Received: 17 August 2018 | Revised: 30 September 2018 | Accepted: 15 October 2018

DOI: 10.1111/and.13198

INVITED REVIEW

WILEY ANDROLOGIA

Effect of phosphodiesterase type 5 inhibitors on prostate cancer risk and biochemical recurrence after prostate cancer treatment: A systematic review and meta-analysis

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Funding information
Scientific Research Project of The Fifth People's Hospital of Shanghai, Fudan University, Grant/Award Number: 2018WYZT05

Abstract

Recent studies have examined the impact of phosphodiesterase type 5 inhibitors (PDE5-Is) use on the risk of prostate cancer, and biochemical recurrence (BCR) in prostate cancer patients, but the results were inconsistent. A meta-analysis was conducted to assess the associations with all published studies. Databases (PubMed, Web of Science and MEDLINE) were retrieved to identify relevant studies which explored the impact of PDE5-Is use on the risk of prostate cancer, and BCR in prostate cancer patients. The summary results along with 95% confidence intervals (CIs) were calculated. Nine articles were eligible for the inclusion criteria. The pooled analysis showed that PDE5-Is use was not related to the increased risk of prostate cancer (odds ratio (OR), 0.71; 95% CI, 0.40–1.29). Moreover, PDE5-Is use was not linked to BCR risk in prostate cancer patients with erectile dysfunction (ED) following radical prostatectomy or radiation therapy (relative risk (RR), 1.09; 95% CI, 0.89–1.34). The heterogeneity test suggested moderate heterogeneity across studies. PDE5-Is use does not influence the risk of prostate cancer, and BCR in prostate cancer patients. More well-designed studies are warranted to confirm the findings of our analyses.

KEYWORDS
biochemical recurrence, meta-analysis, phosphodiesterase type 5 inhibitors, prostate cancer

1 | INTRODUCTION

Erectile dysfunction (ED) is characterised by the inability to obtain or maintain sufficient penile erection during sexual activity. It can have negative influence on the quality of sexual life in prostate cancer patients and their partners (Wespes et al., 2006). Prostate cancer is the most common cancer among males in the Western countries. Radiation therapy (RT) and radical prostatectomy (RP) are the treatment options for high-risk prostate cancer (Koie et al., 2014; Mottet et al., 2017). However, ED and BCR (i.e., a rise of serum prostate-specific antigen (PSA) level) are very common problems in prostate cancer patients treated with RP or RT (Kundu et al., 2004; Moul, 2003). PDE5-Is such as sildenafil, tadalafil, vardenafil and avanafil are widely indicated for treatment of ED after RP or RT. PDE5-Is inhibit the cyclic guanosine monophosphate-degrading phosphodiesterase 5, activate cGMP-dependent protein kinase G, induce cavernosal smooth muscle relaxation and finally increase blood flow and erection (Aversa, Bruzziches, Pili, & Spera, 2006; Blount et al., 2004; Ravipati, McClung, Aronow, Peterson, & Frishman, 2007).

To date, three studies assessed PDE5-Is use and prostate cancer risk with inconsistent results (Chavez, Scott, Hasan, & Jo, 2013; Jamnagerwalla et al., 2016; Machen, Rajab, Pruszynski, & Coffield, 2017). Furthermore, several epidemiologic studies have explored the impact of PDE5-Is use on BCR risk in prostate cancer patients

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following RP or RT. One study showed that PDE5-Is use after RP may adversely impact BCR (Michl et al., 2015). However, other studies showed inconsistent results and the evidence remained inclusive (Gallina et al., 2015; Jenkins et al., 2016; Jo et al., 2016; Leapman et al., 2016; Loeb et al., 2016). Thus, a systematic review and meta-analysis were performed to quantify the association of PDE5-Is use with the risk of prostate cancer, and BCR in prostate cancer patients with ED following RP or RT.

