

Clinical Research and Methods

Prostate Cancer and Sexually Transmitted Diseases: A Meta-analysis

Marcia L. Taylor, MD; Arch G. Mainous, III, PhD; Brian J. Wells, MD, MS

Background: Prostate cancer is the most common neoplasm of American men and the second most common cause of cancer-related deaths. Research suggests that infection and subsequent inflammation may be an important risk factor in the pathogenesis of prostate cancer. In this meta-analysis, we examine the current epidemiological evidence for the association between specific sexually transmitted diseases (STDs) and prostate cancer. **Methods:** Using an English language search of Medline and CINAHL (Cumulative Index to Nursing and Allied Health) since 1966, 29 case-control studies were identified. These studies included a total of 6,022 cases of prostate cancer and 7,320 controls. Using Review Manager, combined odds ratios (ORs) were calculated for any STDs, gonorrhea, syphilis, and human papillomavirus (HPV) for prostate cancer. **Results:** Significant elevated ORs for prostate cancer were demonstrated for any STDs (1.48, 95% confidence interval [CI] 1.26–1.73), gonorrhea (1.35, 95% CI 1.05–1.83), and human papillomavirus (1.39, 95% CI 1.12–2.06). **Conclusions:** This meta-analysis provides evidence of a higher rate of prostate cancer in men with a history of an exposure to gonorrhea, HPV, or any STD. Further research, especially with cohort studies, is required to confirm this potentially modifiable risk factor.

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Prostate cancer is the most common neoplasm of American men and the second most common cause of cancer-related death in men.¹ Although the cause of prostate cancer is still not certain, known risk factors for prostate cancer include older age, African American race, and family history.^{2,3} Other risk factors such as diet, physical activity, and occupational exposures have been studied with conflicting findings.^{2,3}

Several epidemiological studies have examined the relationship between sexually transmitted diseases (STDs) and prostate cancer. STDs are theorized to increase the risk of prostate cancer by causing inflammation of the prostate, which may then lead to the initiation of carcinogenesis.³ Studies examining the relationship between STDs such as gonorrhea, *Chlamydia*, syphilis, human papillomavirus (HPV), and herpes have, however, yielded conflicting results.⁴⁻³² Some of these studies have shown an elevated odds ratio (OR) associated with history of any STDs while others have not shown this association. If STDs do increase a man's

risk for developing prostate cancer, STDs would be a potentially modifiable risk factor for prostate cancer that could be targeted on a public health level.

A recent meta-analysis of 17 case-control studies, published in 2001, revealed that prostate cancer patients were more likely to have a history of any STD (OR 1.44). There were two weaknesses in this previous meta-analysis. First, the analysis only included 26 of the 29 studies that were available on Medline, CINAHL (Cumulative Index to Nursing and Allied Health), Cancerlit, or HeathStar at that time. Another weakness of this study was the lack of subgroup analyses, which might further elucidate which specific organisms were associated with the increased risk. HPV is of particular interest due to its association with cervical cancer.³³ HPV is capable of *in vivo* replication in the prostate³⁴ and is used to immortalize prostate epithelial cells *in vitro*.³⁵ Epidemiological studies have examined the relationship of HPV infection with prostate cancer but have shown conflicting results.^{5,8,10,13,23,24,27,29,31,32} Thus, a meta-analysis of the available epidemiological studies in this area may provide a clearer picture of the relationship between HPV and prostate cancer. Consequently, this study's purpose was to examine the association between specific STDs and prostate cancer,

From the Department of Family Medicine, Medical University of South Carolina (Drs Taylor and Mainous); and the Department of Family Medicine, Cleveland Clinic Foundation, Strongsville, Ohio (Dr Wells).

using a meta-analysis to pool the results of the current epidemiological evidence.

