



Effect of obesity on the prognosis and recurrence of prostate cancer after radical prostatectomy: a meta-analysis

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Background: Obesity has been found to be closely related to the increased risk of fatal prostate cancer (PCa), however there remains no evidence that further clarifies the relationship between obesity and the postoperative recurrence and poor prognosis of PCa. In this study, a systematic review and meta-analysis were performed to systematically evaluate the effect of obesity on the prognosis and recurrence of PCa after radical prostatectomy (RP).

Methods: A literature search of the PubMed, Web of Science, and Embase databases was performed covering articles published between January 2013 and January 2020. Articles regarding the correlation between body mass index (BMI) and the prognosis and recurrence of PCa following RP were included in the meta-analysis. Two investigators independently screened the literature and extracted relevant data including publication information, key results, number of cancer cases, and multivariable-adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Meta-analysis was performed using RevMan 5.3 and Stata 16.0 software, and forest plots, funnel plots, and sensitivity analysis were also conducted.

Results: A total of 14 articles were included, all of which were analyzed for clinicopathological characteristics. Eight articles reported the biochemical recurrence (BCR) with prostate-specific antigen (PSA) as the predictor, and six articles reported the positive surgical margins (PSM). The meta-analysis showed that obese PCa patients had more postoperative recurrence and poor prognosis compared with the normal weight PCa patients, and the difference was statistically significant (OR =1.25, 95% CI: 1.10, 1.43). BCR exhibited no significant difference between obese and non-obese PCa patients after surgery (OR =1.2, 95% CI: 0.96, 1.46), and there were also no notable differences in PSM between the groups (OR =1.16, 95% CI: 0.99, 1.36). Subgroup analysis showed that obese PCa patients in the Americas (95% CI: 1.11, 1.37) and Europe (95% CI: 1.11, 1.78) were more likely to have surgical recurrence and poor prognosis (OR =1.40). Obese patients in the Americas were also more likely to have BCR after surgery (95% CI: 1.07, 1.36).

Conclusions: Obesity easily leads to poor prognosis and recurrence of PCa after RP.

Keywords: Obesity; prostate cancer (PCa); prognosis; recurrence; meta-analysis

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Introduction

Prostate cancer (PCa) is a common malignancy that poses a threat to the health of men. It has been reported that in 185 countries, 1.3 million new cases and 360,000 deaths

were caused by PCa in 2018, making it the second most prevalent disease among men (1). In China, PCa ranked the sixth among all male cancers in 2015 and its incidence has exhibited a significant upward trend (2). Owing to

the insidious onset of PCa, patients are typically already in advanced stages at the time of diagnosis, resulting in poor prognosis and high mortality (3). Therefore, regular postoperative detection of patients is key to preventing poor prognosis and recurrence of PCa. At present, endocrine therapy, radical prostatectomy (RP) and external radiotherapy are applied in the clinical treatment of PCa. At the same time, gene therapy has gradually attracted people's attention. There are many methods to treat PCA by modifying gene and gene immune regulation (4). In clinical diagnosis, biochemical recurrence (BCR) with serum prostate-specific antigen (PSA) as the predictor and positive surgical margins (PSM) are used to evaluate PCa recurrence and prognosis after RP and external radiotherapy (5).

The risk factors of prostate cancer include age, heredity, region, race and gene change, among which age is the biggest risk factor. On the other hand, obesity is related to diabetes, hypertension, atherosclerosis and other diseases. In recent studies, obesity has been found to be closely related to the increased risk of fatal PCa (6), which accelerates the development of PCa and increases mortality both before and after diagnosis. Ma *et al.* found that a one-unit increase of BMI in obese people led to an approximately 10% increase in the risk of PCa compared with normal weight individuals, and obese people with BMI ≥ 30 kg/m² led to a 20% increase in the risk of PCa (7). In the meta-analysis conducted by Cao *et al.*, a 5 kg/m² increase of BMI was found to increase the risk of PCa-specific death by 20% (8). These findings indicate that obesity is closely associated with the development of PCa. Furthermore, the mortality rate of obese colorectal cancer patients is more than three times higher than that of normal weight patients (9). In addition, obesity also leads to recurrence and poor prognosis in breast and lung cancers (10,11). Thus, it is clear that obesity is a risk factor for postoperative recurrence and poor prognosis in most cancers.

