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REVIEW ARTICLE

Association between vasectomy and risk of prostate cancer: a meta-analysis

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Abstract

Background The debate over the association between vasectomy and prostate cancer has been lasted about 40 years and there is no sign of stopping. In the present study, we aimed to evaluate whether vasectomy is associated with prostate cancer based on the most comprehensive and up-to-date evidence available.

Methods The PubMed, Cochrane Library, and EMBASE databases were systematically searched inception to March 14, 2021 without year or language restriction. Multivariable adjusted risk ratios (RRs) were used to assess each endpoint. Risk of bias was assessed using the Newcastle-Ottawa scale.

Results A total of 58 studies involving 16,989,237 participants fulfilled inclusion criteria. There was significant association of vasectomy with risk of any prostate cancer (risk ratio, 1.18, 95% CI, 1.07–1.31). Association between vasectomy and advanced prostate cancer (risk ratio, 1.06, 95% CI, 1.01–1.12), low-grade prostate cancer (risk ratio, 1.06, 95% CI, 1.02–1.10), and intermediate-grade prostate cancer (risk ratio, 1.12, 95% CI, 1.03–1.22) were significant. There was no significant association between vasectomy and prostate cancer-specific mortality (risk ratio, 1.01, 95% CI, 0.93–1.10).

Conclusions This study found that vasectomy was associated with the risk of any prostate cancer and advanced prostate cancer. From the current evidence, patients should be fully informed of the risk of prostate cancer before vasectomy.

Introduction

Vasectomy is a widely used and highly efficacious long-term contraception method that involves a minor outpatient procedure under local anesthetic. It is less expensive and causes fewer complications than tubal ligation, the analogous female surgical sterilization procedure [1]. An estimated 33 million men worldwide rely on vasectomy for contraception [2].

Prostate cancer is the most common cancer and the second most common cause of cancer-related death among men in the United States. The etiology of prostate cancer is not well-known. Epidemiological evidence suggests that biological, environmental, and social factors all play a role in the initiation and progression of prostate cancer [3]. From the early 1980s, many studies have evaluated the epidemiologic association between vasectomy and prostate cancer. More than one study has been published almost every year over the past 40 years, but with inconsistent results [4–30]. Sheth et al. [31] first reported in 1982 on the relationship between vasectomy and the incidence of prostate cancer, and they found that vasectomy was a protective factor for prostate cancer. However, several high-quality cohort studies [25, 26, 30, 32, 33] obtained completely opposite outcomes and suggested that a positive association between vasectomy and prostate cancer. Meanwhile, a national population-based case-control study [14] from New Zealand found no association between prostate cancer and vasectomy nor with time since vasectomy. Similar results have been founded by several other studies [22, 28, 29, 34, 35].

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41391-021-00368-7.

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Several meta-analyses [36–41] aimed at closuring this debate have been performed, but the results of these studies were inconsistent and inconclusive. The earliest meta-analysis [36] was performed in 2002 and the results showed that men with a prior vasectomy had an increased risk of prostate cancer. However, all three subsequent meta-analyses [37–39] found that vasectomy was not associated prostate cancer risk. Controversially, the findings of two other studies both indicated a weak association between vasectomy and prostate cancer.

Since the publication of the above-mentioned meta-analyses, a number of large-scale and high-quality cohort studies [29, 30, 32, 42] have been published. Adding these studies to the above meta-analysis would augment the sample size, increase the accuracy of the effect size estimates and may change the pattern of outcomes. Therefore, a systematic review and meta-analysis based on the most comprehensive and up-to-date evidence available was performed. We aimed to examine the association between vasectomy and any prostate cancer, low-grade prostate cancer, intermediate-grade prostate cancer, high-grade prostate cancer, localized prostate cancer, advanced prostate cancer, and prostate cancer-specific mortality. This study also evaluated the effect of confounding factors on the association between vasectomy and prostate cancer.

Methods

This study was performed according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement [43] and the guideline for Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [44]. The protocol for this meta-analysis is available in PROSPERO (CRD42020173624).

Search studies

We used an extensive search strategy in order to retrieve as many related studies as possible. We systematic searched the PubMed, Cochrane Library, Web of Science, and EMBASE databases from the inception dates to March 14, 2021, using the keywords *prostate cancer*, *prostate neoplasm*, *prostate carcinoma*, *prostate tumor*, *prostate adenocarcinoma*, *vasectomy*, *vasoligation*, and *deferentectomy* to identify published records assessing the association between vasectomy and prostate cancer. Detailed search strategies are reported in eTable 1 in the Supplementary. References from published guidelines, commentaries, and previous systematic reviews were also considered as additional sources of potential studies. No language or date restrictions were applied in the searches. Two of our investigators independently screened all records to determine eligibility first by titles and abstracts, then by full texts. All disagreements were resolved through consultation with a third reviewer.

Inclusion and exclusion criteria

Studies were selected based on the following inclusion criteria: (1) study types were cohort, case-control, and cross-sectional studies; (2) studies that compared men with and without vasectomy; (3) studies that provided hazard ratios (RR), risk ratio (RR) or odds ratio (OR) relating vasectomy to prostate cancer outcomes, and corresponding 95% confidence interval (CI) (or available data to calculate them); (4) when there was more than one publication analyzing from the same patient cohort, we selected the most complete and recent one. Exclusion criteria were (1) studies lacking comparator groups were excluded, including editorials, traditional reviews, case reports, commentaries and meeting abstracts; (2) studies failed to weigh related confounding factors.

Outcome measures

The primary outcomes were the risk of any prostate cancer and prostate cancer-specific mortality. Secondary outcomes included the diagnoses of low-grade prostate cancer (based on a consistent definition, typically Gleason score ≤ 6), intermediate-grade prostate cancer (based on a consistent definition, typically Gleason score = 7), high-grade prostate cancer (based on a consistent definition, typically Gleason score ≥ 8), localized prostate cancer (based on a consistent definition, typically T1-2, N−, and M−), advanced prostate cancer (based on a consistent definition, typically T3/4, N+, or M+), age at vasectomy, and prostate-specific antigen (PSA) screening.