Methods

Literature Search Strategy

An initial literature search was done using Medline from 1966 to August 2004. The literature search was confined to studies published in the English language. The following terms were used as medical subject headings (MeSH) for the search: prostatic neoplasm, sexually transmitted diseases, *Chlamydia trachomatis*, syphilis, *Treponema pallidum*, gonorrhea, human papillomavirus, papillomavirus infections, and Condyloma acuminatum. The following key words or text words were also used as search headings: prostate cancer, sexually transmitted diseases, *Chlamydia trachomatis*, syphilis, gonorrhea, and human papillomavirus. The same search was performed with CINAHL from 1982 to August 2004. Cancerlit and HeathStar were not searched, since these two databases are now included in Medline. In addition, the references from the identified studies were reviewed to help ensure that all pertinent published papers had been identified.

The literature search identified 30 studies that have investigated the relationship between the exposure to any STD and the diagnosis of prostate cancer. One publication of preliminary results, Ross 1983,⁴ was not included in this meta-analysis because of insufficient information regarding the number of cases and controls. A further literature search of Medline did not reveal a publication of the final results. An attempt was made to contact the author of this study to see if the data were available for inclusion in our meta-analysis, but these attempts were not successful. A total of 29 studies were included in the meta-analysis.

Data Analysis

One potential concern with the meta-analysis design surrounds the issue of "publication bias." Research indicates a bias that favors the publication of studies that show positive results.³⁶ Therefore, there is the potential existence of negative studies on the subject that never made it to publication. A funnel plot was used to assess for possible publication bias. The funnel plot was prepared by plotting the log of the effect size for each of the published studies on the horizontal axis and the precision of these effects on the vertical axis. Using a log transformation of the effect size ensures that negative and positive effects are equally spaced.³⁷

Meta-analysis calculations were made using Review Manager 4.2.2 by the Cochrane Collaboration, 2003. Data were entered for the number of subjects that were exposed or not exposed to an STD for the cases and controls in each study. Exposure to any STD was reported as a dichotomous value of "yes" or "no" and did not account for individuals who may have had

multiple exposures. Positive results from HPV testing, regardless of serotype, were counted as an exposure to an STD.

Data input was double-checked for accuracy, and the ORs calculated by Review Manager were compared to the ORs reported in the original studies. Review Manager software was used to obtain the combined ORs for the following comparisons: any STD and prostate cancer, gonorrhea and prostate cancer, syphilis and prostate cancer, and HPV and prostate cancer. A comparison of *Chlamydia trachomatis* and prostate cancer was not performed since only two studies separately reported exposure to *Chlamydia trachomatis*.

Initially, the data were analyzed using a fixed-effects model. However, the test for heterogeneity, using an inverse variance method, found that the studies were significantly heterogeneous ($P=.03$). Therefore, the analysis was repeated with a random-effects model. Except for syphilis, the two models did not demonstrate significantly different results. The results from both models are presented in the text of this manuscript, but the Figures show only the results of the random-effects model. Study weights were calculated by the Review Manager software, taking into account both total sample size and numbers of exposed participants. The confidence intervals and P values for statistical significance are reported using a two-tailed method.

Quality scores are often used to weight the results in meta-analysis of randomized clinical control trials, and the Jadad score has been used as a validated quality score of individual trials.³⁸ However, no quality score has been developed for the use of case-control studies in meta-analysis. The Cochrane collaborative group in 1999 began a study group that was to address how to rate the quality of nonrandomized studies. These guidelines were to be available in 2001, but they have not been published.³⁹ The Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group stated that the use of quality scores in meta-analyses of observational studies is controversial, and scores constructed in an ad hoc fashion may lack demonstrated validity.⁴⁰ Therefore, we did not attempt to compute quality scores for use in this meta-analysis.

Results

Table 1 describes the characteristics of the 29 included studies. In the study by Strickler,³¹ an estimated OR could not be calculated because there were no exposures to STDs in either the cases or the controls. A funnel plot created from all 29 studies on the association between any STD and prostate cancer is depicted in Figure 1. Overall, the funnel plot appears symmetrical and does not suggest the existence of many negative studies on the subject, thus suggesting that publication bias is likely minimal.