At present, there are numerous studies addressing the relationship between obesity and the occurrence of PCa, however there remains no evidence that further clarifies the relationship between obesity and the postoperative recurrence and poor prognosis of PCa. Although there are many studies on the incidence rate of obesity and its incidence, this study is the first time to perform a systematic review and meta-analysis to evaluate the relationship between obesity and the prognosis of RP and PCa recurrence, so as to provide a reference for the clinical treatment and prognosis evaluation of obese patients with PCa.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-1352>).

Methods

Literature retrieval strategy

A literature search of the PubMed, Web of Science, and Embase databases was performed in English for relevant articles published between January 2013 and January 2020. The search terms were as follows: (“obesity” or “BMI” or “body mass index” or “overweight” or “adiposity”) and (“prostate cancer” or “prostatectomy” or “radical prostatectomy”). The references of retrieved literature were also tracked to find relevant papers.

Screening criteria

Inclusion criteria were as follows: (I) case-control studies on obesity and the prognosis and recurrence of PCa after RP with human study subjects; (II) complete original data, or enough data to calculate the odds ratio (OR) with 95% confidence interval (CI).

Exclusion criteria were as follows: (I) comments, reviews, meta-analyses, animal studies, or *in vitro* cell studies; (II) articles irrelevant to the topic, repetitive studies, and studies with insufficient data and design flaws; (III) studies with unclear conclusions.

Study indicators

Criteria of obesity

The data collected in this study were divided into the test group (obesity population) and the control group (normal weight population). If there were multiple groups in the original literature, the population with body weight >30 kg/m² was classified as the test group.

Related indicators to evaluate surgical prognosis and recurrence

The serum PSA level was measured every 3 months; PSA >0.2 ng/mL in two successive tests after surgery was considered as BCR. PSM is a common indicator in adjuvant radiotherapy and measures the quality of surgery; so the surgical prognosis was primarily evaluated by the PSM of RP specimens.

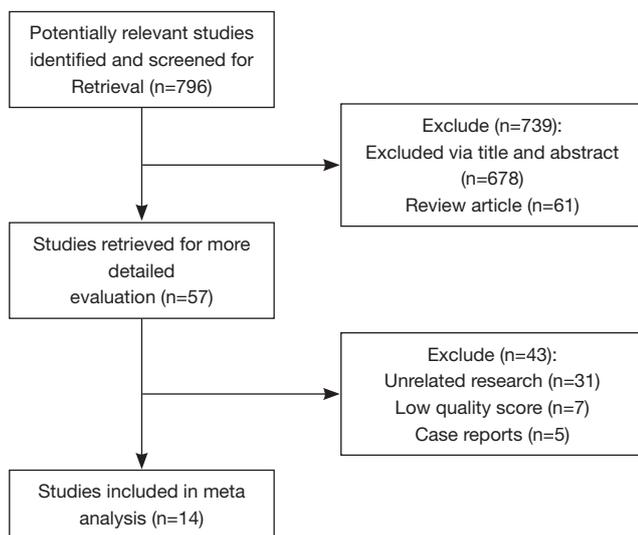


Figure 1 Literature screening process.

Data extraction

Two investigators independently screened the literature and extracted the data. The literature screening process was as follows: first, studies that did not meet the screening criteria requirements were excluded. Next, studies were excluded by reading the abstracts or the full text if necessary. Finally, the corresponding materials were cross-checked to determine the studies included in this meta-analysis.

The following data were extracted: first author's name, year of publication, country, study design, main reported outcomes, number of cancer cases, total number of subjects, study duration, adjusted confounders, and multivariable-adjusted OR with 95% CI. During the data extraction process, disagreements between the two investigators were resolved by referring to the original literature.

Statistical analysis

Review manager (RevMan) 5.3 and Stata 16.0 were used for statistical analysis. Dichotomous variables were compared with weighted mean difference (WMD) and OR with 95% CI. Heterogeneity among the included studies was evaluated using I^2 statistics. An $I^2 > 50\%$ indicated significant heterogeneity, and in these cases, a random effects model (REM) was used. If the heterogeneity was not significant, a fixed effects model (FEM) was applied. Sensitivity analysis and publication bias were analyzed using Stata 16.0 (StataCorp LLC, college station, TX, USA).

