Review Article

Does vasectomy increase prostate cancer risk? An updated meta-analysis and systematic review of cohort studies

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Abstract: Introduction: A positive association between vasectomy and prostate cancer risk has been observed in many case-control and cohort studies. However, additional studies reported no such association. Because clarification of the relationship between vasectomy and prostate cancer incidence is warranted, we retrieved recent high-quality cohort studies up to 2016 to perform an updated meta-analysis to reevaluate this relationship. Methods: We searched online databases, including PubMed, EMBASE, Web of Science, Cochrane Library and Google Scholar, to identify suitable studies through the end of October 2016 with no lower date limit. Summary relative risks (RRs) and 95% confidence intervals (CIs) were obtained using a random effects model. Results: Fourteen studies proved eligible for inclusion, including 21,125 cases and 1,711,788 participants. The pooled RR estimate of 1.07 (95% CI: 0.99-1.16) suggested the absence of a significant association between prostate cancer risk and vasectomy (P = 0.08). However, significant heterogeneity was observed in our study (I² = 61%, P < 0.05). To reduce or explain the high heterogeneity, we conducted a subgroup analysis among the studies using the follow-up duration in years and the different geographic locations of the participants. Furthermore, we performed a sensitivity analysis to assess the heterogeneity by removing one study at a time. When two studies were excluded, the heterogeneity of the remaining 12 studies was acceptable. Conclusion: Our results demonstrate that vasectomy is not associated with prostate cancer risk and support vasectomy as a safe contraception method in men.

Keywords: Vasectomy, prostate cancer, meta-analysis

Background

Vasectomy is a common and permanent birth control method. However, a possible association between vasectomy and increased prostate cancer (PC) risk has raised concerns since the early 1990s, prompting questions about the long-term safety of vasectomy. Prostate cancer is the second most frequently diagnosed cancer in men and the fifth most common cancer reported in the world. Although positive associations between vasectomy and prostate cancer were observed in many case-control and cohort studies [1-9], additional studies found no relationship between them [10-22]. Among the latter, the two largest prospective cohort studies reached contrasting conclusions. Of these two studies, the report from the Health Professionals Follow-Up Study (HPFS) considered that vasectomy was associated with a small increased risk of prostate cancer overall and particularly, an increased incidence of lethal prostate cancer [5]. In contrast, a report that included an analysis of the Cancer Prevention Study II (CPS-II) and the CPS-II Nutrition Cohort did not support associations between vasectomy and either prostate cancer incidence or prostate cancer mortality [10].

Two recent meta-analyses attempted to explore the relationship between prostate cancer incidence and vasectomy from pooled cohort studies. However, despite their inclusion criteria, these meta-analyses failed to retrieve a high number of cohort studies: one included 10 cohort studies [23] and the other included 9 [24]. Two large prospective cohort studies
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The association between vasectomy and prostate cancer risk warrants clarification. Therefore, we retrieved additional and more robust cohort studies to perform an updated meta-analysis to reevaluate the relationship between vasectomy and prostate cancer incidence up to 2016.

Methods

Study search strategy

We searched online databases, including PubMed, EMBASE, Web of Science, Cochrane Library and Google Scholar, to identify suitable studies through the end of October 2016 with no lower date limit. All initially identified studies were further filtered on the basis of predetermined relevant Medical Subject Heading (MeSH) terms or keywords. The following MeSH terms or keywords were used with all possible combinations considered: vasectomy, vasoligation, prostate neoplasms, prostate cancer, prostate carcinoma, prostate adenocarcinoma, cohort studies and human. We attempted to contact all corresponding authors when data were missing.

Identification of articles and data abstraction

The original published articles from 660 relevant citations were retrieved for full review using the following inclusion criteria: 1. the study used a cohort design; 2. the study reported the association between vasectomy and prostate cancer risk; 3. the study reported relative risks (RRs) or hazard ratios (HRs) to estimate prostate cancer outcomes after vasectomy, and the corresponding 95% confidence intervals (CIs); and 4. the study was published in English. We included 14 studies by this pro-

Figure 1. Flowchart for the record selection process of the meta-analysis.