2 | METHODS

2.1 | Literature and search strategy

Two authors (YGW and XFQ) independently retrieved PubMed, Web of Science and MEDLINE to identify relevant articles. Independent search strategies and search terms were used for each outcome as follows: (a) phosphodiesterase type 5 inhibitors and prostate cancer risk: (["phosphodiesterase type 5 inhibitor" or "phosphodiesterase type 5 inhibitors" or "sildenafil" or "vardenafil" or "tadalafil" or "avanafil"] and ["prostate cancer"]); and (b) phosphodiesterase type 5 inhibitors and biochemical recurrence risk: (["phosphodiesterase type 5 inhibitor" or "phosphodiesterase type 5 inhibitors" or "sildenafil" or "vardenafil" or "tadalafil" or "avanafil"] and ["biochemical recurrence" or "prostate cancer recurrence"]). The databases were searched from their inception to May 2018.

2.2 | Selection criteria and data extraction

The inclusion criteria were as follows: (a) Published literatures evaluated the impact of PDE5-Is on the prostate cancer risk and/or biochemical recurrence (BCR) in prostate cancer patients; (b) hazards ratio (HR), odds ratio (OR) or relative risk (RR) estimates along with 95% confidence intervals (CIs) from multivariate-adjusted models were reported. Comments, review articles and meta-analysis were excluded.

Two authors (YGW and XFQ) independently extracted the following data: (a) name of the first author; (b) publication year; (c) country; (d) design type; (e) period of the study; (f) the number of patients in each group; (g) the multivariate-adjusted HR, OR or RR estimates with their 95% CIs for each category; and (h) adjusted factors in multivariate models.

2.3 | Statistical analysis

The OR or HR was considered approximations of RR when a study outcome (cancer incidence) was relatively low (Cummings, 2009; Hernan, 2010). The pooled OR and 95% CI were calculated to quantify the relation of PDE5-Is use with the risk of prostate cancer. The summary RR was calculated for the BCR analysis.

The heterogeneity across studies was assessed by use of Cochran's chi-square-based Q statistic and was quantified with I^2 statistic. The random-effects model was adopted in the presence of heterogeneity ($p < 0.10$) (DerSimonian & Laird, 2015); otherwise, fixed-effects model was used (Mantel & Haenszel, 1959). Generally, I^2 value above 50% was considered as evidence of moderate heterogeneity.

Sensitivity analysis was conducted to investigate the impact of each study on the pooled estimate through exclusion of one study at a time and calculating the pooled effect size of the remaining studies.

Publication bias was assessed using funnel plot analysis and Egger's regression model (Egger, Davey, Schneider, & Minder, 1997). p Value less than 0.05 was regarded as statistically significant. Data analysis was done by use of Stata 14.0 (Stata Corporation, College Station, TX, U.S.A.).

3 | RESULTS

3.1 | Literature search and study characteristics

The process of study selection is presented in Figure 1. Concerning the relation between PDE5-Is use and prostate cancer risk, a total