Results

Basic characteristics of the included literature

A total of 796 potentially relevant studies were retrieved according to the retrieval strategy. Of these, 678 irrelevant studies were excluded through reading titles and abstracts, and a further 61 review articles were also excluded. The remaining 57 articles were included. After reading the full texts, 31 unrelated articles, seven studies with a low quality score, and five case reports were also excluded. Finally, 14 articles were included in this meta-analysis. The specific literature screening process and results are shown in *Figure 1*, and the basic characteristics of the 14 included articles are displayed in *Table 1*.

Comparison of postoperative recurrence and prognosis in obese and non-obese PCa patients

A total of 14 articles regarding obesity and postoperative recurrence and prognosis were included (12-25). As shown in *Figure 2*, a significant heterogeneity among the studies was identified ($I^2 = 71.0\%$, $P = 0.000$), so the REM was used. It was confirmed that obese PCa patients had more postoperative recurrence and poor prognosis compared with the non-obese PCa patients (OR = 1.25, 95% CI: 1.10, 1.43, $P < 0.001$). As $I^2 > 50\%$, which indicated high heterogeneity among the studies, a subgroup analysis was carried out to determine the source of heterogeneity. It was divided into three groups according to region: Asia (OR = 1.22, 95% CI: 0.86, 1.74), the Americas (OR = 1.23, 95% CI: 1.11, 1.37), and Europe (OR = 1.40, 95% CI: 1.11, 1.78) (*Figure 2*). The results showed no heterogeneity among different regions. Also, the funnel plot was symmetrical, indicating a lower probability of publication bias in the included literature (*Figure 3*). Sensitivity analysis was performed by removing the studies one by one; the result showed that the pooled effect size was still statistically significant, and the forest plot direction did not change significantly before and after removal (*Figure 4*).

BCR conditions in obese and non-obese PCa patients after surgery

A total of eight articles were included to report the BCR condition of patients (15,18-20,22-25). Firstly, obvious heterogeneity among the studies was identified ($I^2 = 79.2\%$, $P < 0.001$) (*Figure 5A*), so the REM was used for meta-

Table 1 Basic characteristics of the included literature

No.	First author	Year	Sample time	Country	Sample size	Age (years)	Follow-up time (months)	Study design	Outcome measured
1	Lijiang Sun	2019	2005–2014	China	422	68 [47–82]	19.4 [0.3–88.9]	Retrospective	PSM
2	Wen Liu	2020	2005–2014	China	1,016	68 [41–79]	NR	Retrospective	PSM
3	Farnoosh Nik-Ahd	2020	1988–2017	US	4,766	63 [58–66]	88.8	Retrospective	PSM
4	Ross J. Mason	2018	2007–2010	US	698	61.8	72	Retrospective	BCR
5	M Francesca Monn	2016	2011–2012	US	12,454	63.3	NR	Retrospective	WC
6	Agnes B. Maj-Hes	2017	2000–2011	Austria	6,519	61 [57–66]	28 [21–49]	Retrospective	PSM
7	R Asmar	2013	1994–2007	US	1,428	59.1	43.2	Retrospective	BCR
8	Michel Wissing	2019	2006–2013	Canada	1,714	41–80	69 [54–87]	Retrospective	BCR
9	Kyo Chul Koo	2014	2005–2011	South Korea	880	64.5±7.4	58.2	Retrospective	BCR
10	N Hayashi	2014	2002–2009	Japan	703	64	38.4	Retrospective	PSM
11	Keisuke Goto	2017	2005–2014	Japan	2,003	68 [45–83]	34 [0–108]	Retrospective	BCR
12	Iilir Agalliu	2015	2005–2012	US	610	60	30.8	Retrospective	BCR
13	Young Dong Yu	2018	2006–2017	South Korea	2,997	66.0±6.8	39.6	Retrospective	BCR
14	Heather J. Chalfin	2014	1982–2012	US	11,152	58	60 [12–324]	Retrospective	BCR

NR, not reported; BCR, biochemical recurrence; PSM, positive surgical margins; WC, wound complications [including superficial surgical site infection (SSI), deep SSI, organ/space SSI and dehiscence].

analysis. The meta-analysis showed no significant difference in BCR incidence between obese and non-obese patients after surgery (OR =1.20, 95% CI: 0.96, 1.49). Secondly, due to the high heterogeneity, a subgroup analysis was carried out to determine the source of heterogeneity. It was divided according to region into an Asia subgroup and an Americas subgroup. The result of subgroup analysis showed that the heterogeneity was from the literature in Asia; meanwhile, obese patients in the Americas were relatively prone to BCR after surgery (OR =1.21, 95% CI: 1.07, 1.36). To determine the sensitivity of the meta-analysis results, the studies were eliminated one by one; the result showed that the pooled effect size was still statistically significant, and the forest plot direction did not change significantly before and after removal (*Figure 5B*).