Table 1
Characteristics of Included Studies

Study ID	Participants	STD Exposure
Adami 2003	238 cases and 210 population controls	HPV 16, 18, 33 via serology
Baker 1981	81 cases and 224 controls with BPH	Syphilis Gonorrhea Herpes by serology
Checkoway 1987	40 cases and 64 controls with BPH	Any STD
Dillner 1998	165 cases and 230 population controls matched by age and residency	HPV 11, 16, 18, 33, and/or chlamydia via serology
Ewings 1996	159 cases and 325 hospital and BPH controls	Any STD
Hayes 2000	981 cases and 1,315 population controls	Syphilis Gonorrhea HPV via serology
Heshmat 1975	75 cases and 75 hospital controls matched by age	Gonorrhea
Hiatt 1993	238 cases and 238 population controls matched by age and race	Gonorrhea
Hisada 2000	48 cases and 63 population controls matched by age and race	HPV 16 via serology
Honda 1988	216 cases and 216 population controls matched by age and residency	Gonorrhea Syphilis
Hsieh 1999	320 cases and 246 hospital controls	Gonorrhea Any other STD
Ilic 1996	101 cases and 202 hospital controls matched by age and residency	Gonorrhea
Krain 1973	136 cases and 136 population controls matched by age and residency	Any STD
Krain 1974	221 cases and 221 controls matched by age and race	Any STD
La Vecchia 1993	271 cases and 685 hospital controls	Gonorrhea
Lees 1985	83 cases and 166 hospital and BPH controls matched by age	Any STD
Mandel 1987A*	250 cases and 238 hospital controls matched by age and race	Any STD
Mandel 1987B*	250 cases and 240 population controls matched by age and race	Any STD
Mishina 1985	100 cases and 100 population controls matched by age and residency	Gonorrhea Syphilis
Moyret-Lalle 1995	27 cases and 24 controls with adenomas	HPV 16 via PCR
Noda 1998	38 cases and 71 controls with BPH	HPV 16, 18, 31, 33, 35, 52, 58 via PCR
Oishi 1990	100 cases and 200 controls in one hospital and one BPH, both matched by age	Any STD
Rosenblatt 2001	753 cases and 703 population controls matched by age	Gonorrhea Syphilis Chlamydia
Rosenblatt 2003	642 cases and 570 population controls matched by age	HPV via serology
Ross 1987	284 cases and 284 population controls matched by age	Any STD
Serth 1999	47 cases and 37 BPH controls	HPV 16 via PCR
Steele 1971	39 cases and 74 hospital controls matched by age	Any STD
Strickler 1998	63 cases and 61 controls with BPH matched by race	HPV via PCR
Wideroff 1996	56 cases and 42 controls with BPH	HPV 6, 11, 16, 18, 31, 33, 45 via PCR

* This study analyzed the data with both hospital and case controls. From the numbers presented in their manuscript we were not able to combine the data so the results from each control group are used separately.

HPV—human papillomavirus
STD—sexually transmitted disease
PCR—polymerase chain reaction
BPH—benign prostatic hypertrophy

Figure 2 reports the results from the analysis of any STD and prostate cancer. All of these studies were case-control in design, with a range of cases from 27 to 981 and controls from 24 to 1,315.⁵⁻³² Matching criteria was not the same across the 29 studies. Some studies used matching criteria such as age, race, and place of residency, while others used hospital, population, or men with benign prostatic hyperplasia as controls. The overall OR for prostate cancer is elevated in both the fixed (1.45 with a 95% CI of 1.30–1.61) and random effects (1.48 with a 95% CI of 1.26–1.73) models.

