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SEXUALLY TRANSMITTED INFECTIONS AND RISK OF PROSTATE CANCER: REVIEW OF HISTORICAL AND EMERGING HYPOTHESES

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ABSTRACT/SUMMARY

Since the early 1950s when sexually transmitted infections (STIs) were first proposed as a possible risk factor for prostate cancer, numerous epidemiologic studies have been conducted. Initially, these studies were primarily small case-control studies with retrospective, self-reported assessment of a narrow range of STIs, typically either any STIs, or gonorrhea and syphilis. However, as new STIs have been discovered/recognized, new and better tests to detect histories of STIs have been developed, and new resources for prostate cancer research have been created, epidemiologic studies have expanded to include a wider range of STIs, and have moved towards more rigorous, prospective study designs and serologic assessment of STI histories. The results of these studies are reviewed and discussed, as well as possible new avenues of research, such as *Trichomonas vaginalis* infection and infections not typically considered to be sexually transmitted.

EARLY HYPOTHESES FOR SEXUALLY TRANSMITTED INFECTIONS AND PROSTATE CANCER

Early hypotheses related to a sexually transmitted etiology of prostate cancer were initially motivated by contemporary, epidemiologic patterns of prostate cancer occurrence. In the early 1950s, Ravich and Ravich [1, 2] noted a higher prostate cancer prevalence among mainly uncircumcised non-Jewish than circumcised Jewish men, similar to patterns for penile cancer and cervical cancer among female partners of these men, leading them to propose that observed patterns might be explained by sexual transmission of a virus or other carcinogenic agent contained within the smegma of uncircumcised males. Subsequent investigators [3-5] further proposed additional hypotheses related to infection, sexual behavior, and sexual frustration to explain other contemporary patterns of prostate cancer occurrence by marital, paternal, and racial status. Together, these observations and hypotheses led to a series of investigations beginning in the early 1970s to examine possible associations between STIs and sexual behavior in relation to prostate cancer.

Selection of STIs

STI markers:

Most early investigations of STIs and prostate cancer assessed either a history of any STIs or individual histories of gonorrhea and syphilis as markers or possibly vectors of the potentially causative STI or sexual behavior [6-9]. These STIs were likely selected because they were the most common, well-known, and symptomatic STIs at the time, making them also more readily assessed by self-report, medical record abstraction, or registry query.

Prostate inflammation:

Other early studies focused specifically on gonorrhea because it frequently led to

secondary gonococcal prostatitis in the pre- and early-antibiotic era, and because prostate inflammation had previously been hypothesized as a cause of atrophy and subsequent prostate cancer ([9-11] and references therein). This inflammation-atrophy-prostate cancer hypothesis has since gained further support with the observation of morphological and epigenetic transitions between areas of inflammation-associated, highly proliferative, atrophic prostatic epithelium, which have been termed proliferative inflammatory atrophy (PIA) lesions, and areas of high-grade prostatic intraepithelial neoplasia (PIN) and adenocarcinoma. According to this developing hypothesis, PIA lesions are believed to form as a result of prostate epithelial cell damage and destruction caused by secretion of oxygen- and nitrogen-based reactive molecules from inflammatory cells, such as neutrophils and macrophages. Over time, small subsets of cells within these regenerative lesions are believed to acquire somatic genomic alterations, such as hypermethylation of the oxygen radical detoxifying glutathione S-transferase P1 gene, making them more susceptible to genomic damage. This increased susceptibility to genomic damage has then been postulated to lead to the development of PIN lesions or cancer in the setting of continued or repeated inflammation and cell injury/death [12].

