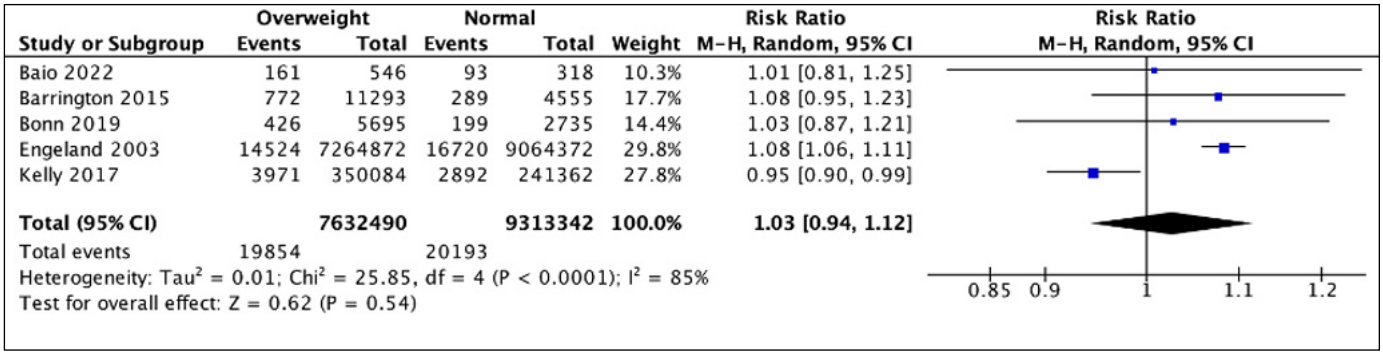

Figure 3. *Forest plot showing prostate cancer risk in overweight vs normal weight patients.*

Table 2. *Characteristic of studies*

Author; year of publication	Study design	Location	Population	Number of participants; Mean age ±SD	BMI classification
Baio et al [9] 2022	Single-center retrospective study	Italy	Patients undergoing transrectal ultrasound (TRUS)-guided initial multicore (≥10) prostate biopsies between May 2010 and December 2018 at Department of Urology of Umberto I Hospital in Nocera Inferiore.	1,079 patients; 69.4 (7.8) y	Underweight: <18.5 kg/m^2 Normal: 18.5–24.99 kg/m^2 Overweight: 25–30 kg/m^2 Obese: >30 kg/m^2
Kelly et al [10], 2017	Prospective cohort study	Washington, USA	Participants were men with uncompensated volunteers from the general population with no prior medical history of any cancer (except nonmelanoma skin cancer [NMSC]). Participants were followed for incident cancer diagnoses and cause-specific mortality.	69,873 patients; 62.58 (5.33) y	Underweight: <18.5 kg/m^2 Normal: 18.5–24.99 kg/m^2 Overweight: 25–30 kg/m^2 Obese: >30 kg/m^2
Barrington et al [20] 2015	Prospective cohort study	Seattle, USA	Participants were healthy men with had a PSA concentration less than 4 ng/mL (to convert to micrograms per liter, multiply by 1.0) and a normal result on a digital rectal examination (DRE).	African American: 3,398 patients; 59.2 (7.0) y Non-hispanic white: 22,673 patients; 63.4 (6.3) y	18.0 – <25.0 25.0 – <27.5 27.5 – <30.0 30.0 – <35.0 35.0 – 50.0
Cantarutti et al [21], 2015	Retrospective cohort study	Sweden	Patients were pathologically or cytologically verified adenocarcinoma of the prostate (ICD-10:C61), diagnosed between July 1, 2001 and October 31, 2003.	3,161 patients; 67 (7.1) y	<22.5 22.5 – <25.0 25.0 – <27.5 ≥27.5
Gong et al [22], 2006	Randomized, placebo-controlled trials	Texas, USA	Patients with a normal digital rectal exam and prostate-specific antigen (PSA) level of V3 ng/mL, as well as no history of prostate cancer, severe benign prostate hyperplasia, or clinically significant coexisting conditions.	1,936 patients; 63.7 (5.6) y	<25.0 25.0 – 26.9 27.0 – 29.9 ≥30
Giovanucci et al [23], 2003	Retrospective cohort study	Washington, USA	Patients with prostate cancer from February 1, 1986, through January 31, 2000 without a positive family history of prostate cancer.	2,896 patients; ≥60 y	<21.0 21.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 ≥30
Fowke et al [24] 2015	Prospective cohort	Asia (multiple countries)	18 cohorts from the Asian Cohort Consortium, recruited from 1963 to 2001, followed up to 2006, without a history of cancer.	294,389; 53.7 (10.4) y (at baseline)	12–19.9 20–22.4 22.5–24.9 25–50
Gong et al [25], 2007	Case control	Seattle, USA	Newly diagnosed, histologically confirmed prostate cancer patients diagnosed between January 1993 through December 1996, aged 40 to 64 years.	752	<25 25–29.9 ≥30
Bonn et al [26], 2019	Randomized controlled trial	Seattle, USA	Male participants without a history of prostate cancer, recruited from 1985 to 1994, with BMI between 18–60 kg/m^2	11,886; 67.5 (5.9) y	18–24.9 25–29.9 30–34.9 ≥35
Discacciati et al [27], 2011	Prospective cohort	Sweden	Eligible men aged 45–79 years who filled a self-administered questionnaire from 1997–1998, followed up until December 2008. Incident of prostate cancer were confirmed by the Swedish National Cancer Register.	26,969	<21 21–22.9 23–24.9 25–27.4 27.5–29.9 >30
Engeland et al [11], 2003	Prospective cohort	Norwegia	Men with body weight and height measurement measured between age 20–75 years during 1963–1975, followed up until prostate cancer diagnosis, emigration, death, age 100 years, or June 2001. Prostate cancer diagnosis is determined through Cancer Registry of Norway.	951,459; 44.5 y (at baseline)	<18.5 18.5–24.99 25–29.99 ≥30
Moller et al [12], 2014	Prospective cohort	Denmark	Men age 50–64 years at baseline, recruited in 1993–1997, and followed up until December 2011. Prostate cancer is determined through the Danish Cancer Register and Danish Death Register.	26,977; median 56 (52–60) y (at baseline)	Low or normal: 15,4–24,9 Overweight: 25–29.9 Obese: ≥30
Efstathiou et al [13], 2011	RCT	USA	Patients with histologically confirmed prostate cancer with complete pre-treatment BMI information. Patients were randomized to 2 groups of treatment: arm I received goserelin acetate after radiotherapy; arm II receiver goserelin at recurrence.	N/A	Normal: <25 Overweight: 25–29.9 Obese: ≥30