Figure 3 is the results from the analysis of gonorrhea and prostate cancer. Eleven studies from 1975 to 2001 were used for this analysis.^{6,7,11,12,14-16,19,20,22,26} The overall OR is significantly elevated in both the fixed (1.35 with a 95% CI of 1.11–1.64) and random (1.39 with a 95% CI of 1.05–1.83) effects models. Figure 4 shows the results from analysis of syphilis and prostate cancer. A total of seven studies from 1981 to 2001^{6,7,10,14,20,22,26} were used for this analysis, which also showed an elevated OR of 1.61 (95% CI of 1.08–2.39) in the fixed effects model although the OR is not significant in the random effects

model (OR of 1.42 with 95% CI of 0.76–2.64).

Figure 5 shows the results from the analysis of HPV and prostate cancer. Ten studies from 1995 to 2003 were used for this analysis.^{5,8,10,13,23,24,27,29,31,32} These studies either used serologic or polymerase chain reaction evidence of HPV infection since HPV infection is usually asymptomatic in men. The combined OR in a fixed effects model for this data was also elevated at 1.39 (95% CI of 1.13–1.71) and at 1.52 (95% CI of 1.12–2.06) in the random effects model.

Discussion

This meta-analysis revealed a significant association between prostate cancer and all STDs, as well as with the specific infections of gonorrhea and HPV. However, there was no significant