Risk-of-bias assessments

The Newcastle-Ottawa Scale (NOS) [45] was used to assess the risk of bias. The scale evaluates three elements: selection of the study groups, comparability of groups, and ascertainment of exposure and outcome. Studies with 7–9 scores were arbitrarily considered to be of high quality, those with 5–6 scores were classified as intermediate quality, and those with less than 4 scores were classified as low quality. Assessment of the risk of bias was performed independently by two of us. A third reviewer was consulted in case of disagreements.

Data extraction

After assessment of full-text articles, data were independently extracted by two investigators for further evaluation of qualitative and quantitative analyses. All extracted data were cross-checked to ensure their reliability. Discrepancies

were resolved by a senior reviewer. Data extraction was performed using a standardized data collection form. The following information was extracted from all included studies: lead author, publication year, study interval, region, participant characteristics, follow-up duration, age, outcomes, simple size, the number of patients with vasectomy, the number of patients diagnosed with prostate cancer, effects estimate with 95% CIs for the association of vasectomy and prostate cancer. Furthermore, we searched for baseline characteristics, methods, and important confounding factors to establish comparability. If multiple effects estimates were reported in the eligible studies, we extracted one from the largest adjusted pattern to reduce the risk of possible unmeasured data confounding.

Statistical analysis

The association between vasectomy and prostate cancer was assessed, and each type of grade, stage, age at vasectomy, and PSA screening have been considered. We performed meta-analysis to calculate risk ratios (RRs) and 95% CIs. Higgins I^2 statistic was used to evaluate the heterogeneity across the publications. $I^2 \geq 50\%$ indicated significant statistical heterogeneity [46]. If no significant heterogeneity ($I^2 < 50\%$) was found, a pooled estimate was calculated with the fixed-effects model (Mantel–Haenszel method). Otherwise, a random effects model (DerSimonian and Laird method) was selected. Subgroup analyses based on type of study, study location, risk-of-bias, follow-up duration, year of publication were conducted to explore the source of heterogeneity and assessed the influence of various exclusion criteria on the overall risk estimate. The funnel plots and Egger's test were conducted to assess the publication bias of this meta-analysis. $P > 0.05$ for Egger's test indicated no significant publication bias [47]. Sensitivity analyses were conducted to assess the stability of the results and to reduce the effect of individual publications on overall outcomes.

All meta-analyses were performed using Stata SE 12.0 (Stata Corp LP, College Station, TX, USA). All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Studies retrieved and characteristics

A total of 1135 articles were retrieved from PubMed, Cochrane Library, and EMBASE databases. After removal of duplicates, 538 potentially eligible records were identified. Titles and abstracts of these records were screened for inclusion. After a full-text review of 103 records, 58 of them met the inclusion criteria. The full screening procedure and the reasons for exclusion are summarized in Fig. 1 and eTable 2 in the Supplementary.

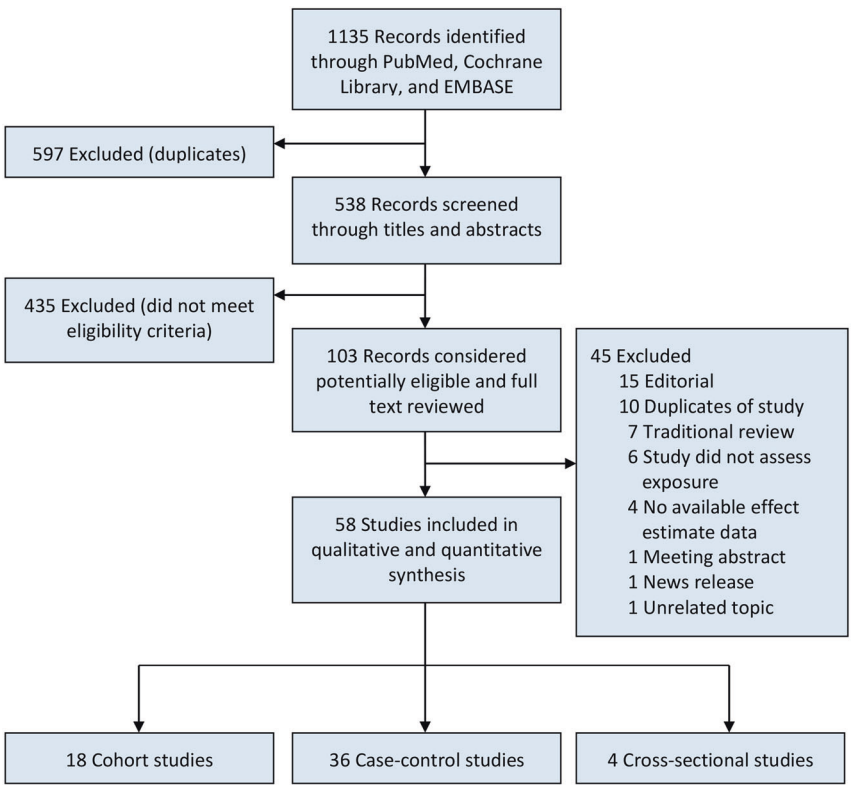

Fig. 1 Literature Search and Screening Process.

Table 1 Characteristics of 58 included studies.