Table 2. *Continued*

Author; year of publication	Study design	Location	Population	Number of participants; Mean age ±SD	BMI classification
Genkinger et al [14], 2020	Prospective cohort	Multiple countries	Data from The Pooling Project of Prospective Studies of Diet and Cancer, consisting of 15 studies from multiple countries. BMI were self reported during adulthood, and prostate cancer identified from medical record as defined by ICD-9	N/A	<21 21–22.9 23–24.9 25–29 30–34.0 ≥35
Jochems et al [15], 2020	Prospective cohort	Sweden	Five population-based Swedish cohorts followed from 1971 to 2016. Diagnosis was linked to the Swedish Cancer Register and mortality from Swedish Cause of Death Register.	37.5 (13.6) y	<22.5 22.5–24.9 25–27.4 27.5–29.9 ≥30
Liang et al [16], 2014	Prospective cohort	USA. Puerto Rico, Canada	Men age >55 y with no clinically suspicious DRE and PSA <4 ng/ml, followed from 2008. BMI was measured at date of most recent biopsy,	66 (6) y	<25 25– <30 ≥30
Rodriguez et al [17], 2007	Prospective cohort	USA	Men who filled a self-administered questionnaire at 1992. Cancer followed up 2003 and outcome identified through self report, medical records, state cancer registries, or national death index.	N/A	<25 25– <27,5 27.5– >30 30– <35 ≥35
Lavalette et al [18] 2018	Case control	France	Population-based case contrl study that included prostate cancer incident from 2012–2013 (n = 819), match to controls by age (n = 879)		<25 25–29 ≥30
Perez-Cornago et al [19], 2017	Prospective cohort	Multiple countries	Men who completed self-administered quesetionnaires. Prostate cancer incidence followed up through insurance records and multiple registries, as defined by ICD-10. Follow up 13.9 y.	50 (11.2) y 52.5 (9.4) y 53.3 (8.9) y	<25 25–29.9 ≥30

BMI – body mass index; PSA – prostate specific antigen; DRE – digital rectal examination; ICD – International Classification of Diseases

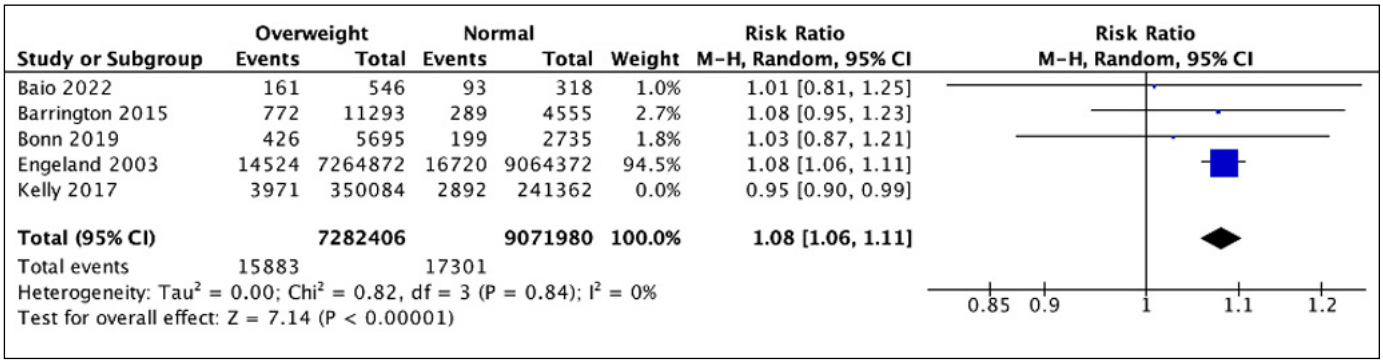

Figure 4. *Sensitivity analysis of overweight vs normal weight patients.*

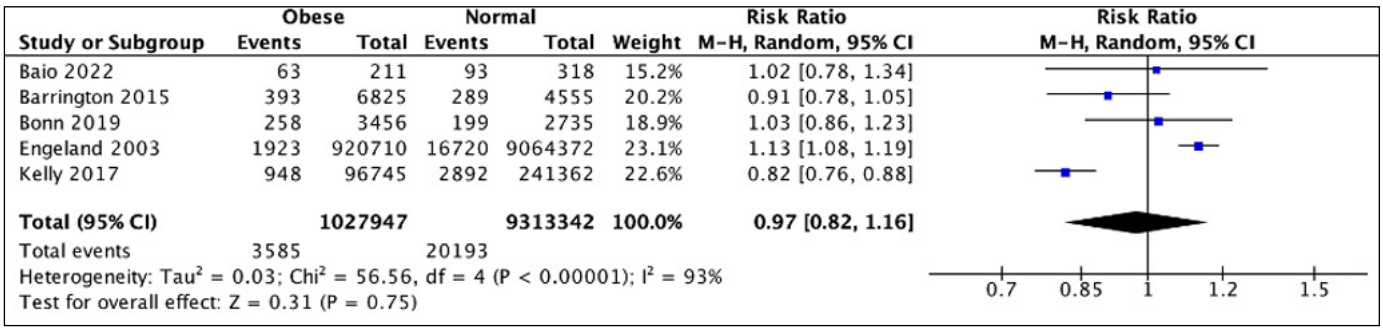

Figure 5. *Forest plot showing prostate cancer risk in obese vs normal weight patients.*