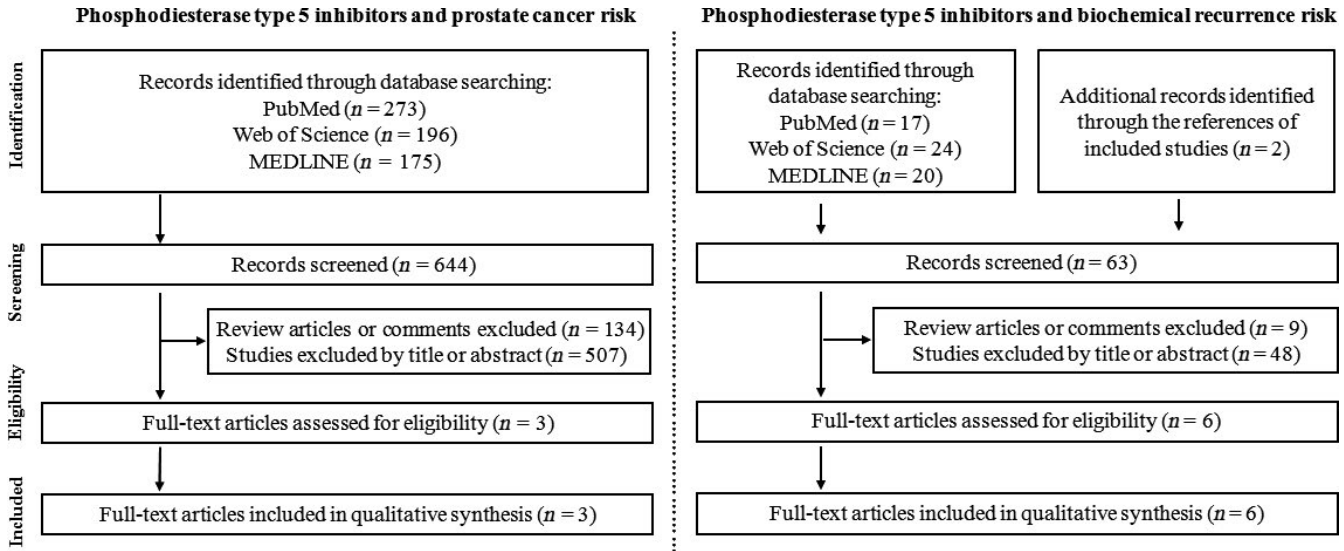

FIGURE 1 Flow chart of study selection in the meta-analysis

TABLE 1 Characteristics of the included studies for the risk of prostate cancer analysis

References	Country	Study design	Study period (years)	PDE5-Is (event/total)	No PDE5-Is (event/total)	Total No. of patients	Primary exposure	Adjusted estimate (s) (95% confidence interval, CI)	Adjusted factors
Chavez et al. (2013)	USA	Cohort	7 (2000–2006)	97/2,362	258/2,612	4,974	All filled prescriptions for PDE5-Is	OR: 0.4 (0.3, 0.5)	Age, race, BPH and PSA
Jamnagerwalla et al. (2016)	USA	Case–control	4	71/364	1,391/6,137	6,501	Baseline PDE5-Is use	OR: 0.90 (0.68, 1.20)	Age, race, geographic region, PSA, prostate volume, baseline DRE, BMI, family history of prostate cancer, coronary artery disease, smoking, impotence, diabetes and dutasteride use
Machen et al. (2017)	USA	Case–control	12 (2000–2011)	219/671	175/511	1,182	PDE5-Is use before a prostate cancer diagnosis	OR: 1.02 (0.78, 1.35)	Age, race and PSA

Note. BMI: body mass index; BPH: benign prostatic hyperplasia; DRE: digital rectal examination; OR: odds ratio; PSA: prostate-specific antigen.

of 644 titles and abstracts were initially identified and assessed, but most of them were excluded as their outcome was not relevant to our analysis. Finally, three articles were evaluated in detail with regard to their fulfilment of the inclusion criteria. Regarding the impact of PDE5-Is use on BCR, 63 articles were identified and six articles were selected for qualitative synthesis.

The main characteristics of the selected studies are shown in Tables 1 and 2. Among these nine articles, three studies in three articles reported on the relation of PDE5-Is use with prostate cancer risk (Chavez et al., 2013; Jamnagerwalla et al., 2016; Machen et al., 2017), and 11 studies in six articles reported on the relation between PDE5-Is use and BCR risk in prostate cancer patients after treatment (Gallina et al., 2015; Jenkins et al., 2016; Jo et al., 2016; Leapman et al., 2016; Loeb et al., 2016; Michl et al., 2015). All studies were adjusted for potential confounders.

3.2 | Primary analysis

The primary result for the relation between PDE5-Is use and prostate cancer risk is presented in Figure 2. PDE5-Is exposure was not related to an increased risk of prostate cancer (OR, 0.71; 95% CI, 0.40–1.29). The RR of individual study and the pooled RR for the impact of PDE5-Is use on the BCR risk in prostate cancer patients after treatment are presented in Figure 3. Preliminary analysis showed PDE5-Is use was not linked to the increased risk of BCR among males with prostate cancer after treatments (HR, 1.09; 95% CI, 0.89–1.34).