Included study	Study population/ location	Study interval	Follow-up duration, y	Age[a],y		Outcome(s)	Sample size, No.	PCa, No.
				Vasectomy	No vasectomy			
Cohort studies ($n = 18$)								
Husby 2020	Denmark	1977–2014	24.8	38.3	NA	PCa, localized PCa, advanced PCa	2150162	26238
Seikkula 2020	Finland	1987–2014	11.13	39.7 (35.9–44.0)	NA	PCa	38124	413
Davenport 2019	US	1995–2011	18	61.8	60.8	PCa, low-grade PCa, high-grade PCa, localized PCa, advanced PCa	160571	13885
Smith 2017	Eight European countries[b]	1992–2012	15.4	52.0 (47.0–57.0)	54.0 (48.0–60.0)	PCa, high-grade PCa, localized PCa, advanced PCa	84743	4377
Shoag 2017	US	1993–2009	24	61.5 (4.8)	63.1 (5.4)	PCa, low-grade PCa, intermediate-grade PCa, high-grade PCa, advanced PCa	76693	978
Nayan 2016	Canada	1994–2012	10.9	37.3 (6.2)	37.3 (6.2)	PCa, intermediate-grade PCa, high-grade PCa, advanced PCa	653214	3462
Jacobs 2016	US	1982–2012	21.4	NA	NA	PCa, low-grade PCa, high-grade PCa, localized PCa, advanced PCa	363726	9133
Tangen 2016	US	1994–2003	7	NA	NA	PCa	8052	574
Eisenberg 2015	US	2001–2009	NA	NA	NA	PCa	873485	4905
Siddiqui 2014	US	1986–2010	24	51.8	55.5	PCa, low-grade PCa, intermediate-grade PCa, high-grade PCa, localized PCa, advanced PCa	49405	6023
Romero 2012	Brazil	2006–2011	1.8	NA	NA	PCa	2121	58
van Leeuwen 2011	The Netherlands	1993–2008	11.1	63	63	PCa, high-grade PCa, advanced PCa	19950	2420
Goldacre 2005	England	1963–1999	Vasectomy,12.7; no vasectomy, NA	NA	NA	PCa	184253	656
Rohrmann 2005	US	1989–2004	8.3	49.2 (9.0)	54.8 (11.3)	PCa, low-grade PCa, high-grade PCa, localized PCa, advanced PCa	3373	78
Lynge 2002	Denmark	1977–1995	12.7	NA	NA	PCa,	57931	46
Hiatt 1994	US	1979–1985	4.6	47.4 (13.0)	NA	PCa	43432	238
Schuman 1993	US	NA	Vasectomy, 8.3; no vasectomy, 8.8	36	NA	PCa	21180	13
Giovannucci 1993	US	1976–1989	11	42.0 (7.0)	42.2 (7.1)	PCa	25340	96
Case-control studies ($n = 36$)								
Nair-Shalliker 2017	Australia	2006–2014	NA	65.6	59.0	PCa	2056	1181
Cossack 2014	US	NA	NA	NA	NA	PCa	74	24
Hennis 2013	Barbados	2002–2011	NA	67.2 (9.0)	67.0 (9.2)	PCa	1904	NA
Jia 2013	China	2008–2013	NA	NA	NA	PCa	258	86

Table 1 (continued)

Included study	Study population/ location	Study interval	Follow-up duration, y	Age[a],y		Outcome(s)	Sample size, No.	PCa, No.
				Vasectomy	No vasectomy			
Kobayashi 2012	Canada	1997–1999	NA	65.1 (6.0)	63.6 (6.9)	PCa	414	80
Mazdak 2012	Iran	2005–2009	NA	73.1 (7.5)	67.9 (8.3)	PCa	190	95
Ganesh 2011	India	1999–2001	NA	64	45	PCa	275	123
Weinmann 2010	US	1974–2000	NA	NA	NA	PCa	1697	768
Sridhar 2010	US	2000–2005	NA	NA	NA	PCa	3710	1237
Tyagi 2010	India	1998–2000	NA	69.7	65.6	PCa	909	303
SchwingI 2009	China, Nepal, and Korea	1994–1997	NA	66.6 (6.1)	66.4 (6.1)	PCa	1173	294
Holt 2008	US	2002–2005	NA	NA	NA	PCa	1943	1001
Liang 2007	China	2005–2006	NA	69.5	69.0	PCa	186	62
Pourmand 2007	Iran	2005–2007	NA	70.5 (8.3)	65.7 (9.9)	PCa	205	130
Sunny 2005	India	1993–1996	NA	71.2	64.4	PCa	1170	390
Patel 2005	US	1996–1998	NA	NA	NA	PCa	1304	700
Jian 2004	China	2001–2002	NA	NA	NA	PCa	404	130
Lightfoot 2004	Canada	1995–199	NA	NA	NA	PCa	2354	744
Cox 2002	New Zealand	1996–1998	NA	66.3	65.1	PCa	2147	923
Emard 2001	Canada	1984–1993	NA	68.2 (2.8)	67.9 (2.9)	PCa	6349	2962
Lesko 1999	US	1992–1996	NA	NA	NA	PCa	2616	1216
Stanford 1999	US	1993–1996	NA	NA	NA	PCa	1456	753
Platz 1997	India	1993–1994	NA	67.3	59.1	PCa	1153	175
Zhu 1996	US	1989–1991	NA	NA	NA	PCa	433	175
Ewings 1996	England	1989–1991	NA	NA	NA	PCa	484	159
Andersson 1996	Sweden	1989–1991	NA	70.0 (6.1)	69.8 (6.2)	PCa	508	256
John 1995	US and Canada	1987–1991	NA	70.5	70.0	PCa	3278	1642
Rosenberg 1994	US	1977–1992	NA	NA	NA	PCa	7580	553
Hsing 1994	China	1989–1992	NA	NA	NA	PCa	776	138
Wei 1994	China	NA	NA	NA	NA	PCa	81	27
Hayes 1993	US	1986–1989	NA	NA	NA	PCa	2257	965
Spitz 1991	US	NA	NA	NAA	NA	PCa	703	343
Mettlin 1990	US	1982–1988	NA	68.4 (7.5)	64.9 (8.5)	PCa	3202	614
Newell 1989	US	1985–1987	NA	NA	NA	PCa	220	NA
Honda 1988	US	1979–1982	NA	NA	NA	PCa	392	1988
Ross 1983	US	1972–1980	NA	NA	NA	PCa	220	110

Table 1 (continued)

Included study	Study population/ location	Study interval	Follow-up duration, y	Age[a],y		Outcome(s)	Sample size, No.	PCa, No.
				Vasectomy	No vasectomy			
Cross-sectional studies ($n = 4$)								
Alqahtani 2015	US	2007–2011	NA	64.2 (14.7)	64.2 (14.7)	PCa	12000718	642383
Garzotto 2003	US	1993–2000	NA	66	66	PCa	1239	300
Chacko 2002	US	1998–2001	NA	65 (39–86)	65 (39–86)	PCa	303	144
DeAntoni 1997	US	1993–1995	NA	61.7 (8.0)	61.7 (8.0)	PCa	95961	766

PCa prostate cancer, *US* the United States, *IQR* interquartile range, *NA* not available.
[a]Age reported as median (interquartile range) or mean (standard deviation).
[b]Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden, and the United Kingdom.