Table 3. *Summary of findings reported in the studies*

Author; year of publication	BMI (Mean; SD)	PSA (Mean ±SD)	Incidence of prostate cancer (n/total; IR)	Mortality cases (n/total; MR)	Measures of association	Other risk factors
Baio et al[9], 2022	Underweight: 17.8 (0.7) Normal: 23.5 (1.2) Overweight: 27.1 (1.4) Obese: 32.5 (2.7)	22.6 (18.8) 15.0 (45.6) 14.3 (33.4) 11.9 (15.9)	3/4 (75) 93/318 (29.3) 161/546 (29.5) 63/211 (29.9)	N/A	N/A RR: 1.00 RR: 1.21 RR: 1.60	Age, duration of obesity, medication use, comorbidities, daily diet and exercise
Kelly et al,[10] 2017	N/A	N/A	11 (623.1) 2892 (1198.2) 3971 (1134.3) 948 (979.9)	0 91 (38) 124 (39.2) 40 (48.9)	0.60 (0.33 – 1.09) N/A 0.95 (0.91 – 1.00) 0.87 (0.81 – 0.94)	Age
Barrington et al,[11] 2015	N/A	N/A	289/4555 439/6140 333/5153 299/5092 94/1733	N/A	HR: 1 (reference) HR: 1.12 (0.97 – 1.30) HR: 1.04 (0.89 – 1.22) HR: 0.96 (0.82 – 1.13) HR: 0.94 (0.74 – 1.19)	Age, race/ ethnicity, education, smoking, history of diabetes, and family history of prostate cancer
Cantarutti et al,[12] 2015	21 (1.2) 24 (0.68) 26 (0.7) 30 (2.7)	138 (489.4) 107 (485.6) 78 (322.5) 68 (254.7)	168/296 433/850 447/932 507/954	77/296 177/850 189/932 215/954	HR: 1.33 (1.02–1.74) HR: 1.00 (reference) HR: 1.01 (0.81–1.23) HR: 1.17 (0.96–1.43)	Age, lifestyle factors
Gong et al,[13] 2006	Mean BMI: 27.6 ±4.1	N/A	N/A	N/A	HR: 1.00 HR: 0.91 (0.79–1.05) HR: 0.96 (0.83–1.10) HR: 0.96 (0.83–1.10)	Age, race, treatment, diabetes, and family history of prostate cancer in first-degree relatives.
Giovanucci et al,[14] 2003	N/A	N/A	64 cases 284 cases 624 cases 708 cases 290 cases 165 cases	N/A	RR: 0.76 (0.59 to 0.99) RR: 0.92 (0.80 to 1.05) RR: 1.0 (reference) RR: 0.92 (0.83 to 1.03) RR: 0.98 (0.85 to 1.12) RR: 0.96 (0.80 to 1.14)	Age; time period; height; smoking history; history of diabetes mellitus; racial group; vigorous activity level; total energy intake.
Fowke et al[15], 2015	Mean BMI: 22.6 ±3.3	N/A	N/A	142 188 184 120	HR: 0.98 (0.79–1.23) HR: 0.92 (0.75–1.13) HR: 1.0 (reference) HR: 1.08 (0.85–1.36)	Age, education, ppopulation density, marital status, history of severe cancer, heart disease, or stroke at baseline
Gong et al[16], 2007	Mean BMI: 26.7 ±3.9	N/A	N/A	16/257 19/367 15/128	HR: 1.0 (reference) HR: 1.11 (0.55–2.25) HR: 2.64 (1.18–5.92)	Age at diagnosis, race, smoking status, Gleason score, stage at diagnosis, and primary treatment.
Bonn et al,[17] 2019	N/A	N/A	199/2735 426/5695 193/2545 65/911	N/A	HR: 1.0 (reference) HR: 1.01 (0.85–1.2) HR: 1.07 (0.88–1.30) HR: 1.11 (0.84–1.47)	N/A
Discacciati et al,[18] 2011	N/A		27/17,487 72/50,419 163/94,253 150/111,322 79/55,507 47/34,885 (in person-years)	11/16,426 35/47,524 63/88,804 59/104,705 29/51,989 23/32,679 (in person-years)	For incidence: RR: 0.96 (0.84–1.09) RR: 1.00 (reference) RR: 1.02 (0.95–1.08) RR: 1.03 (0.9–1.2) RR: 1.07 (0.86–1.33) RR: 1.15 (0.75–1.74) For mortality: RR: 0.91 (0.75–1.11) RR: 1.00 (reference) RR: 1.05 (0.95–1.16) RR: 1.11 (0.89–1.36) RR:1.16 (0.83–1.63) RR: 1.34 (0.7–2.55)	BMI at age 30, age at baseline, total energy intake, total physical activity, smoking status, family history of prostate cancer, diabetes
Engeland et al[19], 2003	24.9	N/A	147/130,103 16,720/9,064,372 14,524/7,264,872 1923/920,710 (in person-years)		RR: 0.78–1.08 RR: 1.00 (reference) RR: 1.07 (1.05–1.09) RR: 1.09 (1.04–1.15)	N/A