included 69,033 participants published this year (2016) [10, 22]. Nayan, M., et al used a population based approach and relied on validated, comprehensive databases [22]. Neither meta-analysis included the two large prospective studies on this topic published this year (2016). These shortcomings may challenge the results obtained from the meta-analyses. Given the frequency of vasectomy, even a small increased risk of prostate cancer would constitute a major public health problem. It is better to make well-informed choices about long-term methods of birth control.
### Table 1. Characteristics of the 14 eligible studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study population/location</th>
<th>Time period (years)</th>
<th>Mean duration of follow-up (years)</th>
<th>Range of age (years) mean SD</th>
<th>Diseased/participants (n)</th>
<th>Adjusted RR (95% CI)</th>
<th>Variable adjustment</th>
<th>NOS score (max: 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sidney et al. (1991)</td>
<td>the Northern California Kaiser Permanente Medical Care Program, USA</td>
<td>1977-1987</td>
<td>6.8</td>
<td>45.8</td>
<td>135/20466</td>
<td>1 (0.7-1.6)</td>
<td>Age, race, marital status, and date and location of the examination</td>
<td>7</td>
</tr>
<tr>
<td>Nienhuis et al. (1992)</td>
<td>Oxford record linkage study, UK</td>
<td>1970-1986</td>
<td>6.6</td>
<td>25-49</td>
<td>6/35442</td>
<td>0.44 (0.1-4.0)</td>
<td>Age</td>
<td>6</td>
</tr>
<tr>
<td>Giovannucci et al. (1993)</td>
<td>the Health Professionals Follow-up Study (HPFS), USA</td>
<td>1986-1990</td>
<td>4</td>
<td>40-75</td>
<td>300/47855</td>
<td>1.66 (1.25-2.21)</td>
<td>Age, region, race, marital status</td>
<td>5</td>
</tr>
<tr>
<td>Giovannucci et al. (1993)</td>
<td>Nurses’ Health Study (NHS) reported vasectomy as the couple’s form of contraception, USA</td>
<td>1976-1989</td>
<td>13</td>
<td>N*</td>
<td>96/29214</td>
<td>1.56 (1.03-2.37)</td>
<td>N*</td>
<td>5</td>
</tr>
<tr>
<td>Hiatt et al. (1994)</td>
<td>the Kaiser Permanente Medical Care Program, USA</td>
<td>1978-1985</td>
<td>7</td>
<td>47.4±13</td>
<td>238/43432</td>
<td>0.8 (0.5-1.3)</td>
<td>Age, race, education level</td>
<td>6</td>
</tr>
<tr>
<td>Moller et al. (1994)</td>
<td>Danish record-linkage study, Denmark</td>
<td>1977-1989</td>
<td>12</td>
<td>N*</td>
<td>165/73917</td>
<td>0.98 (0.84-1.14)</td>
<td>N*</td>
<td>6</td>
</tr>
<tr>
<td>DeAntoni et al. (1997)</td>
<td>Prostate cancer awareness week, USA</td>
<td>1993-1995</td>
<td>3</td>
<td>40-95</td>
<td>766/95961</td>
<td>1.07 (0.88-1.3)</td>
<td>N*</td>
<td>5</td>
</tr>
<tr>
<td>Lyng et al. (2002)</td>
<td>Denmark</td>
<td>1977-1995</td>
<td>12.7</td>
<td>25-49</td>
<td>46/733203</td>
<td>0.98 (0.73-1.31)</td>
<td>Age</td>
<td>7</td>
</tr>
<tr>
<td>Goldacre et al. (2005)</td>
<td>National Health Service (NHS), UK</td>
<td>1963-1999</td>
<td>12.7</td>
<td>20-59</td>
<td>656/184253</td>
<td>0.74 (0.45-1.14)</td>
<td>Age, place of residence</td>
<td>7</td>
</tr>
<tr>
<td>Rohmann et al. (2005)</td>
<td>CLUE II cohort study, USA</td>
<td>1989-2004</td>
<td>8</td>
<td>35.2±6.9</td>
<td>78/3373</td>
<td>2.03 (1.24-3.32)</td>
<td>Age, body mass index, cigarette smoking history, family history of prostate cancer, alcohol consumption, intake of food</td>
<td>8</td>
</tr>
<tr>
<td>Romero et al. (2012)</td>
<td>Brazil Health Care System, Brazil</td>
<td>2006-2011</td>
<td>1.8</td>
<td>&gt; 40</td>
<td>57/2118</td>
<td>0.26 (0.06-1.04)</td>
<td>Age, race, ethnicity, family history, school level, increased blood pressure, diabetes mellitus and urethritis</td>
<td>7</td>
</tr>
<tr>
<td>Siddiqui et al. (2014)</td>
<td>Health Professionals Follow-up Study (HPFS), USA</td>
<td>1986-2010</td>
<td>24</td>
<td>40-75</td>
<td>6023/49405</td>
<td>1.1 (1.04-1.17)</td>
<td>Age, race, height, current body mass index, vigorous physical activity, smoking, diabetes, family history of prostate cancer, multivitamin use, intake of supplemental vitamin E and alcohol, and history of PSA testing</td>
<td>8</td>
</tr>
<tr>
<td>Jacobs et al. (2016)</td>
<td>The Cancer Prevention Study-II (CPS-II) Nutrition Cohort study, USA</td>
<td>1992-2011</td>
<td>20</td>
<td>40-80</td>
<td>9133/66542</td>
<td>1.02 (0.99-1.2)</td>
<td>Age, race, education, body mass index, and smoking</td>
<td>8</td>
</tr>
<tr>
<td>Nayan et al. (2016)</td>
<td>Multiple validated healthcare databases in Ontario</td>
<td>1994-2012</td>
<td>10.9</td>
<td>20-65</td>
<td>3462/326607</td>
<td>1.02 (0.95-1.09)</td>
<td>visits to specialists, urologists, and emergency departments in the year before the index date; and visits to general practitioners between the index date and end of follow-up</td>
<td>8</td>
</tr>
</tbody>
</table>