The characteristics of the included studies were presented in Table 1. Of the 58 selected studies, 18 were cohort studies [7, 8, 22, 25–30, 32–35, 42, 48–51], 36 were case-control studies [4–6, 9–14, 16–21, 23, 24, 52–70], and 4 were cross-sectional studies [15, 71–73]. The number of participants from each included study for meta-analysis ranged from 74 to 12000718 participants (median, 2354 participants; mean, 287,953 participants). Overall, our meta-analysis comprised 16,989,237 participants, of which 4,836,935 (28.5%), 54,081 (0.3%) and 12,098,221 (71.2%) were from cohort studies, case-control studies and cross-sectional studies, respectively. All participants from 20 countries on five continents (Europe, North America, South America, Asia and Oceania). The geographic distribution of the studies included are shown in Fig. 2. Duration of follow-up varied widely among prospective cohort studies (ranging from 1.8 to 24.8 years). The patients with and without vasectomy were similar in age. Eight studies [22, 25, 27–30, 42, 48] focused on the effect of vasectomy on cancer-specific mortality. Only one study [30] found vasectomy reduced prostate cancer-specific mortality (RR = 0.54, 95% CI: 0.51–0.58), while seven other studies showed no significant association between vasectomy and prostate cancer-specific mortality (all $p > 0.05$). Detail assessment of risk of bias are summarized in eTable 3 in the Supplementary. Fifteen cohort studies [22, 25–30, 32–35, 42, 48, 49, 51] and nine cross-sectional studies [10, 14, 19, 24, 56, 61–63, 68] were assessed as having a low risk of bias.

Meta-analysis

Any prostate cancer

As shown in Fig. 3, the data from all 58 included studies were pooled to assess the association between vasectomy and any prostate cancer. Overall results showed that vasectomy significantly increases the risk of any prostate cancer (RR = 1.18, 95% CI: 1.07–1.31). However, there was significant heterogeneity among these studies ($I^2 = 93.8\%$, $p < 0.0001$). Similar outcomes were observed among cohort studies (RR = 1.09, 95% CI: 1.04–1.14) and case-control studies (RR = 1.20, 95% CI: 1.06–1.35). The funnel plots and Egger's test were used to evaluate the publication bias of the literatures. The shape of the funnel plots (Fig. 4) seemed symmetrical for all analyses, indicating no significant publication bias from the Egger's test ($p = 0.666$, eFig. 1 in the Supplementary).

Different stages of prostate cancer

Nine cohort studies [22, 25, 27–29, 32, 33, 42, 48] evaluated the association vasectomy and prostate cancer, stratified by grade. As shown in Fig. 5, the pooled results showed that vasectomy was associated with localized prostate cancer

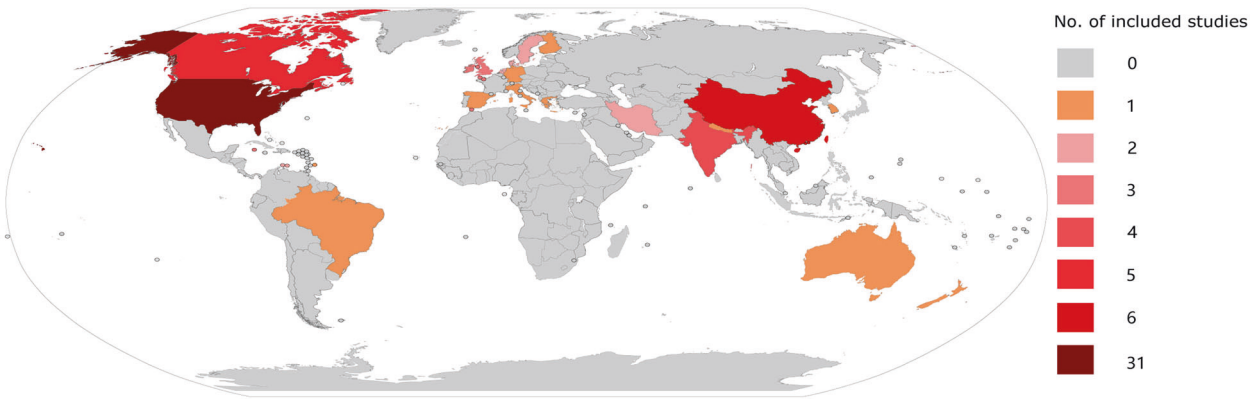

Fig. 2 Geographic distribution of included studies.

(RR = 1.08, 95% CI: 1.05–1.11; $I^2 = 46.7\%$) and advanced prostate cancer (RR = 1.06, 95% CI: 1.01–1.12; $I^2 = 0.0\%$).

Different grades of prostate cancer

Eight cohort studies [22, 25, 27–29, 33, 42, 48] evaluated the association between vasectomy and prostate cancer, stratified by grade. As shown in Fig. 6, the pooled results indicated that vasectomy increased the risk of low-grade (RR = 1.06, 95% CI: 1.02–1.10; $I^2 = 0.0\%$) and intermediate-grade (RR = 1.12, 95% CI: 1.03–1.22; $I^2 = 9.8\%$) prostate cancer, but did not increase the risk of high-grade (RR = 1.05, 95% CI: 0.96–1.14; $I^2 = 36.1\%$) prostate cancer.

Subgroup analyses

Table 2 summarizes results of subgroup analyses for vasectomy and the risk of any prostate cancer. Vasectomy significantly increased the risk of any prostate cancer in participants in Europe (RR = 1.11, 95% CI: 1.04–1.19) and North America (RR = 1.23, 95% CI: 1.07–1.42), but was not statistically significant in participants in Asia (RR = 1.10, 95% CI: 0.75–1.60) and Oceania (RR = 0.98, 95% CI: 0.84–1.15). Subgroup analyses based on risk-of-bias stratification showed that vasectomy was significantly associated with prostate cancer risk in studies with low risk of bias (RR = 1.09, 95% CI: 1.04–1.14), but not significant in studies with intermediate (RR = 1.19, 95% CI: 1.00–1.41) and high (RR = 1.31, 95% CI: 1.02–1.70) risk of bias. Vasectomy significantly increased the risk of prostate cancer in studies with follow-up duration longer than 10 years (RR = 1.07, 95% CI: 1.04–1.11), but not significant in studies with follow-up duration <10 years (RR = 1.11, 95% CI: 0.75–1.64). We grouped all included studies according to the year of publication, with a 10-year interval (2011–2020, 2001–2010, 1991–2000, and 1981–1990). Results from subgroup analyses showed that studies published in the last decade (2011–2020) were more inclined to vasectomy significantly increased the risk of prostate cancer (RR = 1.21, 95% CI: 1.03–1.42), but not significant in studies with published in 2001–2010 (RR = 1.11, 95% CI: 0.95–1.31), 1991–2000 (RR = 1.21, 95% CI: 1.00–1.46), and 1981–1990 (RR = 1.38, 95% CI: 0.97–1.97).