In addition to proposing gonorrhea as a possible inflammatory cause of prostate cancer, Wynder and colleagues [10] further proposed that "frequent venereal infections or untreated chronic venereal infection" might be of interest because these infections were also believed to contribute to prostatitis; in this case, non-gonococcal prostatitis. Indeed, in the pre- and early-antibiotic era, prostatitis due to organisms other than *Neisseria gonorrhoeae*, the causative agent of gonorrhea, was frequently observed in both men with gonococcal urethritis who may have acquired additional sexually transmitted organisms at the time of infection with *N. gonorrhoeae*, and men with non-gonococcal urethritis [13]. However, no early studies, to our knowledge,

investigated any of these other common causes of STI-specific prostatitis, possibly because some, such as *Trichomonas vaginalis*, were generally less well recognized and less frequently investigated or diagnosed in men, making them difficult to assess by self-report, while others, such as *Chlamydia trachomatis*, had not yet been discovered or recognized as sexually transmitted pathogens. Therefore, these pathogens would not be investigated in relation to prostate cancer until several decades later.

Carcinogenic STI therapy:

Rather than focusing on prostate inflammation, Lees and colleagues [14] investigated syphilis, a very rare cause of granulomatous prostatitis [15], because of the potentially carcinogenic effects of pre-antibiotic era, parenteral, arsenical therapy for syphilis.

Viral transformation:

Finally, other groups investigated herpesviruses, such as herpes simplex virus type 2 (HSV-2), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), because they: 1) had been demonstrated to have transforming properties; 2) had been observed in malignant prostate tissue/cell lines; and 3) were believed to be involved in the development of other cancers, such as cervical cancer and Burkitt's lymphoma [8, 16-20]. Primitive serologic tests were available for these viruses as early as the 1970s, making it possible to assess histories of these infections by serology rather than or in addition to self-report or medical record abstraction.

Since these early hypotheses were first proposed, several new STIs have been discovered or recognized, and new and better methods to investigate STI histories have been developed; however, the rationale behind investigation of these STIs has remained largely the same over the years, primarily focused on prostate inflammation and viral transformation.

RESULTS FOR EARLY STUDIES OF STIS AND PROSTATE CANCER

STIs assessed by self-report, medical record abstraction, or registry query:

Considering early studies of STIs and prostate cancer conducted among men more likely to have been infected in the pre-antibiotic era, several observed suggestive positive associations for histories of any STIs [6-8, 21] and gonorrhea [9, 11, 17], while others observed null or suggestive inverse associations for these STIs [10, 14, 22-25] (Table 1). Fewer studies investigated a history of syphilis in relation to prostate cancer [14, 17, 23], one of which observed a positive association [14], and the other two observed generally null, unstable results [17, 23]. With respect to other STIs or symptoms of STIs, one study observed a suggestive positive association for self-reported history of urethral discharge (possibly indicative of gonorrhea or another exudative STI) [26], while another observed unstable positive and null associations for "recurrent genital sores" (possibly indicative of genital herpes) and pediculus pubis (pubic lice), respectively [17]. Finally, in studies with sufficient numbers of exposed participants, suggestive positive associations were observed for histories of STIs or STI symptoms among participants' female partners, including histories of any STIs [8] and "genital infection" [26], with prostate cancer among participants. Most other investigations of participants' female partners had too few exposed participants to interpret their findings [23-28]. Taken together, these findings suggested that one or more of the more commonly reported STIs, such as gonorrhea, or another unmeasured or unknown correlated STI, might be associated with risk of prostate cancer.

Interpretation of study findings:

Information bias:

One concern for interpretation of early study findings is the possibility that many may

have been influenced by biases, such as recall and interviewer biases, because most early studies were case-control in design with retrospective, self-reported assessment of STI histories. This type of study design and exposure assessment allows for the possibility that participants' knowledge of their prostate cancer status or awareness of their physicians' or interviewers' knowledge of their status may have influenced their responses to study questions, particularly sensitive questions, such as those related to STI histories. This knowledge may have led prostate cancer cases to reply more truthfully to questions about STI histories than controls, thereby possibly leading to a higher reported lifetime prevalence of STIs among cases than controls. In some early studies of STIs and prostate cancer, interviewers were also likely aware of both participants' cancer status and study hypotheses, which may have led them to question prostate cancer cases more thoroughly for information on STI histories than controls, thereby possibly further contributing to a higher reported lifetime prevalence of STIs among cases than controls.