PSM conditions in obese and non-obese PCa patients after surgery

A total of five articles were included to report the PSM condition of patients (12–14,17,21). Firstly, obvious heterogeneity was identified among the studies ($I^2=50.9\%$, $P<0.001$) (*Figure 6A*), so the REM was used for meta-

analysis. The meta-analysis showed no significant difference in PSM condition between obese and non-obese patients after surgery (OR =1.16, 95% CI: 0.99, 1.36). Secondly, due to the high heterogeneity, a subgroup analysis was carried out to determine the source of heterogeneity. It was divided according to region into an Asia subgroup, an Americas subgroup, and a Europe subgroup. The result of the subgroup analysis showed that the heterogeneity was from the literature in different regions; meanwhile, obese patients in Asian were relatively prone to PSM after surgery (OR =1.36, 95% CI: 0.91, 2.02). To determine the sensitivity of the meta-analysis results, the studies were eliminated one by one; the result showed that the pooled effect size was still statistically significant, and the forest plot direction did not change significantly before and after removal (*Figure 6B*).

Discussion

The tumor microenvironment is crucial in the occurrence, development, and progression of cancers. For example, chronic inflammation is an important factor driving the development of cancer, and epidemiological data shows a close relationship between chronic inflammation and the

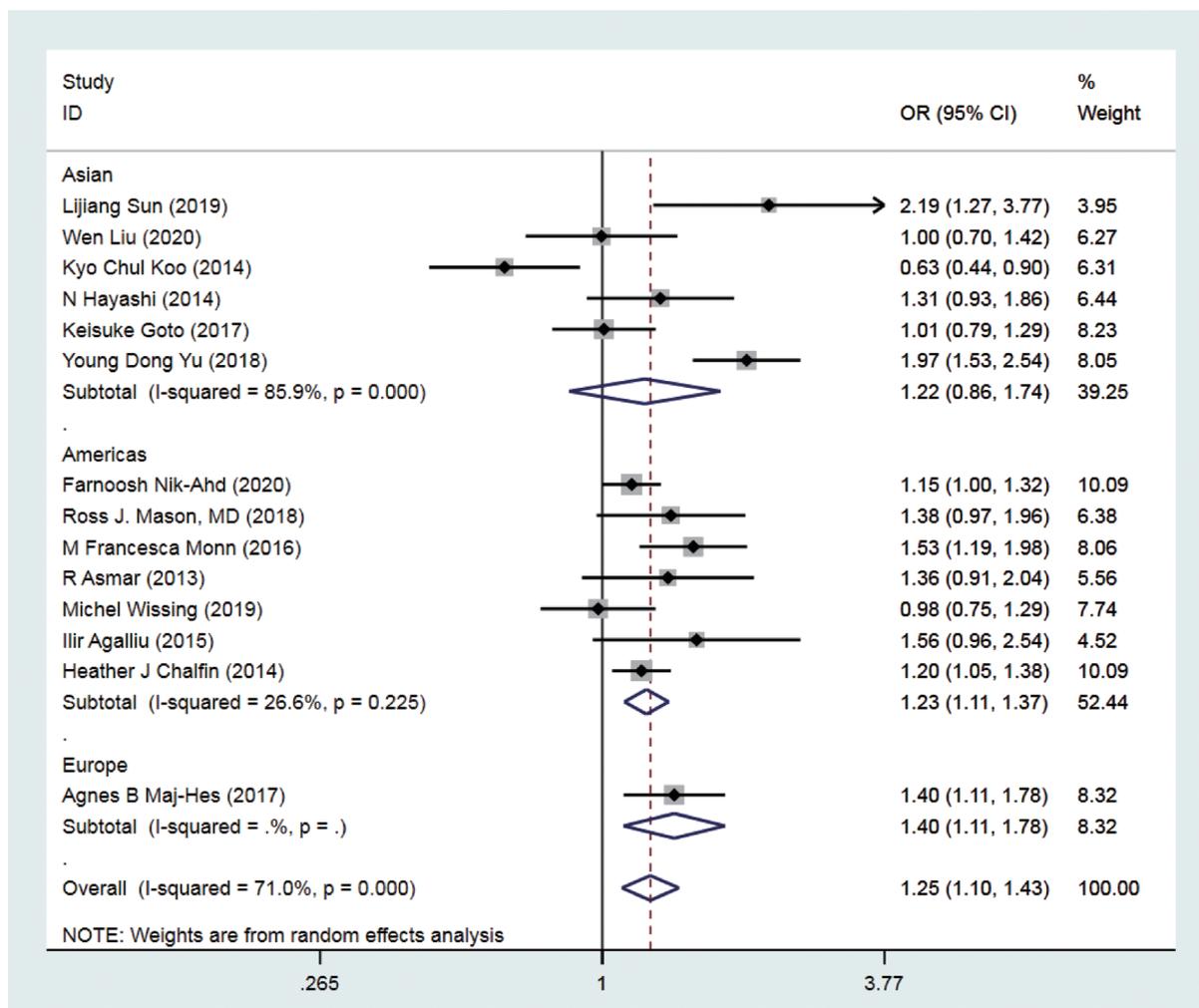


Figure 2 Forest plot of postoperative recurrence and poor prognosis in obese and non-obese PCa patients. OR, odds ratio; CI, confidence interval; PCa, prostate cancer.