Table 3. *Continued*

Author; year of publication	BMI (Mean; SD)	PSA (Mean ±SD)	Incidence of prostate cancer (n/total; IR)	Mortality cases (n/total; MR)	Measures of association	Other risk factors
Moller et al[20], 2014	N/A	N/A	649/9,251 920/13,486 244/4,140	92/649 147/920 51/244	For incidence: HR: 1.00 (reference) HR: 0.94 (0.85–1.04) HR: 0.86 (0.74–0.99) For mortality: HR: 1.00 (reference) HR: 1.08 (0.83–1.40) HR: 1.43 (1.01–2.01)	Age
Efstathiou et al,[21] 2011	Median 26.6 (16.2–44.8) (Arm I) Median 26.6 (14.7–47.9) (Arm II)	N/A	N/A	34/241 98/402 37/145	HR: 1.00 HR: 1.78 (1.2–2.63) HR: 1.79 (1.13–2.86)	N/A
Genkinger et al,[22] 2020		N/A	N/A	133/1817 369/5546 687/11518 1426/25407 338/6176 74/1270	R: 0.96 (0.9–.901.02) RR: 1.00 RR: 1.02 (0.99–1.06) RR: 1.00 (0.96–1.05) RR: 0.94 (0.89–1.00) RR: 0.9 (0.81–1.00)	Race, education, marital status, alcohol, smoking, physical activity, family history, diabetes, vitamin use, dietary calcium
Jochems et al,[23] 2020	24.6 ± 3.4	N/A	7198/122,300 10,876/135,792 9124/100,791 3792/45,181 1881/27,838	1080/122,300 2059/135,792 2132/100,791 971/45,181 506/27,838	For incidence: HR: 0.92 (0.89–0.96) HR: 1.00 (reference HR: 1.01 (0.98–1.04) HR: 0.92 (0.89–0.97) HR: 0.87 (0.82–0.92) For mortality: HR: 0.91 (0.85–0.99) HR: 1.00 HR: 1.1 (1.03–1.18) HR: 1.09 (1.0–1.19) HR: 1.2 (1.08–1.34)	Age, ,smoking status, region, country of birth, education
Liang et al,[24] 2014	Median 27.7 (IQR 25.4–30.6)	Median 4.1 (IQR 2.8–5.3)	364/702 954/1600 584/956	N/A	N/A	N/A
Rodriguez et al,[25] 2007			1935/25,102 1742/22,195 920/12,675 556/8,365 99/1654	N/A	RR: 1.00 RR: 1.02 (0.95–1.08) RR: 0.95 (0.88–1.03) RR: 0.89 (0.81–0.98) RR: 0.83 (0.68–1.02)	Age
Lavalette et al[26], 2018			297 377 134		OR: 1.00 OR: 0.98 (0.78–1.23) OR: 0.91 (0.67–1.23)	
Perez-Cornago et al[27], 2017	N/A	N/A	50678 68736 21698		For incidence: HR: 1.00 (reference HR: 0.98 (0.93–1.03) HR: 0.89 (0.82–0.96) For mortality: HR: 1.00 (reference HR: 1.04 (0.89–1.2) HR: 1.29 (1.06–1.58)	Education, smoking, diabetes, marital status, diabetes

BMI – body mass index; PSA – prostate specific antigen; MR – mortality rate; HR – hazard ratio; N/A – not applicable; DRE – digital rectal examination; IQR – interguartile range

RESULTS

Study characteristics

A total of 217 articles was obtained, with further 107 studies excluded due to the irrelevancy. After assessed for eligibility, we included 19 studies in the review with only 13 studies with similar and complete outcomes eligible for statistical analysis. The flow diagram and search strategy were shown in Figure 1 and Table 1. Included studies for review were shown in Table 2 and 3.

Impact of body mass index on risk of prostate cancer

a. Risk of prostate cancer in underweight patients (BMI <18,5 kg/m²)
Three studies were included to assess risk of prostate cancer in underweight patients compared to normal weight patients. Overall result showed underweight patients have 0.44 prostate cancer risk compared to normal weight patients. However, results were not significant with considerable heterogeneity (I^2 = 99%) (Figure 2).

b. Risk of prostate cancer in overweight patients (BMI 25–30 kg/m²)
Five studies compared risk of prostate cancer in overweight patients compared to normal weight. The result was not significant, with RR 0.99 (95%CI 0.91–1.08) (Figure 3). Considerable heterogeneity was detected (I^2 = 85%), thus sensitivity analysis was performed. Kelly et al. was identified as an outlier, and upon removal, heterogeneity becomes 0%, with significant increased risk for prostate cancer in overweight patients (RR: 1.08; 95% CI 1.06–1.11; p <0.00001) (Figure 4).

c. Risk of prostate cancer in obese patients (BMI >30 kg/m²)
Five studies assessing prostate cancer risk in obese patients were included for analysis. Result was not significant, showing that risk of prostate cancer is 0.97 times in obese patients compared to normal weight patients (95% CI 0.82–1.16) (Figure 5). Sensitivity analysis identified Kelly and Barrington et al. as outlier, and upon removal, heterogeneity decreases from 93% to 0%. Results also become significant, showing that obese patients are 1.12 times at risk for prostate cancer compared to normal weight patients (95% CI 1.07–1.17; p <0.00001) (Figure 6).