Confounding:

Another factor that may have led to false positive associations is the possibility of confounding by hormone levels, as these may have contributed to both increased sexual activity and thus increased likelihood of acquiring an STI, as well as increased risk of prostate cancer. To our knowledge, no early studies were able to address this possible concern, nor did any adjust for correlates of hormone-associated libido.

Etiologic relevance of the STI exposure:

Although early studies may have been susceptible to information biases and confounding, and thus to observing false positive associations, they may have also been more likely to capture STI histories of possibly greater relevance for prostate carcinogenesis than studies that have since been conducted because early participants were more likely to have passed through

adolescence and early adulthood (when men typically acquire STIs [29]) before antibiotics had been developed. During this pre-antibiotic period, 1) some STIs, such as syphilis [30], were more prevalent and more evenly spread throughout the population (i.e., less restricted to specific populations), thus increasing the likelihood of infection and repeat infections; 2) several STIs, such as gonorrhea and syphilis, were more likely to persist because of ineffective treatment; and 3) many STIs were more likely to result in sequela, such as prostatitis or prostatic abscess in the case of gonorrhea [31]. Therefore, the likelihood of single or multiple episodes of assessed STIs and co-infections, and their duration and probability of sequela, were likely greater among participants in earlier that later studies. We have previously hypothesized that these characteristics may be important for prostate carcinogenesis because each may increase the chance and/or duration of either asymptomatic or symptomatic prostate involvement. Multiple episodes of STIs may be more relevant for carcinogenesis than single episodes because of increased cumulative probability of prostate involvement with each STI episode and increased cumulative probability of inflammatory immune injury with each episode that involves the prostate. Infections of longer duration may also be more relevant for carcinogenesis than shorter infections because of the greater length of time afforded to infectious agents to ascend to the prostate and the greater potential duration of prostate involvement. Finally, sequela, such as clinical prostatitis, are relevant to prostate carcinogenesis because they directly represent prostate involvement and possible inflammatory immune damage to prostate epithelium [32].

Etiologic relevance of the prostate cancer outcome:

A final consideration for interpretation of early study findings for STIs and prostate cancer is the spectrum of prostate cancer presentation in these studies. All early studies were conducted before the introduction of prostate specific antigen (PSA) testing for early detection of

prostate cancer; therefore, these studies may have included a higher proportion of clinically manifest prostate cancer, such as cancer that was detectable by digital rectal examination or had progressed to metastases, than later studies. These clinically manifest or life-threatening prostate tumors may potentially have differing etiology than tumors that never progress to clinically-manifest disease [33]. Therefore, considering this issue together with all aforementioned issues, it is difficult to determine the relative contributions of possible biases in study design, confounding, greater STI exposure, and later prostate cancer presentation to observed findings from early studies of predominantly self-reported STIs and prostate cancer.

STIs assessed by serology or other laboratory methods:

As mentioned previously, primitive serologic assays were available for several herpesviruses as early as the 1970s and 80s, allowing for seroepidemiologic investigations of HSV-2, CMV and EBV infection in relation to prostate cancer. Results from these early studies were generally mixed; while some observed suggestive positive associations for HSV-2 [17] and CMV [19] seropositivity, others observed null or suggestive inverse associations for these viruses and EBV [8, 16] (Table 1). A few additional small studies also investigated herpesvirus nucleic acids and antigens in prostate tissue with generally unstable results [17, 18, 20].

Interpretation of study findings:

Non-differential exposure misclassification:

Although serologic studies are not susceptible to recall and interviewer biases, exposure misclassification may still have been introduced into early studies of herpesviruses and prostate cancer, especially studies of HSV-2, because of the extensive cross-reactivity between HSV-2 antigens and those expressed by the more common HSV-1 [34]. This cross-reactivity may have led to a considerable number of individual false positive test results and falsely elevated

seroprevalences, as evidenced by a comparison of HSV-2 seroprevalences from older studies (51-66% among controls [16, 17]) and more recent studies (24.3% among men and women 60-69 years of age) [35]. Although this cross-reactivity is unlikely to have been differential by case-control status, its considerable extent makes interpretation of study findings difficult.