3.3 | Subgroup and sensitivity analyses

Statistically significant heterogeneity was observed in prostate cancer studies (p, 0; I^2, 93.0%) and BCR studies (p, 0.039; I^2, 47.7%). The analysis by study design subgroups revealed no significant relation between PDE5-Is use and prostate cancer risk in case–control studies (OR, 0.96; 95% CI, 0.79–1.17). No evidence of heterogeneity was detected in case–control studies (Figure 2). To evaluate the difference in risk of BCR among patients taking PDE5-Is medications following RP or RT, studies were classified into two subgroups; eight studies included a population primarily treated with RP; and three studies included patients treated with radiotherapy. In our subgroup analyses, PDE5-Is use was not associated with BCR among patients treated with RP (RR, 1.12; 95% CI, 0.90–1.39). PDE5-Is use following RT for prostate cancer also was not in relation to BCR (RR, 0.88; 95% CI, 0.53–1.47) (Figure 3). Subgroup analyses according to study design (cohort and case–control studies) also found no association between PDE5-Is use and BCR (RR, 1.10; 95% CI, 0.84–1.43 for cohort; RR, 1.03; 95% CI, 0.65–1.61 for case–control). Obvious heterogeneity was detected both in cohort studies (p, 0.052; I^2, 49.8%) and in case–control studies (p, 0.056; I^2, 65.3%) (figure not shown).

In sensitivity analysis with the leave-one-out method, our results revealed that no individual study significantly altered the summary RR for PDE5-Is use on BCR risk, with pooled RR varying from 0.98 (95% CI, 0.76–1.26) to 1.12 (95% CI, 0.87–1.43), suggesting the results were statistically robust (Figure 4).

TABLE 2 Characteristics of the included studies for the association between PDE5-Is use and BCR risk of prostate cancer after definitive therapy

References	Country	Study design	Study period	PDE5-Is (event/total)	No PDE5-Is (event/total)	Total No. of patients	Primary exposure	Primary treatment(s) received	Adjusted estimate(s) (95% confidence interval, CI)	Adjusted factors	5-year BCR-free survival estimates, PDE5-Is versus non-PDE5-Is, if available
Michl et al. (2015)	Germany	Cohort	11 (2000–2010)	Unknown/1,110	Unknown/3,642	4,752	Regular use of PDE5-Is	Radical prostatectomy	HR: 1.38 (1.11, 1.70)	Age, BMI, smoking, preoperative PSA, Gleason score, surgical margin status and pathologic stage	84.7% versus 89.2%, $p = 0.0006$
Gallina et al. (2015)	Italy	Cohort	10 (2004–2013)	Unknown/674	Unknown/1905	2,579	Postoperative PDE5-Is use	Radical prostatectomy	HR: 1.18 (0.85, 1.63)	Age, year of surgery, preoperative PSA, Gleason score and surgical margin status	88.7% versus 91.2%, $p = 0.5$
Jo et al. (2016)	Korea	Cohort	10 (2005–2014)	Unknown/829	Unknown/253	1,082	Postoperative PDE5-Is use	Radical prostatectomy	HR: 1.47 (0.765, 2.826)	Age, BMI, year of surgery, preoperative PSA, Gleason score, pathologic stage and surgical margin status	91% versus 87.1%, $p = 0.092$
Loeb et al. (2016): 1	Sweden	Case–control	5 (2006–2010)	137/3,198	111/1936	5,134	All filled prescriptions for PDE5-Is after prostate cancer treatment	Radical prostatectomy	OR: 0.86 (0.64, 1.16)	Marital status, education, income, PSA, clinical stage, Gleason score, proportion of positive biopsies, pathologic stage, prostatectomy Gleason grade group and surgical margin status.	Unknown
Loeb et al. (2016): 2	Sweden	Case–control	5 (2006–2010)	13/286	32/640	926	All filled prescriptions for PDE5-Is after prostate cancer treatment	Radiotherapy	OR: 0.98 (0.49, 1.97)	Marital status, education, income, PSA, clinical stage, Gleason score and proportion of positive biopsies.	Unknown
Leapman et al. (2016): 1	USA	Cohort	Unknown	Unknown/3,089	Unknown/758	3,847	Baseline use of PDE5-Is	Radical prostatectomy	HR: 0.9 (0.3, 2.4)	Age, prostate cancer index sexual function score and pathological characteristics	Unknown
Leapman et al. (2016): 2	USA	Cohort	Unknown	Unknown/3,089	Unknown/758	3,847	Ever use of PDE5-Is	Radical prostatectomy	HR: 0.7 (0.5, 1.1)	Age, prostate cancer index sexual function score and pathological characteristics	Unknown