Prostate cancer-specific mortality

Seven cohort studies [22, 25, 27–29, 42, 48] reported on the association between vasectomy and prostate-specific mortality. As shown in Fig. 7, vasectomy did not increase prostate cancer-specific mortality (RR = 1.01, 95% CI: 0.93–1.10). There was no significant heterogeneity ($I^2 = 11.1\%$, $p = 0.345$), and the funnel plots (eFig. 2) and Egger's ($p = 0.792$, eFig. 3 in the Supplementary) showed little publication bias among these studies. Sensitivity analysis showed that our results were relatively stable. (eTable 4)

Age at vasectomy and PSA screening

Six cohort studies [25, 28, 32, 33, 35, 42] and eleven case-control studies [9, 11, 12, 14, 17, 19, 20, 62, 63, 65, 68] reported effect estimates stratified by age at vasectomy. Of those, several studies [12, 17, 28, 65, 68] found that the relationship between vasectomy and the risk of prostate cancer was stronger among patients who underwent their vasectomy performed at a younger age. On the contrary, some studies [11, 33] found that the patients who were older when they underwent their vasectomy were at higher risk for incident any prostate cancer. The rest of these studies supported that age at vasectomy had no effect on development of prostate cancer. Since the age groupings between these studies were not exactly the same, we could only select studies with consistent groupings for data pooling. eFigure 4 shows results of the meta-analysis. Vasectomy

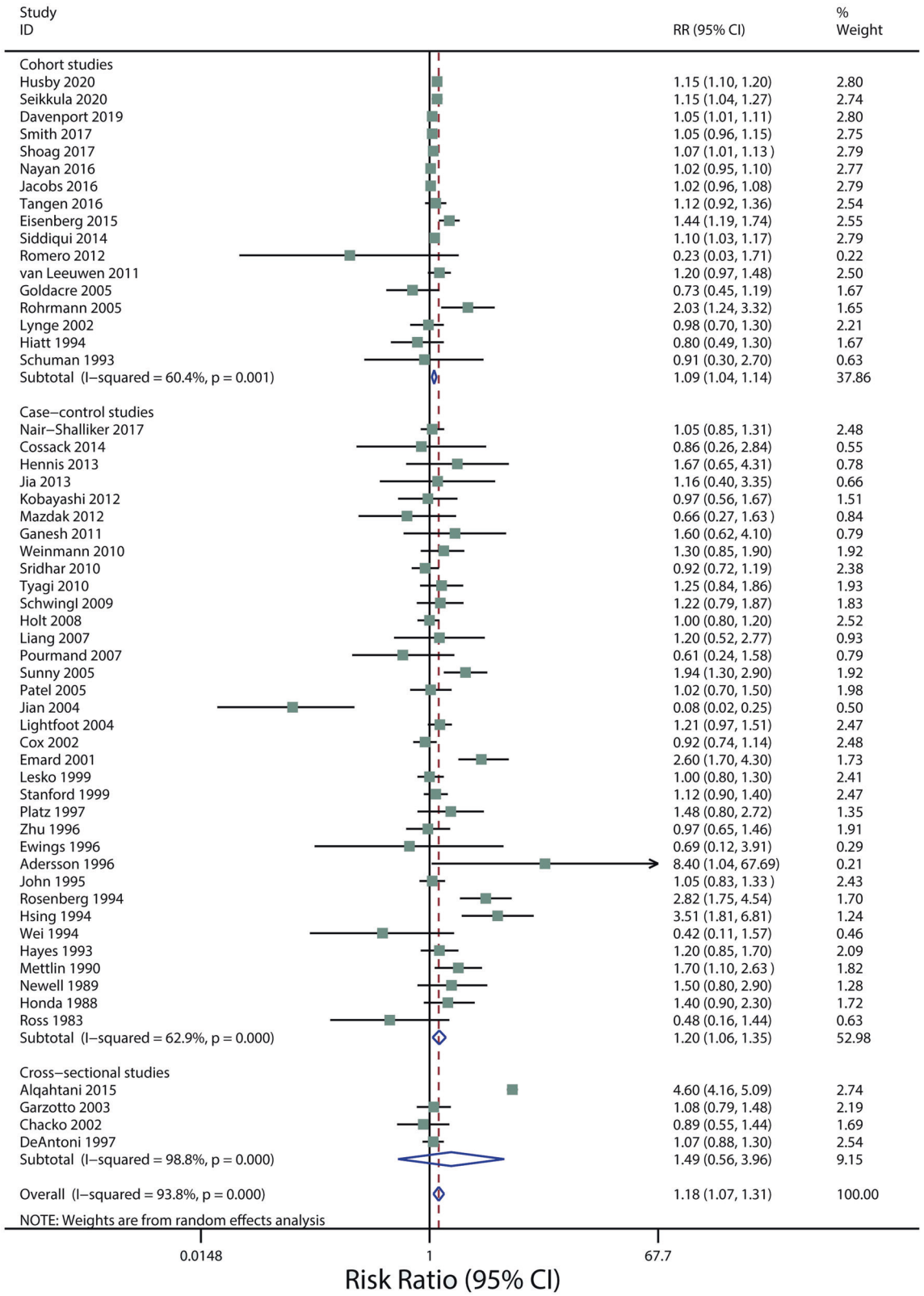

Fig. 3 Forest Plots of Meta-analysis for the Association Between Vasectomy and Any Prostate Cancer.

after age 40 was associated with prostate cancer risk (RR = 1.29, 95% CI: 1.00–1.66; $I^2 = 44.3\%$). That was not significant before age 40 (RR = 1.26, 95% CI: 0.76–2.08; $I^2 = 47.2\%$). PSA screening was considered as a variable in seven cohort studies [25, 28–30, 42, 48, 49]. Studies [25, 29, 30, 42] reporting regular PSA screening rate have found that the rate of regular PSA screening and the incidence of prostate cancer in vasectomized men were significantly higher than those without vasectomy. eFigure 5 showed results of the meta-analysis, regular PSA screening was associated with prostate cancer (RR = 1.06, 95% CI: 1.04–1.09; $I^2 = 0.6\%$) among vasectomized men.