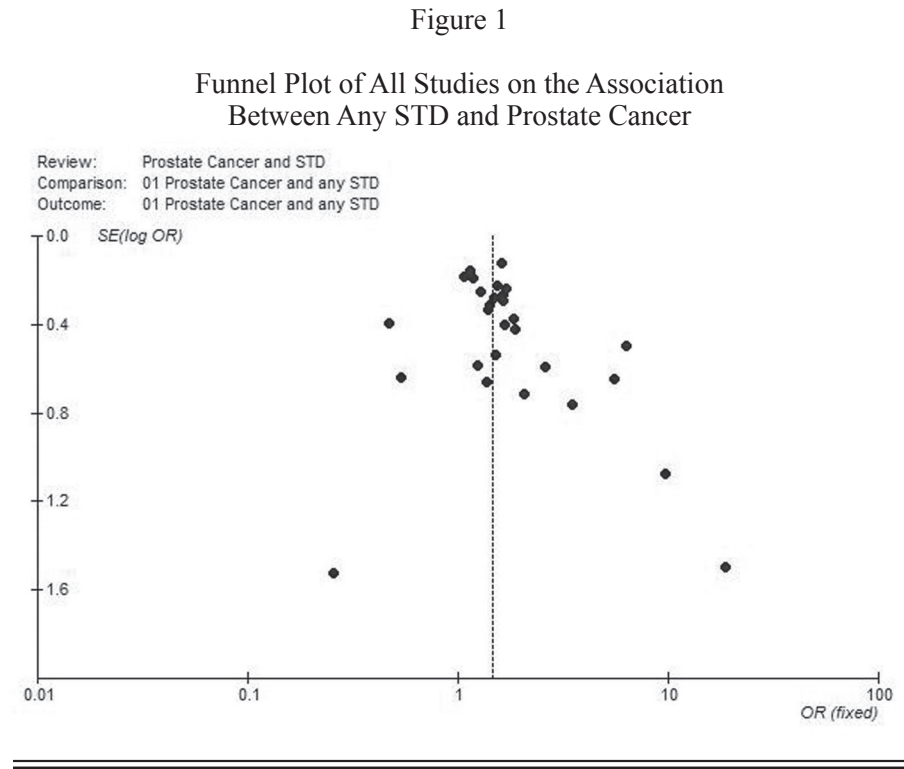


Figure 2
 Any STD and Prostate Cancer

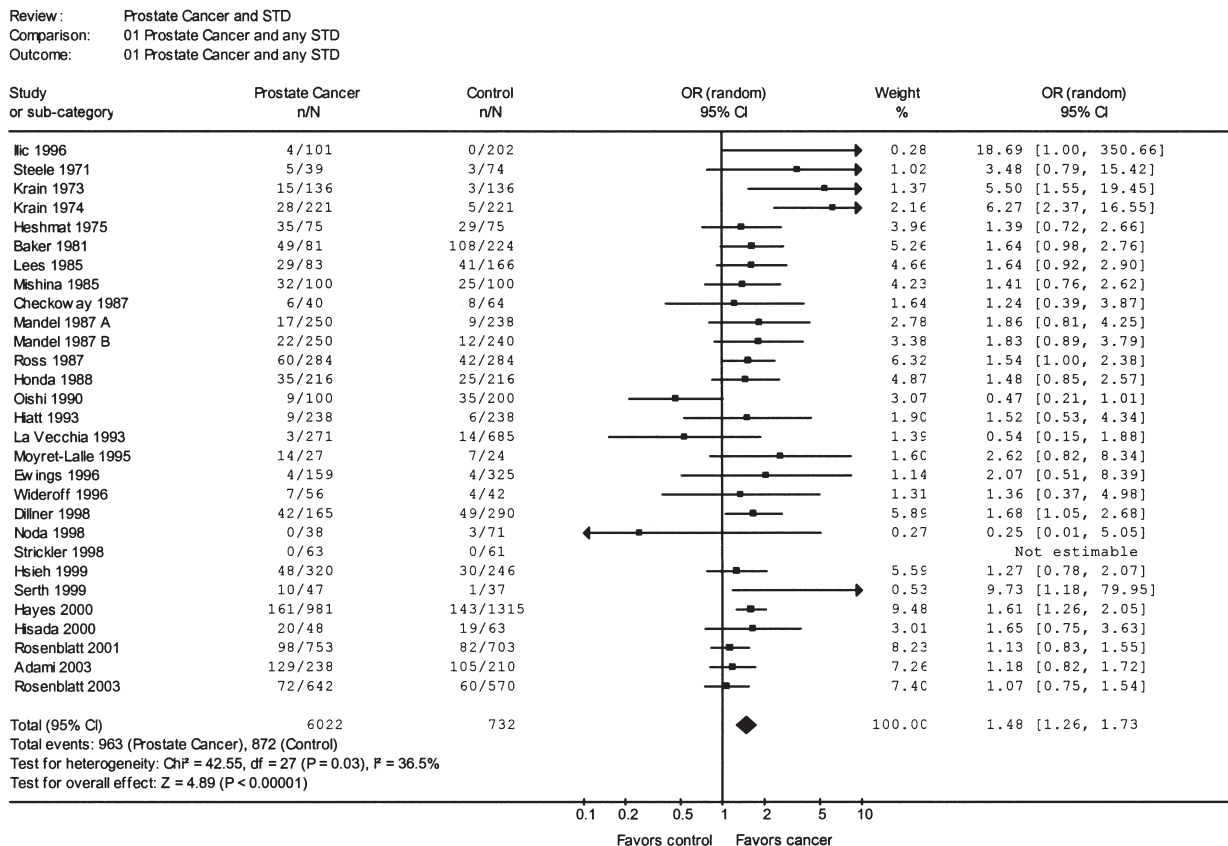