progression of liver, pancreatic, and bladder cancers (26). Obesity is usually caused by excessive deposition of adipose tissue, which can easily induce abnormal metabolism of steroid hormones and cytokines, thus resulting in chronic inflammation (27). Studies have found that obesity-related cancers, such as breast cancer and cancers of internal organs, occur near fat accumulation, suggesting that biological changes in fat often locally promote the occurrence and development of a variety of cancers in people with elevated BMI (28). Dickerman *et al.* demonstrated that both obesity and weight gain in adults are associated with advanced PCa, as well as the high risk of recurrence and survival of PCa (29). Vidal *et al.* reported that obesity may have a stronger association with PCa in some patient subgroups

(such as black men) (30).

In this study, obese PCa patients had more postoperative recurrence and poor prognosis compared with non-obese patients. Obesity was a risk factor for recurrence and poor prognosis in PCa patients in Asia, Europe, and the Americas. There was significant heterogeneity among the studies caused by differences in patient characteristics, treatment, BMI measurement time, or follow-up time. More studies are required to investigate and determine the relevant reasons.

BCR has been defined as an indicator of PCa recurrence after RP or radiotherapy (31). REM was applied in this meta-analysis, and the results showed no significant difference in the incidence of BCR between obese and non-

obese patients. However, in the Americas, obese patients had a markedly higher incidence of BCR compared with non-obese patients. This is because the inflammatory response of the body leads to the increase of PSA in the blood (32), and there is a possibility of false positives due to over-diagnosis in the PSA test. Furthermore, BMI classification criteria are different in different countries.

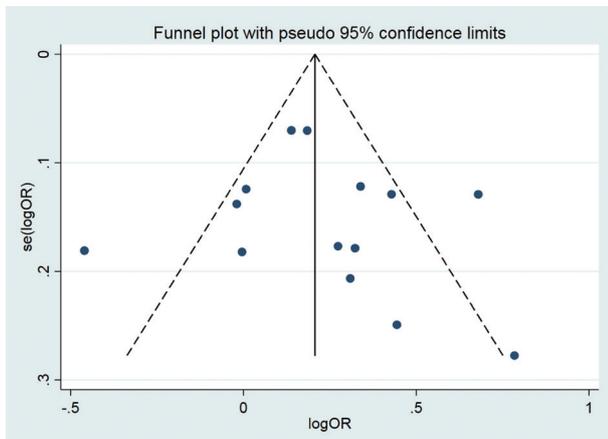


Figure 3 Funnel plot of postoperative recurrence and poor prognosis in obese and non-obese PCa patients. OR, odds ratio; PCa, prostate cancer.