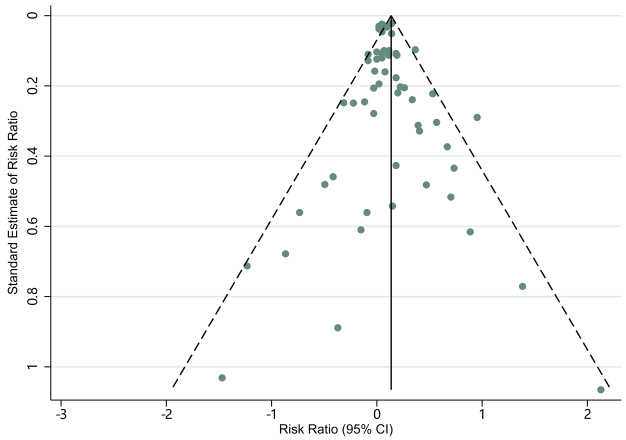

Fig. 4 Funnel Plots for Publication Bias in the Studies Investigating Vasectomy and Any Prostate Cancer Risk.

Discussion

The debate over the association between vasectomy and prostate cancer has been lasted about 40 years. Numerous original studies, meta-analyses, reviews, editorials, comments and meeting abstracts tried to end this debate. These publications demonstrated either inconsistent or contradictory results. The present meta-analysis included current comprehensive and updated clinical evidence and minimized heterogeneity through subgroup analysis and quality evaluation. Results of this meta-analysis showed that vasectomy was significantly associated with a higher incidence of any prostate cancer. Meanwhile, the associations between vasectomy and low-grade, intermediate-grade, and advanced prostate cancer were similar to those for any diagnoses of prostate cancer. However, the prostate cancer-specific mortality was not affected by previous vasectomy. We also found that vasectomy was not associated with high-grade prostate cancer. Furthermore, subgroup analyses showed that these results were consistent with those published in the past decade with sufficient follow-up and low risk of bias.

Several limitations of previous meta-analyses lead to their results should be interpreted with caution. First, they

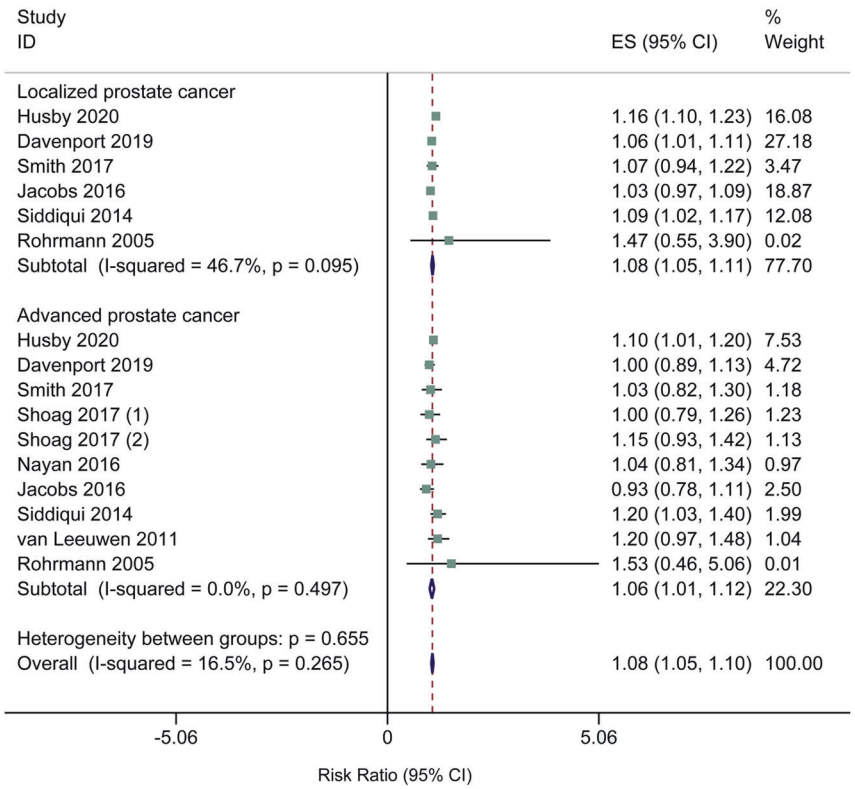

Fig. 5 Forest Plots of Meta-analysis for the Association Between Vasectomy and Localized and Advanced Prostate Cancer.