Continues

TABLE 2 Continued

References	Country	Study design	Study period	PDE5-Is (event/total)	No PDE5-Is (event/total)	Total No. of patients	Primary exposure	Primary treatment(s) received	Adjusted estimate(s) (95% confidence interval, CI)	Adjusted factors	5-year BCR-free survival estimates, PDE5-Is versus non-PDE5-Is, if available
Leapman et al. (2016): 3	USA	Cohort	Unknown	Unknown/3,089	Unknown/758	3,847	Time-dependent use of PDE5-Is	Radical prostatectomy	HR: 1.3 (0.6, 2.7)	Age, prostate cancer index sexual function score and pathological characteristics	Unknown
Leapman et al. (2016): 4	USA	Cohort	Unknown	Unknown/421	Unknown/576	997	Baseline use of PDE5-Is	Radiotherapy	HR: 4.6 (0.6, 37.3)	Age, prostate cancer index sexual function score and pathological characteristics	Unknown
Leapman et al. (2016): 5	USA	Cohort	Unknown	Unknown/421	Unknown/576	997	Ever use of PDE5-Is	Radiotherapy	HR: 0.6 (0.3, 1.5)	Age, prostate cancer index sexual function score and pathological characteristics	Unknown
Jenkins et al. (2016)	USA	Case–control	Unknown	59/295	58/360	655	Postoperative PDE5-Is use	Radical prostatectomy	OR: 1.52 (0.95, 2.43)	Age, PSA, Gleason score, surgical margin status, seminal vesicle involvement, extra capsular extension and lymph node involvement	Unknown

Note. BCR, biochemical recurrence; HR, hazard ratio; OR, odds ratio; PDE5-Is, phosphodiesterase type 5 inhibitors; PSA, prostate-specific antigen.