RESULTS FOR LATER STUDIES OF STIS AND PROSTATE CANCER

STIs assessed by self-report, medical record abstraction, or registry query:

Case-control studies:

Since the first early studies of STIs and prostate cancer were conducted, several additional case-control studies have investigated possible associations between a history of any STIs and individual histories of gonorrhea, syphilis, and other STIs typically assessed by self-report in relation to prostate cancer. Many, but not all [36, 37], of these later studies observed suggestive positive associations for histories of any STIs [38, 39] and gonorrhea [40-44] where sufficient numbers of exposed participants existed (Table 2). A few additional studies with much smaller numbers of exposed participants observed generally unstable estimates [45-48]. For syphilis, only one case-control study had sufficient numbers of exposed participants to evaluate its association with prostate cancer; this study observed a positive association for both self-reported and serologically detected history of syphilis [41]. Although unstable, estimates from the remaining case-control studies of syphilis were also generally supportive of a positive association when considered together [37, 42-45, 48]. Finally, generally unstable results or no reported exposure were observed in other studies of genital herpes [37, 42, 43, 45, 49], genital warts [42, 48, 50], urethritis [42], chancroid [37], “other” STIs [36, 37, 43, 45], and cervical cancer among participants’ female partners [43, 47]. Thus, similar to earlier case-control studies, later case-control studies generally observed suggestive positive associations for a history of any

STIs and individual histories of gonorrhea and possibly syphilis, where sufficient numbers of exposed participants existed.

Interpretation of study findings:

Etiologic relevance of the STI exposure and prostate cancer outcome:

As compared to participants in earlier case-control studies, those in later studies were less likely to have passed through adolescence and early adulthood before antibiotics had been discovered and thus may have been less likely to have ever had an STI, to have had multiple episodes of STIs or co-infections, or to have had a lengthy duration of infection or sequela than participants in earlier studies. Indeed, with respect to ever having been infected, self-reported lifetime prevalences of STIs have generally decreased over time in case-control studies, particularly those composed predominantly of Caucasian men. Participants in later studies also typically presented at an earlier stage of prostate cancer than those in earlier studies, which may have possibly shifted the composition of prostate tumors towards those that may have never progressed to clinically manifest or life-threatening disease. Both of these factors – lesser likelihood of extensive STI exposure and earlier prostate cancer presentation – might be expected to decrease the likelihood of observing true positive associations between STIs and prostate cancer.

Confounding:

Similar to findings from earlier case-control studies, those from later studies may also potentially have been influenced by confounding by hormone-associated libido, thereby possibly leading to false positive associations. However, a few results from later studies suggest this possibility may be less of a concern. In both positive studies that adjusted for correlates of libido – sexual activity with prostitutes, number of sexual partners, and frequency of sexual intercourse

– similar positive findings were observed as in unadjusted/lesser-adjusted analyses [39, 41], suggesting that, at least in these two studies, positive results were likely not due to confounding by hormone-associated libido.

Information bias:

Finally, as compared to earlier studies, later case-control studies may have been less susceptible to interviewer bias because many assessed STI histories by self-administered questionnaires and because use of interviewer blinding has likely increased over time. Therefore, later case-control studies should have been less likely to observe false positive associations due to interviewer bias than earlier studies. However, one lingering, possible methodologic concern that may still potentially have contributed to false positive associations in later studies is recall bias, as all later studies assessed STI histories after prostate cancer diagnosis, and as the STI-prostate cancer hypothesis has now been circulating in the medical and lay community for several decades.