Note: *: undefined. NOS score: 1, Representativeness of the exposed cohort; 2, selection of the non-exposed cohort; 3, ascertainment of exposure; 4, demonstration that outcome of interest was not present at start of study; 5 and 6, comparability of cohorts on the basis of the design or analysis; 7, assessment of outcome; 8, was follow-up long enough for outcomes to occur; 9, adequacy of follow-up of cohorts.
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Figure 2. Pooled estimate of the association between vasectomy and prostate cancer.

cess (Figure 1). No attempt was made to restrict the search according to more specific methodological characteristics. The studies were reviewed by two independent investigators (X.D. and XS.Y.) to determine whether they met the eligible criteria for inclusion. Discrepancies between the investigators regarding inclusion were resolved by discussion.

Quality assessment of the included studies

Each included article was appraised by two reviewers (X.D. and XS.Y.) who assessed the methodological quality of the selected studies independently from the included studies. Two reviewers assessed the representativeness and the applicability of the study groups, the comparability of the groups, the evaluation of the outcomes, the data source, the study period, the study population characteristics, the total number of participants, the cases of prostate cancer and the follow-up duration.

Data synthesis and data analysis

STATA version 14.0 (Stata Corporation, College Station, TX, USA) was used to analyze the strength of the association between vasectomy and prostate cancer risk from the summary RRs and 95% CIs using a random effects model. Statistical heterogeneity was assessed by the chi-square $X^2$ test and was expressed by the $I^2$ index as described by Higgins et al. $P$ values $< 0.05$ was considered to indicate statistical significance. $I^2 < 50\%$ indicated acceptable heterogeneity. We conducted a single sensitivity analysis with one cohort trial omitted from the primary analysis at a time. Subgroup analysis was also used to evaluate the heterogeneity by dividing the group according to the patient geographic location and follow-up duration. We used Begg’s adjusted rank correlation test and Egger’s regression asymmetry test to detect publication bias; $P < 0.05$ for both tests was considered to represent significant statistical publication bias.

Results

Literature search and study characteristics

We identified 264 unique citations, whereas 396 were excluded because they were duplicates. During further screening, we excluded
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243 citations that did not meet one or more inclusion criteria (e.g., studies that were reviews, comments, case reports, case-control studies or other types of excluded studies). During full-text screening we excluded an additional 7 articles. Finally, 14 studies proved eligible, including 21,125 cases and 1,711,788 participants (Figure 1) [5-10, 15-22].