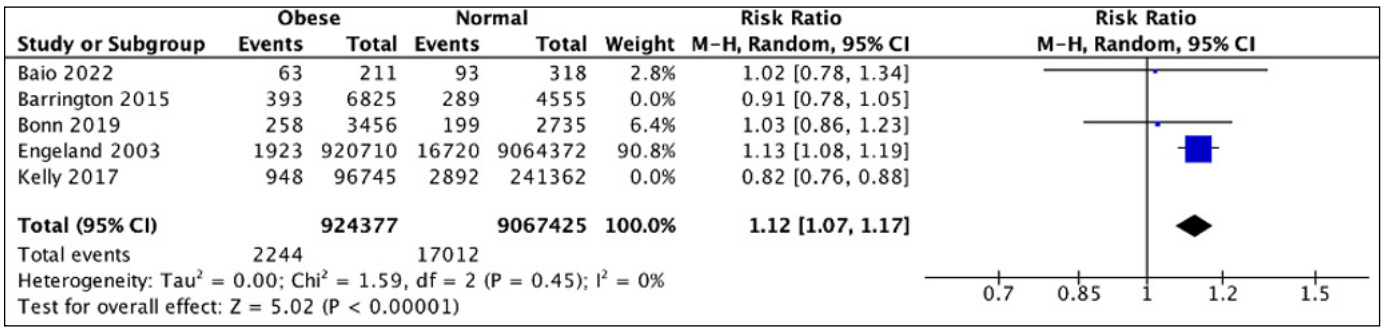

Figure 6. *Sensitivity analysis of obese vs normal weight patients.*

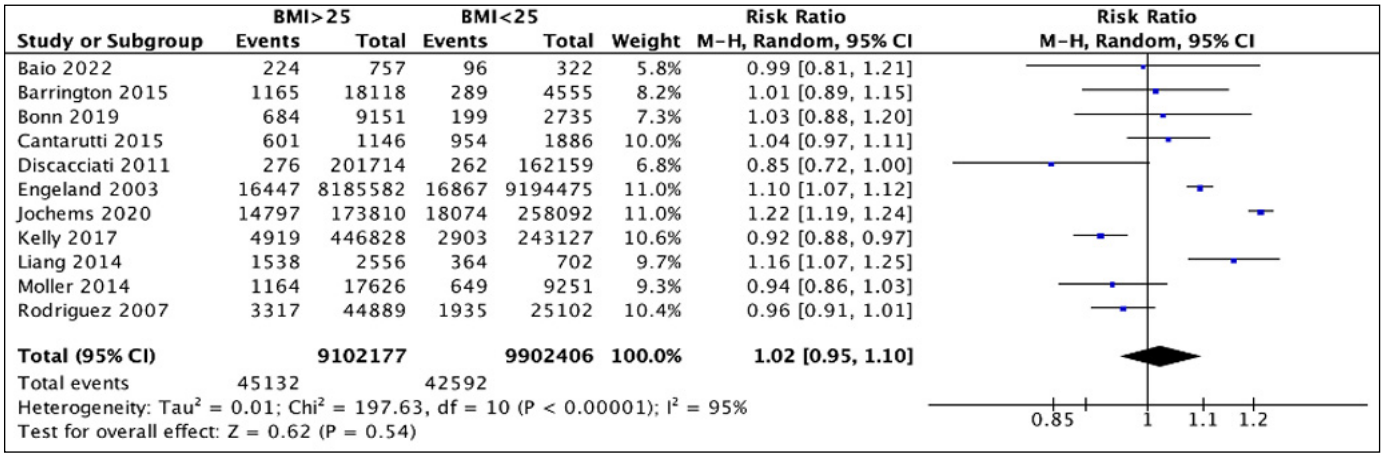

Figure 7. *Forest plot showing prostate cancer risk in overweight and obese patients vs underweight and normal patients.*

d. Risk of prostate cancer in overweight and obese patients (BMI >25 kg/m²)
Additional comparison between overweight and obese patients compared to normal and/or underweight patients was also done. Result of analysis showed no significant difference with high heterogeneity (I^2 = 95%) (Figure 7). However, upon sensitivity analysis, heterogeneity drops to 16%, with Discacciati, Jochems, Kelly, Liang, Moller, and Rodriguez et al identified as outliers. Results become significant, showing that patients with BMI >25 are 1.07 times at risk for prostate cancer compared to patients with BMI <25 (95% CI 1.04–1.11; p <0.0001) (Figure 8).

Mean difference between cancer and no-cancer group
Analysis was also performed on continuous variable to see BMI difference between prostate cancer group and no prostate cancer group. Two studies which supplied the mean BMI in each group was included in the analysis. No significant difference in BMI was detected between group (MD -0.01; 95% CI -0.09–0.06) (Figure 9).

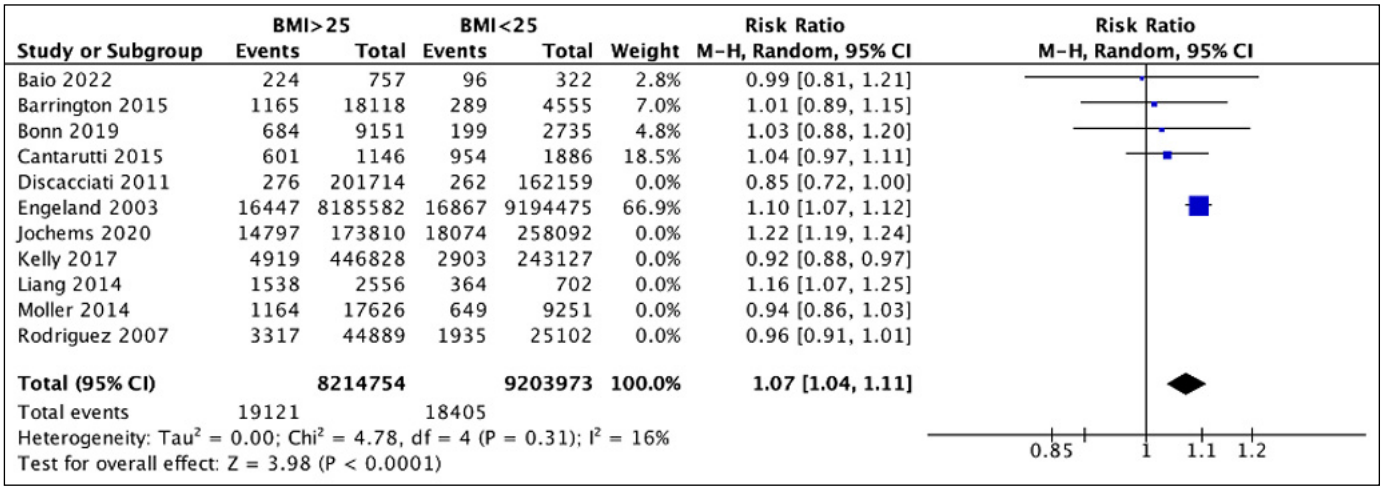

Figure 8. *Sensitivity analysis of overweight and obese vs normal and underweight patients.*