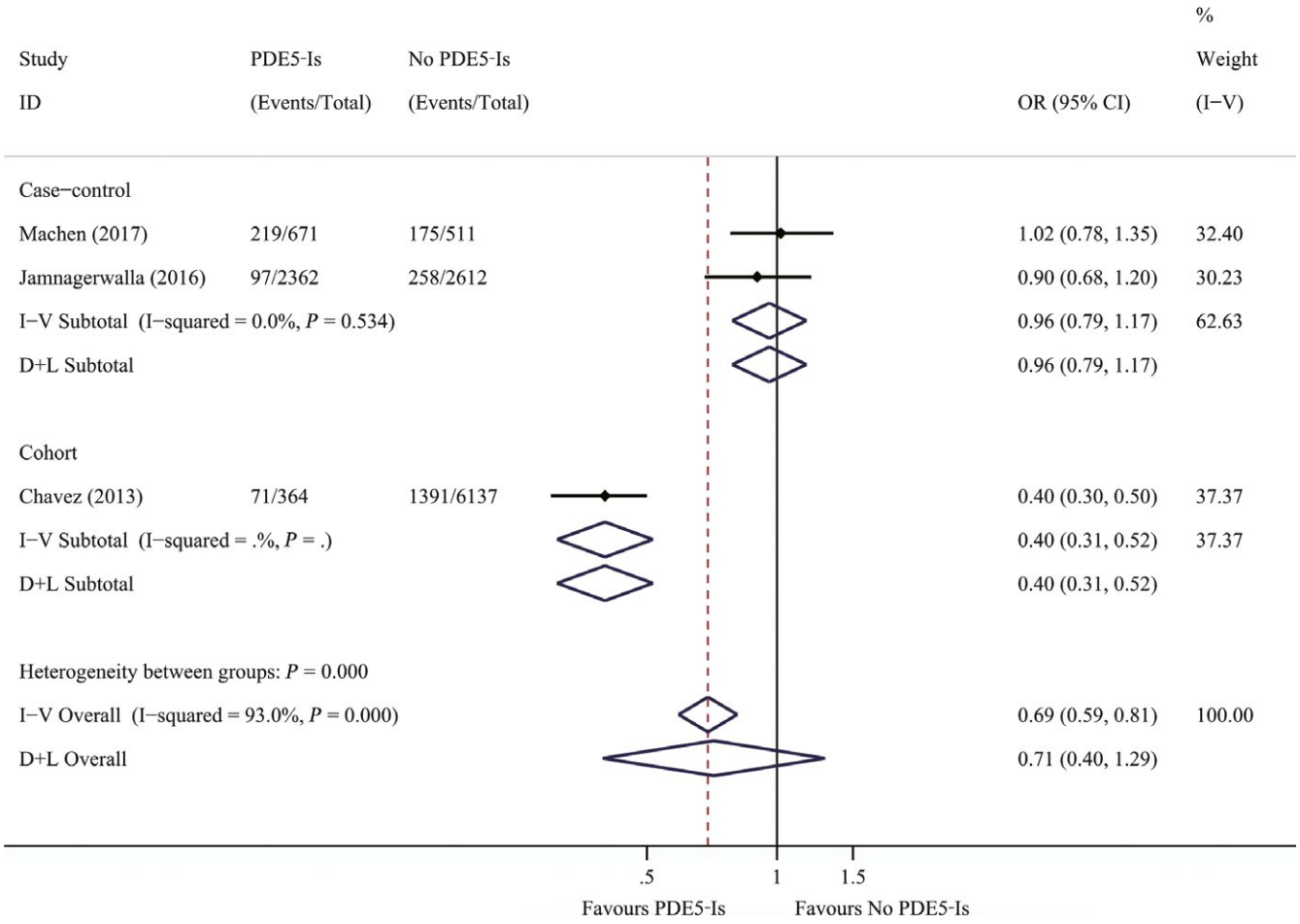

FIGURE 2 Forest plot on the association of PDE5-Is use with prostate cancer risk. The squares and horizontal lines indicate the study-specific relative risks and 95% confidence intervals. The diamonds represent the pooled odds ratio (OR) estimates with corresponding 95% confidence intervals

3.4 | Bias assessment

Funnel plot of the 11 studies on PDE5-Is use and BCR did not show any substantial asymmetry (Figure 5). Egger's regression test also demonstrated no publication bias, with *p* value of 0.836 for the risk of BCR analyses.

4 | DISCUSSION

The US Food and Drug Administration has proclaimed the requirement to assess the safety of PDE5-Is (January–March 2016). Previous two meta-analyses have explored the impact of PDE5-Is use on the risk of melanoma (Loeb, Ventimiglia, Salonia, Folkvaljon, & Stattin, 2017; Wang et al., 2017). To our knowledge, the present meta-analysis is the first to exclusively assess the impact of PDE5-Is use on the prostate cancer risk and BCR risk in prostate cancer patients after treatment. All relevant published epidemiologic studies were systematically reviewed, and the data were combined to evaluate the associations. The present meta-analysis showed PDE5-Is exposure was not linked to an increased risk of prostate cancer. Moreover, our results suggested no increased risk of BCR among prostate cancer patients who used PDE5-Is after treatment with radical prostatectomy or radiotherapy.

No publication bias was observed. Subgroup and sensitivity analyses showed consistent results for the relation between PDE5-Is use and BCR risk after treatment, which indicate that our main findings are robust.

There were also potential limitations in our meta-analysis. First, the sample size of three included studies was relatively small not having enough statistical power to assess the real association between PDE5-Is and prostate cancer risk (Chavez et al., 2013; Jamnagerwalla et al., 2016; Machen et al., 2017). Therefore, the results should be interpreted with caution. Second, statistically significant heterogeneity was found among studies that might be attributed to the different methodologies, study design, population characteristics, confounders and PDE5-Is exposure ascertainment of the included studies. Subgroup analysis was conducted based on study design (cohort and case–control studies), but moderate heterogeneity was still detected both in cohort studies and case–control studies. It is speculated that some studies included in the pooled analysis did not control for the greatest number of