Figure 3

Gonorrhea and Prostate Cancer

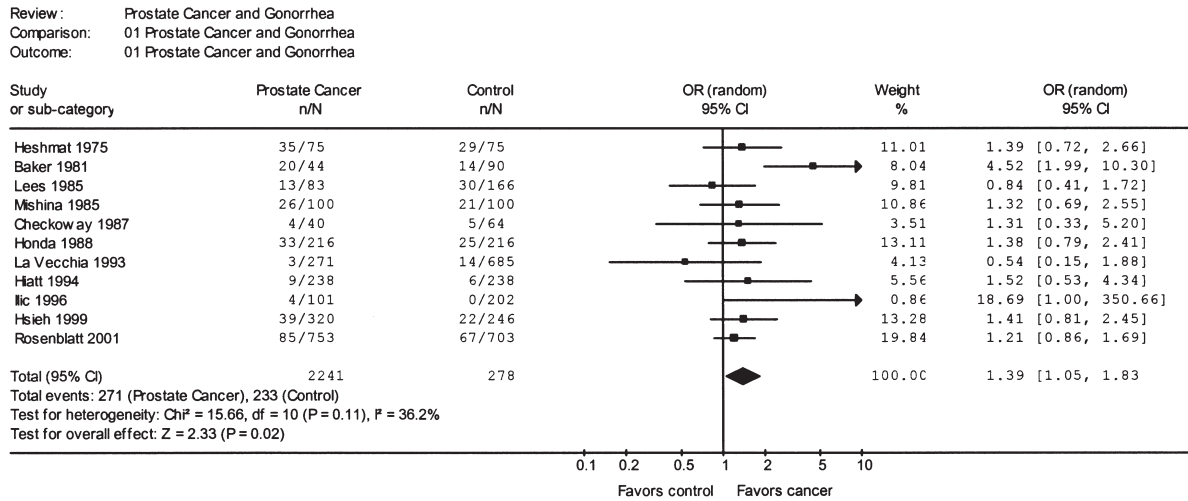
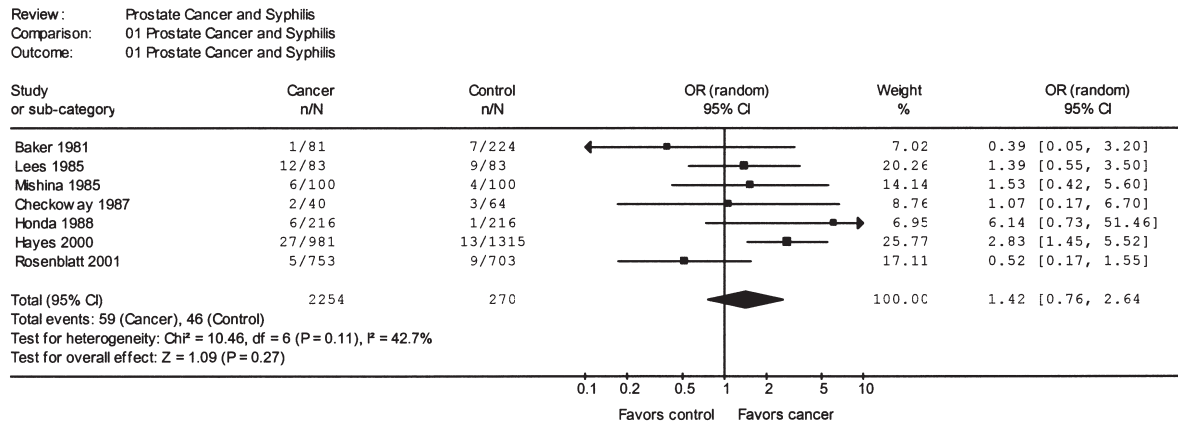