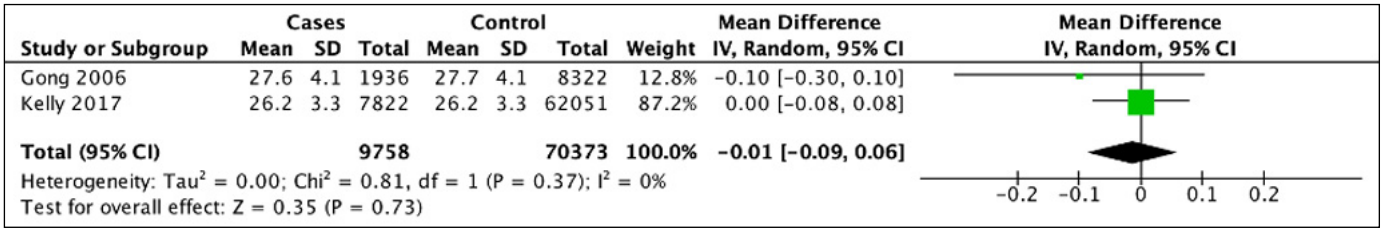

Figure 9. *BMI difference between cancer and healthy cohorts.*

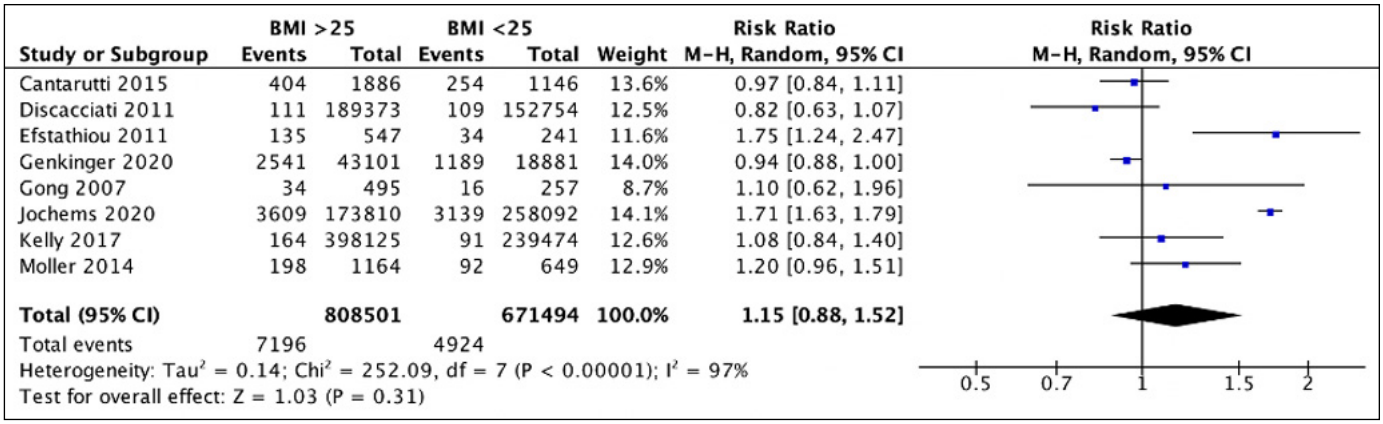

Figure 10. *Mortality risk between overweight and obese patients compared to underweight and normal patients.*

Impact of body mass index on mortality in prostate cancer

Eight studies assessed mortality risk based on BMI. No significant mortality difference was observed between patients with BMI >25 (overweight and obese) compared to BMI <25 (underweight and normal). While BMI >25 increase risk of mortality, result was not significant (RR 1.15; 95%CI 0.88–1.52). High heterogeneity was detected (I^2 = 97%), thus sensitivity analysis was performed (Figure 10). While I^2 value decreases to 0, result favors BMI >25 against mortality (RR 0.94; 95%CI 0.89–1.00) (Figure 11).