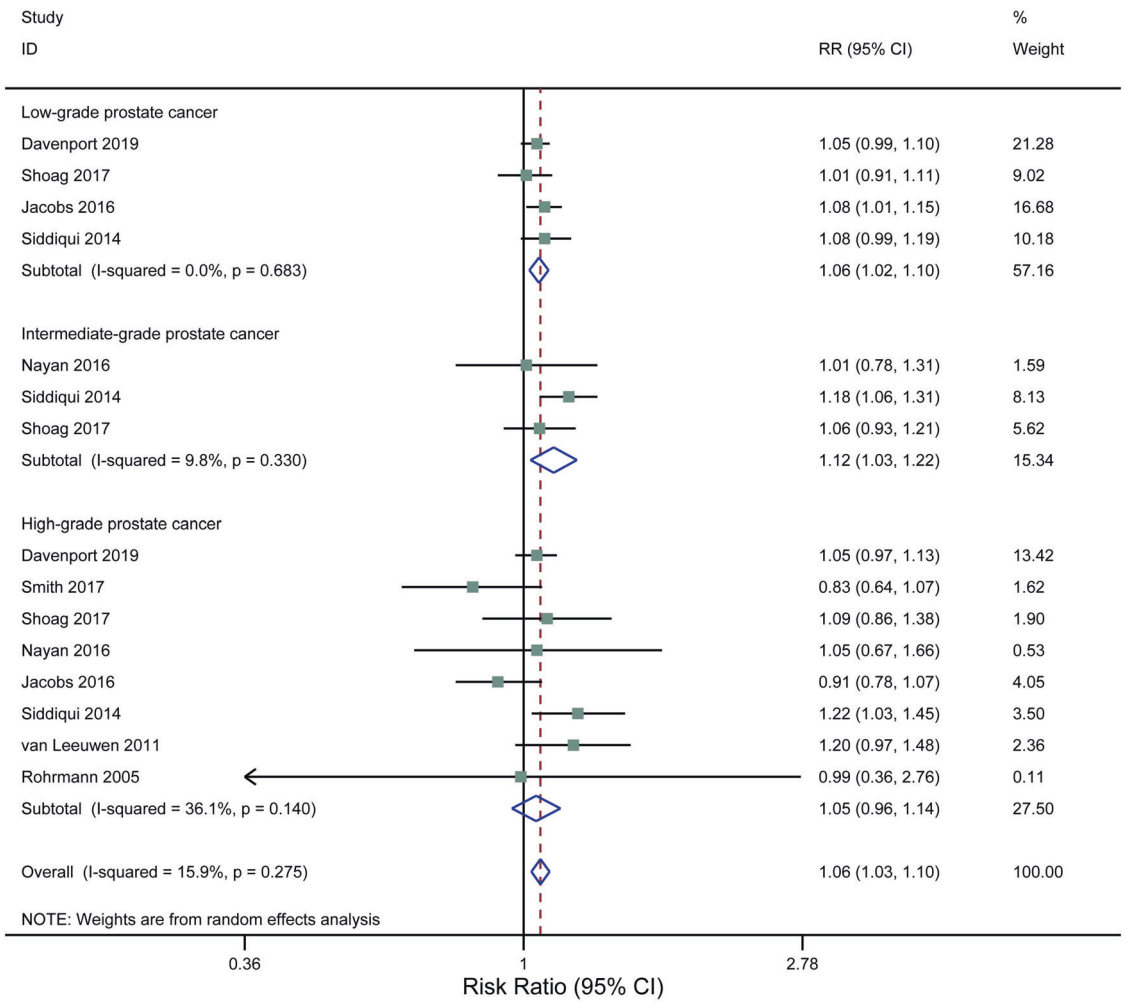

Fig. 6 Forest Plots of Meta-analysis for the Association Between Vasectomy and Low-grade, Intermediate-grade, and High-grade Prostate Cancer.

failed to evaluated the association between vasectomy and different grade and stage of prostate cancer. Some studies [22, 25, 27–29, 33, 48] have reported significant differences in the effects of vasectomy on low-grade, intermediate-grade, and high-grade prostate cancer. Similar differences were found between localized prostate cancer and advanced prostate cancer [22, 25, 27–29, 32, 33, 42, 48]. In the current analyses, vasectomy was not associated with high-grade disease, but significantly increased low-grade, intermediate-grade, localized, and advanced prostate cancer. These finding will help us to reflect on the prevention and management of prostate cancer from another perspective. Second, the potential heterogeneity between related studies on this subject has been a major focus of criticism. Some confounding variables may influence the association between vasectomy and prostate cancer, such as age at vasectomy, PSA screening, and follow-up duration. In the current analyses, we considered important confounding factors and performed effective subgroup analyses, which would be beneficial for more accurate assessment of the association between vasectomy and prostate cancer. Last but not least, the quality of the included studies was highly variable. Standard quality assessment system should be implemented in every included study. In the current analyses, we stratified all included studies based on quality grades, and we found that pooled results of high-quality studies supported statistical association between vasectomy and prostate cancer.

The biologic mechanisms of the association between vasectomy and prostate cancer are not clear. Previous theories include immunologic responses [51], changes to cell proliferation [74] and endocrine function [25]. An animal study [51] confirmed a significant increase in serum sperm autoantigens after vasectomy, which was considered evidence of immune responses due to obstruction. Vasectomy by eliminating the flow of testicular and epididymal fluids to the prostate may also reduce local immune factor, for example lymphocyte activated killer cells, which prevent the development of prostate cancer [75]. Another animal experiment [74]

Table 2 Subgroup analysis of association between vasectomy and any prostate cancer risk.

Variable	No. of studies	No. of participants			Prostate cancer, RR (95%)	*P* Value[a]
		Vasectomy	Prostate cancer	Total		
Study location						
Europe	8	278248	34565	2927968	1.11 (1.04–1.19)	0.12
North America	33	723813	698414	18484047	1.23 (1.07–1.42)	<0.01
Asia	12	619	1953	6780	1.10 (0.75–1.60)	<0.01
Oceania	2	549	2104	4203	0.98 (0.84–1.15)	0.40
Risk-of-Bias						
Low risk	24	969414	77527	9239294	1.09 (1.04–1.14)	<0.01
Intermediate risk	18	2951	11854	79510	1.19 (1.00–1.41)	<0.01
High risk	10	790	4120	8094	1.31 (1.02–1.70)	0.04
Follow-up Duration						
>10 years	11	840417	67631	8321877	1.07 (1.04–1.11)	0.02
≤10 years	5	14411	961	78158	1.11 (0.75–1.64)	0.04
Year of publication						
2011–2020	20	877093	138293	20969240	1.21 (1.03–1.42)	<0.01
2001–2010	18	86564	10868	270650	1.11 (0.95–1.31)	<0.01
1991–2000	14	39449	7076	181195	1.21 (1.00–1.46)	<0.01
1981–1990	4	382	2712	4034	1.38 (0.97–1.97)	0.22

RR risk ratio.

[a]*P* Value for heterogeneity between subgroups.