Figure 4

Syphilis and Prostate Cancer

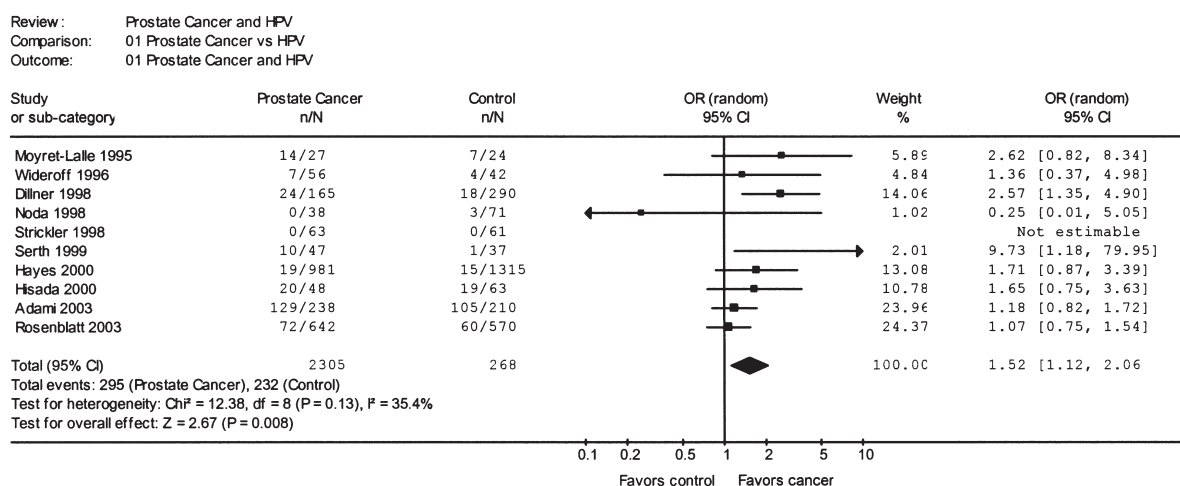


association observed with syphilis in the random effects model. The results of this meta-analysis are consistent with a previous meta-analysis of 17 studies² that also indicated epidemiological evidence of an association between STDs and prostate cancer. To further support this theory, there is the biological plausible theory of STDs leading to inflammation of the prostate and thus causing carcinogenesis.

The findings of this meta-analysis provide new information for clinicians. STDs are a robust risk factor for prostate cancer. However, the risk associated with each specific STD is different. HPV is an acknowledged risk factor for cervical cancer.³³ Cancer associated with HPV in men is particularly troubling since testing for HPV in men is not routinely performed, nor is HPV a reportable disease. Thus, attention to the prevalence and occurrence of HPV in men may be warranted.

Figure 5

HPV and Prostate Cancer



Limitations

There are some limitations of this meta-analysis. All the available studies in the literature were case-control in design. Thus, all the studies are subject to the limitations that come with case-control design, including recall bias, selection bias, and difficulty in establishing a temporal relationship. In addition, some studies included matching criteria for known confounders including age and race while others did not. None of the studies included in this meta-analysis used family history for matching criteria. Most of the studies used patient history for documentation of STDs, which is subject to recall bias, and patients with prostate cancer may be more likely to recall past exposures than healthy subjects. Also, given the social connotations of STDs, patients may not be forthcoming about their history of these or may not recall being diagnosed with STDs. In addition, none of the studies accounted for exposure to multiple STDs or repeated infections with the same organism. The possibility also exists for the subjects to have had an asymptomatic infection especially with *Chlamydia* or HPV.

This meta-analysis was also limited to the English language. However, our search found only three other studies that were published in a language other than English. As with any meta-analysis, the included studies are limited to the ones that have been published, and there is the possibility of unpublished studies that may not have shown an elevated OR associated with STDs. However, this is less likely with this meta-analysis since

our literature search did identify some studies reporting negative results, and the funnel plot appeared to be fairly symmetrical.

Conclusions

Even with these limitations, our meta-analysis of the available epidemiological evidence does support a possible link between STDs and prostate cancer. This finding of a potentially modifiable risk factor for prostate cancer has significant implications. Specifically, extra emphasis may need to be placed on screening and eradication of STDs in men.

Further research needs to be done in this area focusing on using cohort studies and documenting history of STDs either by serological evidence or by medical record. If future research continued to show that STDs do increase a man's development of prostate cancer, this would represent a modifiable risk factor for prostate cancer that could be targeted on a public health level, and screening for STDs in men could be warranted in the future.

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Corresponding Author: Address correspondence to Dr Taylor, Medical University of South Carolina, Department of Family Medicine, 295 Calhoun Street, PO Box 250192, Charleston, SC 29425. 843-792-3678. Fax: 843-792-3598. tyalo@musc.edu.

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