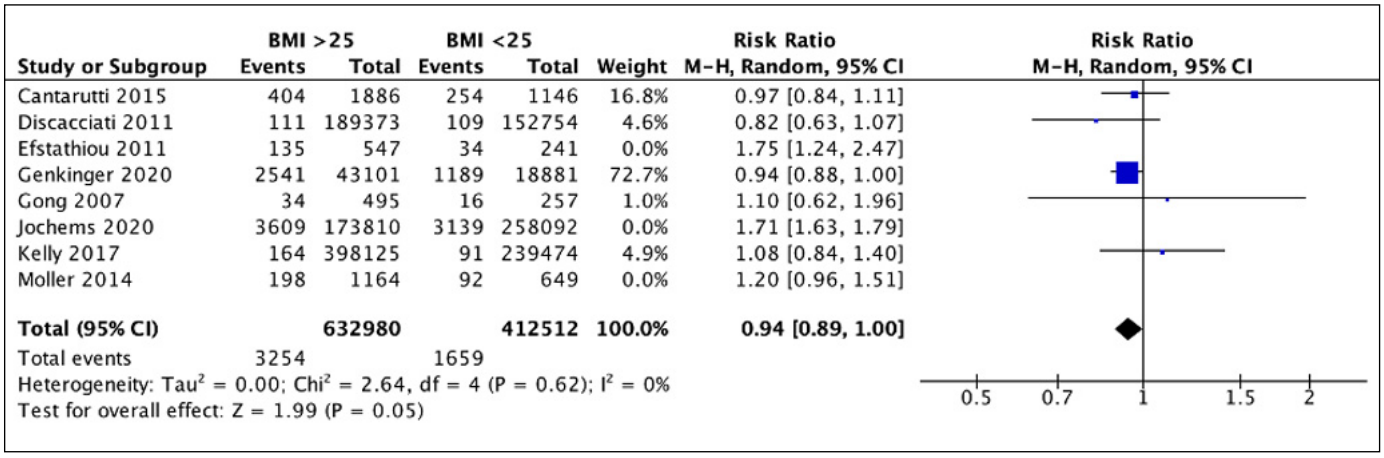

Figure 11. *Sensitivity analysis of mortality risk.*

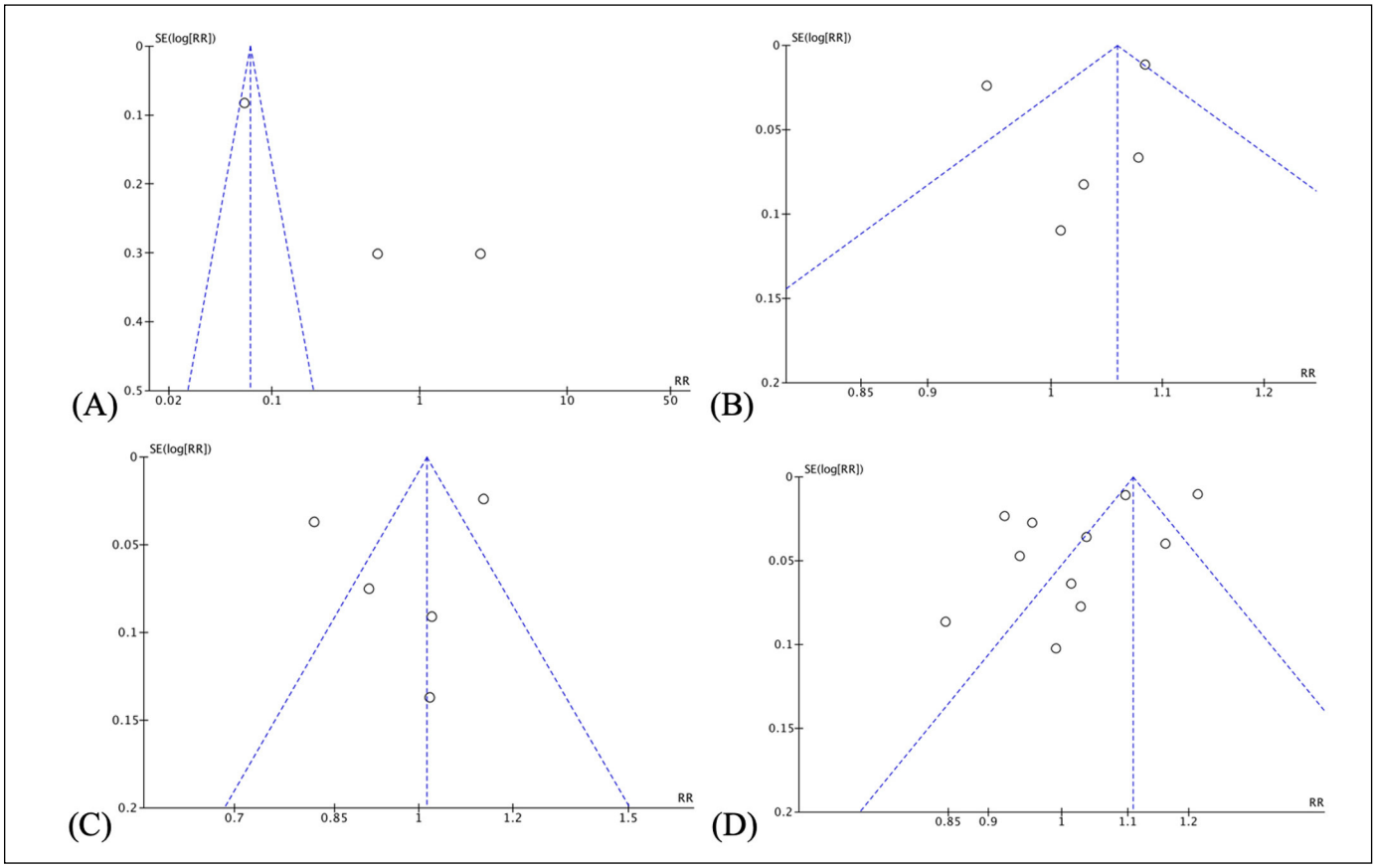

Figure 12. *Publication bias assessment plot of the relative risk of developing prostate cancer;* **(A)** *in underweight patients;* **(B)** *in overweight patients;* **(C)** *in obese patiesnts;* **(D)** *in overweight and obese patients.*

Publication bias

To assess publication bias, funnel plot symmetry was analyzed qualitatively (Figure 12 A–D, Figure 13 A–B). Visual inspection of the funnel plots revealed some asymmetry especially in the analysis of prostate cancer risk in underweight patients, overweight and obese patients, as well as mortality risk in overweight and obese patients, suggesting possible publication bias. This is to be expected due to significant heterogeneity in the analysis, in which some studies showed positive, no, or negative association. However, as a limited amount of study is included in the meta-analysis, funnel plots must be interpreted with caution.

DISCUSSION

Prostate cancer is one of the most common malignancies found in men, also the fifth leading cause of death due to cancer. This study aimed to evaluate the effect of BMI in risk of prostate cancer and its mortality. In our review, we compared the risk of prostate cancer in underweight, normal, overweight, and obese patients. We also compared the risk of mortality between obese and non-obese patients.

In our review, underweight patients were associated with lower risk of prostate cancer, despite the result not significant. This was similar to a population-based cohort conducted by Bhaskaran et al., which reported a decrease in risk of prostate cancers in underweight patients [9]. This review further demonstrated an overall increase in risk of prostate cancer in both overweight and obese patients. The link between BMI and risk of prostate cancer has been reported by previous studies. Tzenios et al [5] conducted an analysis to evaluate the risk of prostate cancer in obese patients, in which 54% of obese patients had a risk compared to those with normal BMI. Potential mechanism related to the higher risk of cancer may lie in the alterations in hormone and metabolic pathway observed in obese patients. It was hypothesized that hyperinsulinemia and/or hypoadiponectinemia in obese patients played a role in development of aggressive neoplastic behavior. There was also an increase in free insulin-like growth factor (IGF-1) that aid in growth of prostate cells [10].