Table 1 shows the study characteristics and methodology for selecting the 14 eligible studies included in the systematic review. All were cohort studies. Eight studies were performed in the United States (USA) [5, 7-10, 17, 19, 21], 4 were performed in Europe [15, 16, 18, 20], 1 was performed in Canada, and 1 was performed in Brazil [6]. The follow-up periods ranged from 1.8 to 24 years. The number of participants included in these studies ranged from 2,118 to 733,203. A total of 21,125 people was diagnosed with prostate cancer. The population data sources were almost all from large epidemiological investigations such as the HPFS program. All publications reported similar outcomes and provided RRs or HRs to estimate prostate cancer outcome after vasectomy, and the corresponding 95% CIs. Among these 14 studies, 4 studies reported a positive association between prostate cancer risk and vasectomy involving 6,497 cases and 129,847 participants [5, 7-9]; the other 10 studies concluded that vasectomy was not associated with increased PC risk and included 14,628 cases and 1,581,941 participants [6, 10, 15-22].

Overall analysis and subgroup analysis

Overall, the pooled RR estimate was 1.07 (95% CI: 0.99-1.16) based on 14 studies using a random effects model, suggesting no significant association between prostate cancer risk and vasectomy (P = 0.08) (Figure 2). Despite the random effects model used, the studies appeared heterogeneous (I² = 61%, P < 0.05). Next, subgroup analysis was performed to attempt to explain the heterogeneity. Based on the differ-
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Different ranges of follow-up years and the geographic locations of these trials, two subgroup analyses were performed. The pooled RR was 1.18 (95% CI: 0.87-1.61) (P = 0.3), I² = 72.3% (P < 0.05) and 1.04 (95% CI: 0.98-1.1) (P = 0.18), I² = 38.7% (P > 0.05) in the group with follow-up lengths less than 10 years and in the group with follow-up lengths more than 10 years, respectively (Figure 3). The heterogeneity was acceptable among those studies with follow-up for > 10 years. We found a significant positive relationship between vasectomy and prostate cancer risk among North American participants with a RR of 1.11 (95% CI: 1.02-1.21) (P = 0.016); however, this positive association was not observed in European males, whose RR was 0.96 (95% CI: 0.84-1.09) (P = 0.49). Our pooled estimates for these studies moreover showed significant heterogeneity for those studies conducted in North America (I² = 68.3%, P = 0.008). However, no significant heterogeneity was observed for the studies conducted in Europe (I² = 0, P = 0.58) (Figure 4).

Sensitivity analysis

To further assess the heterogeneity in these pooled studies, a sensitivity analysis was performed to thereby evaluate the influence of individual studies on the overall risk of prostate cancer. The results are shown in Figure 5. We found that when two trials [7, 9] were excluded, the I² of the pooled estimate decreased from 61% to 32.9%, suggesting that no significant heterogeneity existed (P = 0.11). The pooled estimate of the RR of the remaining 12 studies was 1.04 (95% CI: 0.98-1.09), furthermore indicating no significant difference in the association between prostate cancer risk and vasectomy (P = 0.21) (Supplemental Figure 1).

Publication bias

No evidence of publication bias was observed by visual inspection of the funnel plots (Figure 6) or by the application of Begg’s test (P = 0.91) or Egger’s test (P = 0.91).
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Discussion

We found no association between vasectomy and prostate cancer incidence by a meta-analysis of the data from 14 large cohort studies to date that examined this question. The pooled RR was 1.07 (95% CI: 0.99-1.16). However, significant heterogeneity was observed in our study ($I^2 = 61\%$, $P < 0.05$). The differences in the follow-up duration, populations and years since vasectomy may have introduced variability to this study. To reduce or explain the high heterogeneity, we conducted a subgroup analysis among the studies involving the number of follow-up years and different geographic locations of the participants. The heterogeneity of the group with a follow-up duration of more than 10 years was lower than the group with a follow-up duration of less than 10 years. When the different geographic locations of the participants were considered, no significant heterogeneity was observed for the trials conducted in Europe. Furthermore, no association was observed between vasectomy and prostate cancer risk in the European group using a pooled estimate. We additionally performed a sensitivity analysis to assess the heterogeneity by removing one study at a time. When two studies were excluded, the heterogeneity of the remaining 11 studies was acceptable. Both these two studies [7, 9] were from the United States, one [7] from the CLUE II cohort, which followed patients since 1989, and the other from the HPFS population; both suggested a positive association between vasectomy and prostate cancer. When the remaining 12 studies were pooled, no relationship was observed between vasectomy and prostate cancer incidence.