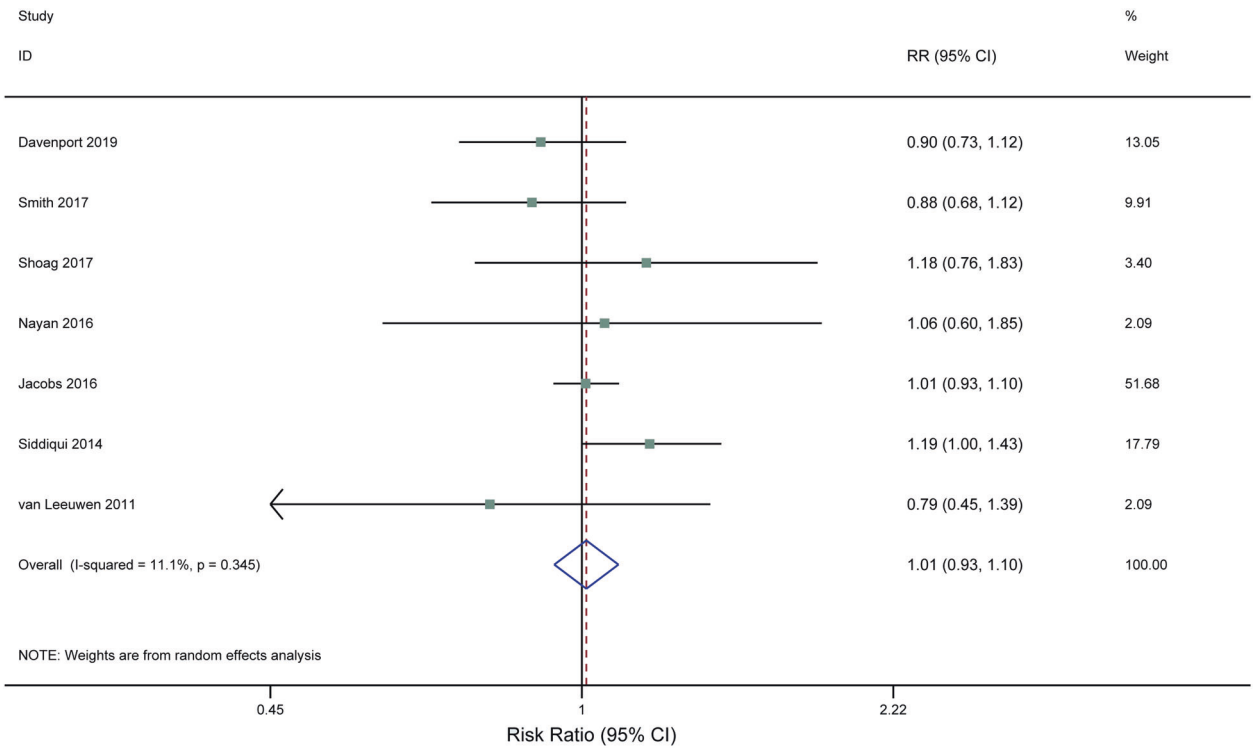

Fig. 7 Forest Plots of Meta-analysis for the Association Between Vasectomy and Prostate Cancer-specific Mortality.

found that the apoptotic cell indices in the secretory epithelium of the ductal system of vasectomized rats was significantly higher than controls. Imbalance of cell proliferation caused by vasectomy may play a special role in the initiation and development of prostate cancer. However, the findings of these animal experiments have

not been corroborated in humans. Therefore, these possible biologic rationales should be interpreted with caution. Serum dihydrotestosterone and testosterone were found to be significantly higher in men with vasectomy than corresponding controls [76]. Disorders in hormone levels may undoubtedly increase risk of prostate cancer.

Some studies have found that low ejaculation frequency increases subsequent prostate cancer risk [76–78]. A prospective cohort study [77] involving 31,925 participants found that more frequent ejaculation throughout adult lift was beneficial for reducing prostate cancer risk, especially for low-risk disease. Vasectomy can be considered as an extreme state with ejaculation frequency as low as zero. Therefore, this finding supports the rationality of vasectomy to increase prostate cancer risk from another perspective. This association may involve the prostate stagnation hypothesis [79]. Prostate stagnation hypothesis suggests that potentially carcinogenic secretions accumulate constantly in the prostate, which may create more opportunity for prostate cancer development.

It is worth noting that men who have undergone vasectomy have a higher likelihood of PSA testing, which may lead to a higher detection rate of prostate cancer. A nationwide population-based cohort by Seikkula [30] found that vasectomized men were more likely to undergo regular PSA tests than other men of the same age. Patients were informed about the possible risks before vasectomy, so they paid more attention to PSA screening and even a healthier general lifestyle, such as quitting smoking and exercising more, which were the protective role of subsequent prostate cancer. A number of previous studies [25, 29, 42, 48, 49], in which PSA screening was accounted for, supported this finding.

The publication year between included studies spans nearly 40 years. Previous studies have reported that the year of publication may be one of the sources of heterogeneity between included studies [36]. Results of subgroup analyses based on publication year showed that studies published in the last decade (2011–2020) were more inclined to vasectomy significantly increased the risk of prostate cancer, but not significant in studies with published before 2010. It was not difficult to find that the risk-of-bias of studies published the last decade was relatively lower. This may support the positive association between vasectomy and prostate cancer risk from another perspective.

This study has several limitations. First, some included studies did not report baseline, such as age vasectomy [4–24, 26, 27, 29, 30, 34, 48–52, 54–61, 63, 65–69, 71–73], follow-up duration [4–6, 9–21, 23, 24, 26, 52–61, 63, 65–69, 71, 73]. The subgroup results might have been different if all individuals were reported. Second, some case-control studies and cross-sectional studies were of poor quality and, for example, used unclear ascertainment of exposure [6–8, 11, 21–23, 25, 33, 35, 49, 50, 54–59, 61, 65, 67, 69]. Third, this meta-analysis is based on observational studies because randomized controlled trials concerning this topic are neither currently available nor likely to be conducted in the future. Fourth, publication bias between included studies cannot be completely eliminated. Subgroup analyses and sensitivity analyses have been performed to reduce the heterogeneity. Sixth, follow-up duration and age at vasectomy, it was difficult to obtain complete data, which may be confounding factors of the association between vasectomy and prostate cancer.

Conclusions

This study found that vasectomy was associated with the risk of any, localized, advanced, low-grade, and intermediate-grade prostate cancer. Meanwhile, vasectomy was not associated with prostate cancer-specific mortality. Overall, from the current evidence, patients should be fully informed of the risk of prostate cancer before vasectomy.

Author contributions YWX, JCZ, KNZ, ZZ, YQG and KG contributed to the conception and design this study. JCZ, KNZ, LL, WPY, KFM, and HBX carried out the development of the methology. YWX, LC and LL analyzed and interpreted the data. YWX wrote the paper. All authors read and approved the final paper.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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