However, it needs to be highlighted that some of our included studies reported lower risk of prostate cancer in obese patients, which result in high heterogeneity of the analysis [11, 12]. Lower incidence of prostate cancer may be attributed to potential detection bias in obese patients. Several hypotheses have been proposed: hemodilution of prostate-specific agent (PSA) due to increase in blood volume in obese patients, lower accuracy of digital rectal examination (DRE), and larger prostate volume in obesity which may reduce the likelihood of cancer findings in biopsy examination. All those factors may potentially lead to underdiagnosis of prostate cancer in obesity. Obesity-related hemodilution has also been previously reported by Bañez et al., which showed 14% and 18% lower PSA level compared to normal in obese (BMI 30–35 kg/m^2) and severely obese patients (BMI >35 kg/m^2) respectively [13]. Regarding the potential detection bias in obesity, detailed history-taking and physical examination are essential in early diagnosis of prostate cancer.

We also found a higher risk (15% increase) of prostate cancer mortality in higher BMI (BMI >25 kg/m^2), despite the result not significant. Wright et al. also reported a higher mortality rate in BMI 25–25.9 kg/m^2 (RR 1.25; 95%CI 0.87–1.80), BMI 30–34.9 kg/m^2 (RR 1.46; 95%CI 0.92–2.33), and BMI ≥35 kg/m^2 (RR 2.12; 95%CI 1.08–4.15) respectively. Mortality

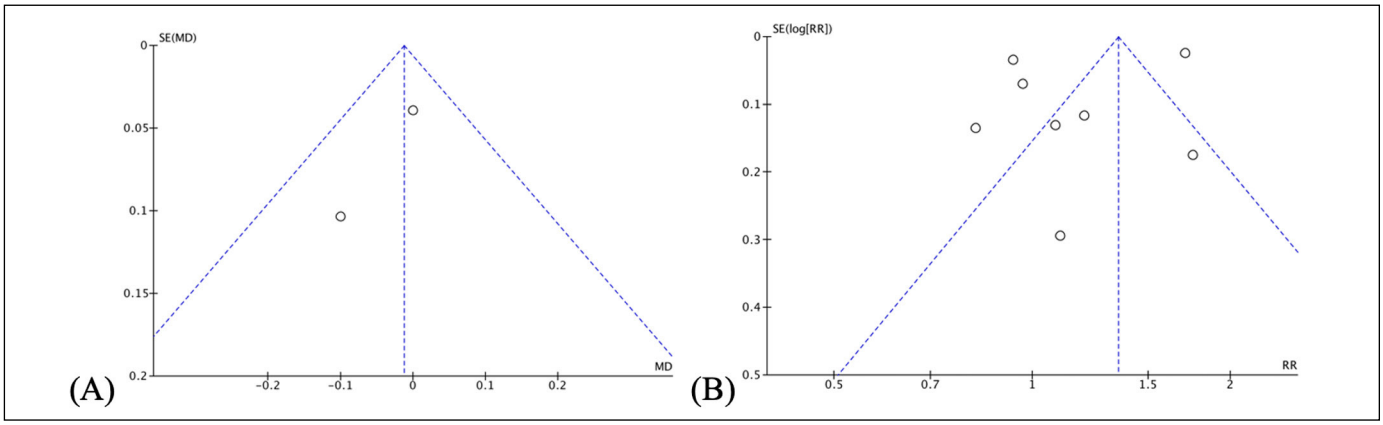

Figure 13. *Publication bias assessment plot;* **(A)** *BMI mean difference in cancer group;* **(B)** *relative risk of mortality in overweight and obese patients.*

rate also correlated with increasing BMI with dose-response association, with up to 20% increase of prostate cancer-specific mortality per 5 kg/m² increase in BMI [14, 15].

There are multiple reasons in which obesity are associated with higher mortality rate. One could be the potential detection bias in obese patients, which lead to the cancer undetected until it progressed to a more advanced stage. Another reason would be regarding the hormonal and metabolic changes in obesity, such as free testosterone level. Testosterone plays a role in maintaining differentiation in epithelium of prostate. Lower free testosterone level in obese patients had been linked to higher risk of high-grade prostate cancer with more aggressive characteristic, which include poorly differentiated and hormone-insensitive cancer cells. This were in line with a meta-analysis conducted by Discaciatti et al. [16], which reported a linear relationship of BMI in advanced prostate cancer for every 5 kg/m² increase. Risk of high-grade prostate cancer was also pronounced in patients with family history of prostate cancer [17] However, more research may be needed to understand the exact pathological mechanism in obesity.

Despite obesity being one of the modifiable factors in incidence and mortality of prostate cancer, there are other factors that need to be considered such as tobacco smoking, alcohol consuption, and dietary factors such as high intake of meat, eggs, fish, and dairy products. Presence of comorbidity such as diabetes mellitus has also been associated with increased risk of prostate cancer [18]. Inconsistent results regarding the association of BMI and risk of prostate cancer between studies may be confounded by these factors. Additionally, BMI value alone does not address fat distribution in the body, in which abdominal obesity were more strongly associated with alternations in metabolic pathways. Patients with abdominal adiposity were associated with higher risk of advanced cancer [19, 20]. Therefore, lowering BMI to normal limits may be beneficial in combating prostate cancer and its associated mortality risk.

There are several limitations to our study. First, we could not perform subgroup analysis to exclude confounding factors due to lack of data between studies. Therefore, some results would be affected by other risk factors of prostate cancer such as smoking, advanced age, and alcohol consumption. Second, we did not segregate prostate cancer-specific mortality to other-cause mortality. The result might be affected since most of the prostate cancer patients are elderly patients with possible underlying comorbidities. Thirdly, parameter of disease severity such as Gleason score was not evaluated, as mortality may correlate with the cancer stage. Further studies should address such issue to define the impact of BMI on risk of prostate cancer more accurately.

CONCLUSIONS

Our study showed significant increase in both risk of prostate cancer and mortality in patients with BMI >25 kg/m², including overweight and obese.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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