These factors may be responsible for the high incidence of BCR in obese patients in the Americas, resulting in differences in the subgroup analysis.

PSM is a recognized indicator of postoperative quality in PCa, and is also an important indicator of postoperative adjuvant radiotherapy and endocrine therapy (33). As early as 2009, heavier PCa patients were found to have a higher risk of PSM after surgery compared with normal weight individuals (34). In this meta-analysis, REM was used for the combined analysis and the subgroup analysis, and both results revealed no significant difference in the incidence of PSM between obese and non-obese patients. This indicates that with the increasing understanding of PCa and the development of medical technology, the occurrence of PSM after RP in obese and non-obese patients has been enhanced.

Conclusions

In summary, this meta-analysis revealed the important relationship between obesity and poor prognosis and recurrence of PCa after RP. However, due to the limited number and quality of the included studies, the above conclusion requires further verification by more high-quality studies.

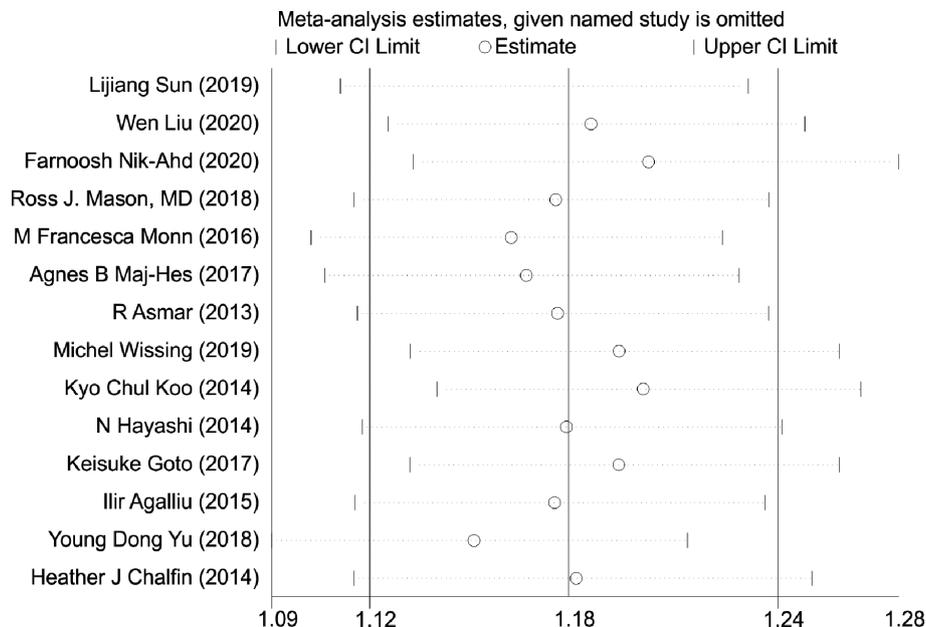


Figure 4 Sensitivity analysis of postoperative recurrence and poor prognosis in obese and non-obese PCa patients. CI, confidence interval; PCa, prostate cancer.