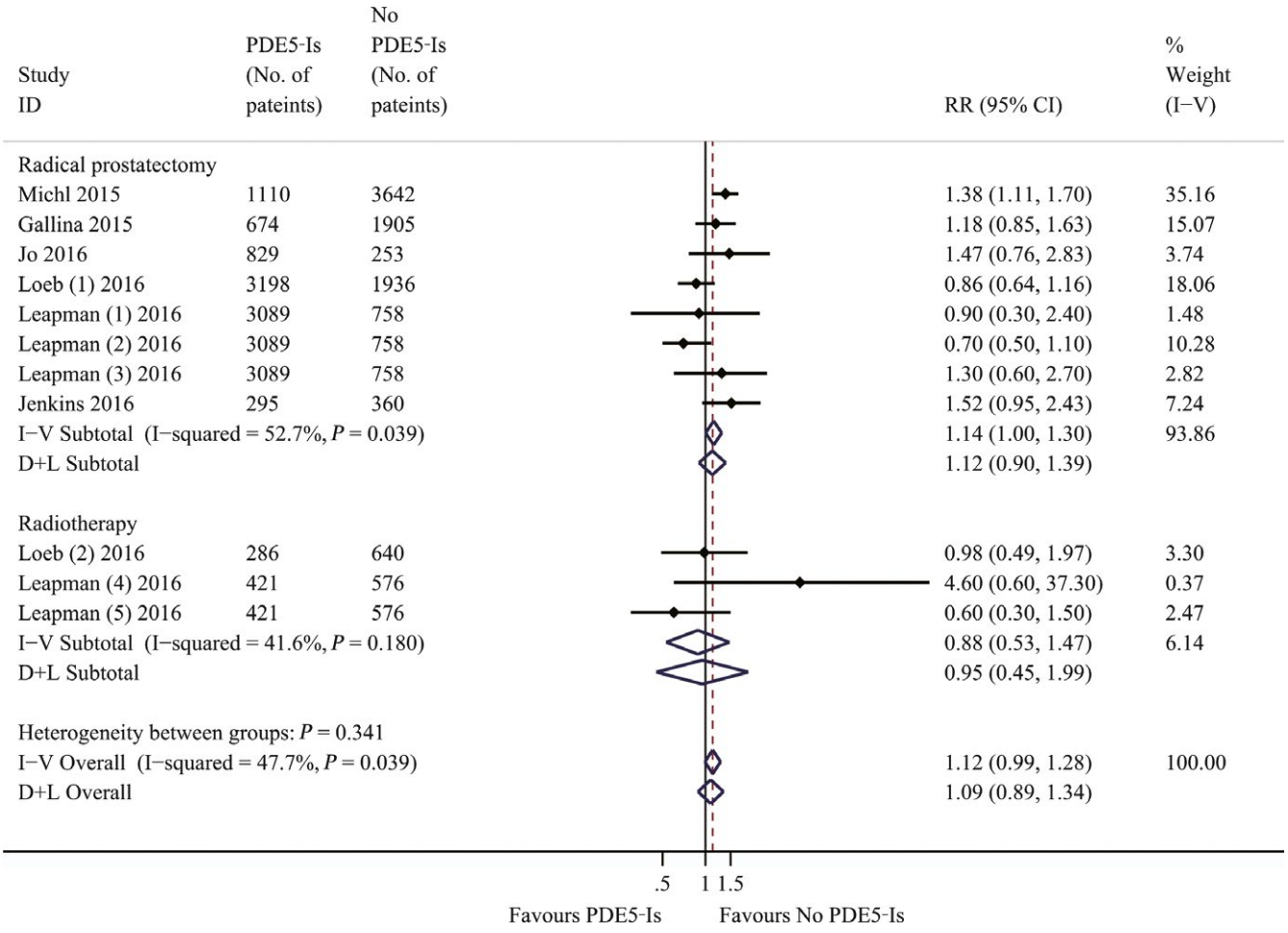

FIGURE 3 Forest plot showing pooled analyses and subgroup analyses for PDE5-Is use and BCR of prostate cancer after treatment. The squares and horizontal lines indicate the study-specific relative risks and 95% confidence intervals. The diamonds represent the pooled relative risk estimates with corresponding 95% confidence intervals