Vasectomy is the foremost safe and effective male contraception operation performed by urologists in the United States with a prevalence rate of 15% [25]. Since the 1990s however, some studies, including cohort and case-control studies, have suggested that vasectomy may be associated with an increased prostate cancer risk [1-9, 26]. This controversy is ongoing considering that two large population
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Studies on the association between vasectomy and prostate cancer risk published in 2014 and 2016 differed in their conclusions [5, 10]. Siddiqui, M. M., et al. reported that among the 49,405 U.S. men in the Health Professionals Follow-Up Study, aged 40 to 75 years at baseline in 1986, 6,023 patients were diagnosed with prostate cancer during follow-up to 2010, including 811 lethal cases (death or distant metastasis). They concluded that vasectomy was associated with a small increased risk of prostate cancer overall, and risk was elevated for high-grade (Gleason score 8 to 10) and lethal disease (death or distant metastasis) [5]. Jacobs, E. J., et al. showed that of the 363,726 men in the Cancer Prevention Study II cohort, 7,451 died as a result of prostate cancer during follow-up from 1982 to 2012. They concluded that in the CPS-II cohort, vasectomy was not associated with prostate cancer mortality. In the CPS-II Nutrition Cohort, vasectomy was not associated with either overall prostate cancer incidence or high-grade prostate cancer incidence [10].

Some potential molecular mechanisms have been proposed to explain the potentially increased prostate cancer risk after vasectomy [27]. The expression of semen TGFβ-1 and TGFβ-3 in men who underwent vasectomy was lower relative to men who did not undergo vasectomy [28]. Because TGFβR3 has an inhibitory effect on PC tumor growth, lower TGFβ levels may contribute to higher PC risk [29]. A study reported that changes in sperm plasma protein behavior may influence PC proliferation [28]. The increased proliferation effect was found in a rat study that examined the effects of vasectomy on the prostate [30]. However, the positive link between vasectomy and prostate cancer risk in those studies may be influenced by some bias, particularly detection bias [27, 31]. For example, in the study of Nayan, M., et al., the unadjusted analysis showed a positive association between vasectomy and PC risk. However, when they adjusted the number of visits to specialists and urologists in the year before the index date and the number of visits to general practitioners and admissions to hospitals between the index date and the end of follow-up, no association remained [22]. This finding suggested that a patient undergoing a vasectomy is more likely to undergo screening for prostate cancer before undergoing the procedure itself. Indeed, men who have a vasectomy require more medical attention and thus are screened more frequently, allowing more cancers to be detected, resulting in a confounder [27].

Two 2015 meta-analyses that both included cohort studies attempted to clarify the association between vasectomy and prostate cancer [23, 24]. However, some study flaws may have undermined the strength of their results. Because no adequate cohort studies on this topic were retrieved at that time, the lack of novel, high-quality research might have influenced the conclusions they obtained. Given the potential plausibility that vasectomy may be associated with PC risk, a current and comprehensive meta-analysis was warranted to clarify this issue. First, our systematic review included 14 cohort trials that notably included the largest sized and highest quality study about the relationship between vasectomy and prostate cancer published this year [10]. Second, the current study also included the largest studied population, including 21,125 prostate cancer cases and 1,711,788 participants. These strengths may have greatly reduced the potential for bias and permitted more reliable results to be obtained.

**Conclusions**

Our results demonstrated that vasectomy was not associated with prostate cancer risk. Based on this result, we suggest that physicians should not present an increased risk of prostate cancer in association with vasectomy in discussions with patients who are concerned about prostate cancer, in accordance with the recommendation by the American Urological Association [25]. This perspective also supports vasectomy as a safe contraception method for men.

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**Disclosure of conflict of interest**

None.
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Abbreviations

CI, confidence interval; CPS-II, Cancer Prevention Study II; HPFS, Health Professionals Follow-Up Study; MeSH, Medical Subject Heading; RR, relative risk; HR, hazard ratio.

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References


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Supplemental Figure 1. Pooled estimate of the remaining 12 studies after omitting two studies on the association between vasectomy and prostate cancer.