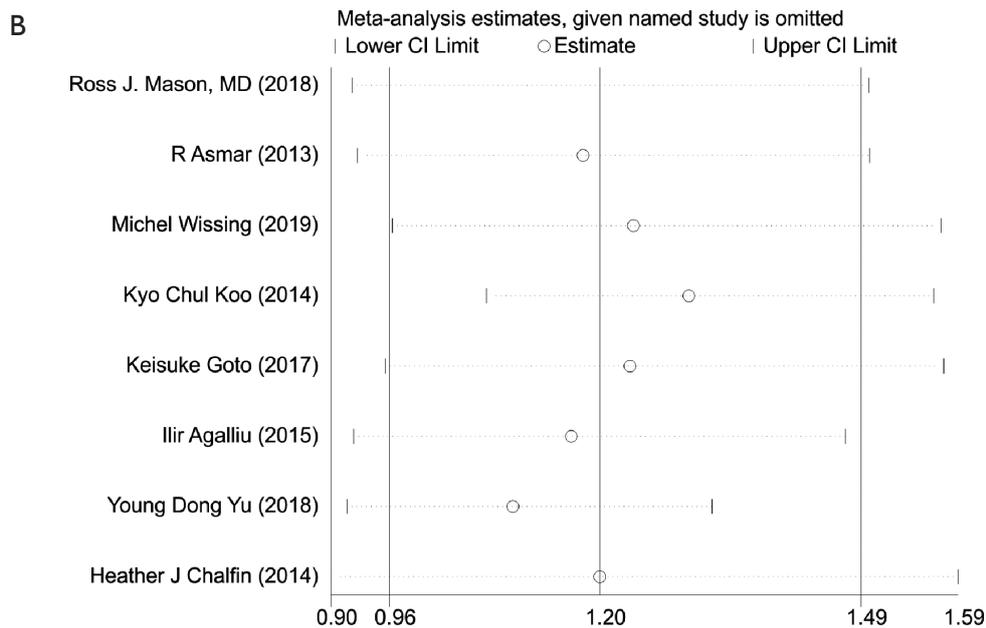
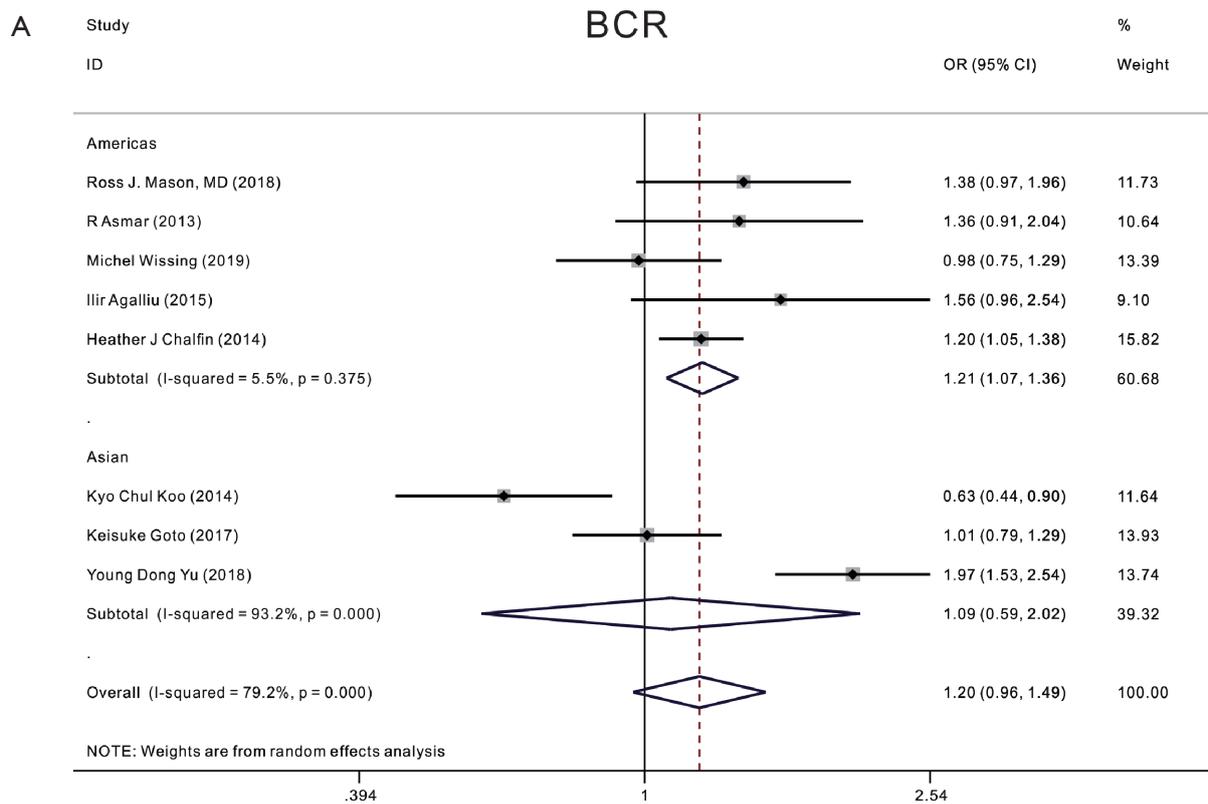


Figure 5 Forest plot (A) and sensitivity analysis plot (B) with BCR as the outcome measure. OR, odds ratio; CI, confidence interval; BCR, biochemical recurrence.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tau-20-1352>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-20-1352>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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