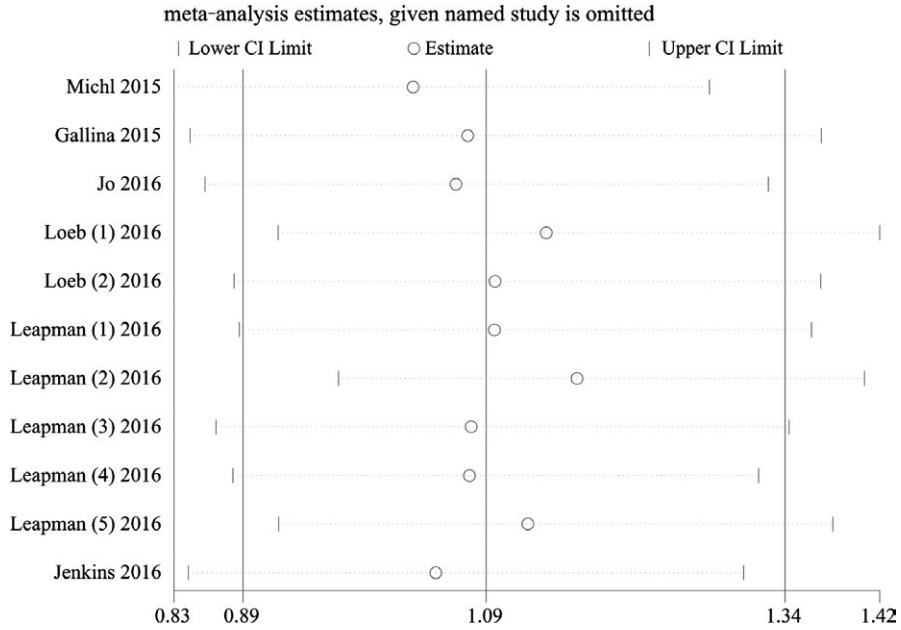

FIGURE 4 Sensitivity analyses for the effect of PDE5-Is use on the BCR of prostate cancer. The two ends of the dotted lines represent the 95% confidence interval

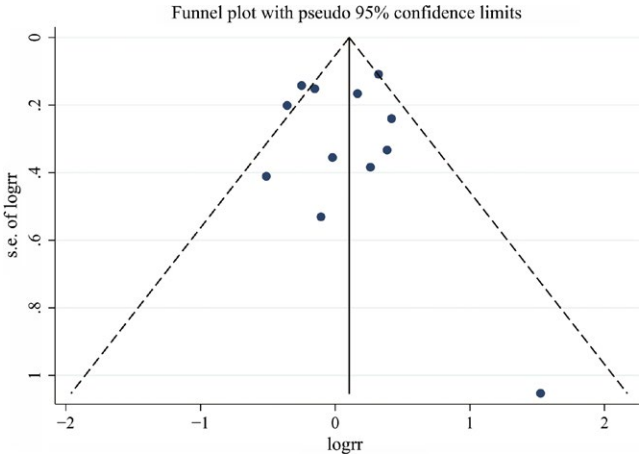

FIGURE 5 Funnel plot of the publication bias for BCR of prostate cancer analysis. Each dot represents a separate study for the indicated association

potential confounders (Chavez et al., 2013; Leapman et al., 2016; Machen et al., 2017), which may bias the estimate of each study and may influence the heterogeneity. Third, the dose–response analyses were not performed in this meta-analysis because data on PDE5-Is dose and frequency were unavailable in some of the included studies (Jenkins et al., 2016; Jo et al., 2016; Leapman et al., 2016; Michl et al., 2015).

In summary, our meta-analysis results indicate that PDE5-Is use does not influence the risk of prostate cancer, and BCR in prostate cancer patients following RP or RT. Future studies with large-scale population and longer follow-up are awaited to fully elucidate the relation between PDE5-Is use and prostate cancer risk.

ACKNOWLEDGEMENTS

The work was supported by Scientific Research Project of The Fifth People's Hospital of Shanghai, Fudan University (No. 2018WYZT05).

CONFLICT OF INTEREST

All authors announced no conflict of interests.

AUTHOR CONTRIBUTIONS

Yougen Wu and Xiaofeng Qu searched literature, extracted data, did the statistical analysis and drafted the manuscript. Yang Wang, Yuting Gu and Ju Xia were responsible for the study selection. Yougen Wu, Qingqing Qian and Yang Hong designed the study.

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How to cite this article: Wu Y, Qu X, Wang Y, et al. Effect of phosphodiesterase type 5 inhibitors on prostate cancer risk and biochemical recurrence after prostate cancer treatment: A systematic review and meta-analysis. *Andrologia*. 2018;e13198. https://doi.org/10.1111/and.13198