Prospective studies:

To our knowledge, only a few studies have prospectively investigated associations between gonorrhea, syphilis and prostate cancer to avoid concerns of recall bias. The first two of these studies were conducted in the 1990s, one of which observed a relatively unstable estimate, possibly supportive of a positive association, between a history of gonorrhea and risk of prostate cancer in a nested case-control study [51], while the second observed a significant inverse association between a history of syphilis and prostate cancer risk in a retrospective cohort study that compared prostate cancer incidence among cases of syphilis reported to the New York State Health Department to incidence in the general New York State population [52] (Table 3). However, this study has been criticized for possible under-ascertainment of prostate cancer cases

that developed outside of the study catchment area in the syphilis cohort [53]. Indeed, inverse associations were also observed for colon, rectum, bladder and lung cancer [52], the latter two of which might be expected to be positively associated with syphilis due to confounding by smoking, as smoking and STI histories tend to be correlated [54]. Until very recently, these were the only two prospective studies in the literature. However, more prospective studies are now beginning to be conducted. In 2006, we published the results of our prospective cohort investigation in the Health Professionals Follow-up Study (HPFS), in which we observed no association for a history of gonorrhea and an unstable, null association for a history of syphilis and risk of prostate cancer [55]. Based on participants' lower reported lifetime prevalence of STIs, which we have previously hypothesized also reflects a lower likelihood of repeat and co-infections [32], as well as their education, socio-economic status, and race/ethnicity, we postulated that histories of gonorrhea and syphilis in this cohort likely reflected only one or two episodes of treated infection with a low likelihood of co-infections. Therefore, our findings suggested that low exposure to gonorrhea and syphilis does not increase risk of prostate cancer [55]. These findings were supported by subsequent results in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, in which the authors observed no association for a history of gonorrhea, and an unstable, possibly inverse association for a history of syphilis among Caucasian participants, who had similarly low reported lifetime prevalences of infection as HPFS participants. Null or generally unstable results were also observed, however, among African-American participants in the PLCO Cancer Screening Trial [56] and among Caucasian and African-American participants in the subsequent California Men's Health Study [57], all of whom had considerably higher reported lifetime prevalences of gonorrhea and syphilis than HPFS or Caucasian PLCO participants. Therefore, these findings suggest that any exposure to

gonorrhea or syphilis, even more extensive exposure, at least as experienced in the U.S. in the current antibiotic era, does not increase risk of prostate cancer.

It is possible, however, that other types of infection may increase risk of prostate cancer – for instance, those more similar to infections experienced in the pre-antibiotic era. This possibility is suggested by findings from the recent California Men's Health Study. While no association was observed for a history of gonorrhea overall in this study population or among U.S. born Latino men (relative risk (RR)=1.02, 95% confidence interval (CI): 0.63-1.67), a suggestive positive association was observed among foreign-born Latino men (RR=1.95, 95% CI: 1.20-3.16), whom the authors hypothesized may have been more likely to have been infected outside of the U.S., and thus not to have received any or timely treatment. This hypothesized lack or delay in treatment may have then led to a longer duration of infection, and a possibly greater likelihood of prostate involvement. A similar, albeit less stable, positive association was also observed for syphilis among Asian-American men, another more recent immigrant group to the U.S. [57]. Therefore, although these sub-group findings may have observed by chance, they leave open the possibility of associations between certain types of STI histories (e.g., untreated STIs, and those of longer duration) and prostate cancer. Thus, additional prospective studies with a greater variety of STI exposures may be warranted to elucidate the possible roles of gonorrhea and syphilis in prostate carcinogenesis.

STIs assessed by serology and other laboratory methods

Since the original hypothesis on STIs and prostate cancer was first proposed, several new STIs have been discovered or recognized as STIs (e.g., infections by oncogenic HPV types, human herpesvirus type 8 (HHV-8) and *C. trachomatis*), and new or considerably better tests to detect histories of other known STIs have been developed (e.g., HSV-2 and *T. vaginalis*

infections). New resources for prostate cancer research have also been created (e.g., cohort studies with blood collection), allowing for prospective investigations of STIs and prostate cancer risk, and serologic detection of STI histories, both of which serve to reduce concerns of recall bias. In general, histories of these newly discovered/recognized STIs are also better assessed by serology than by self-report because many of these STIs tend to be asymptomatic in men, and infrequently diagnosed in symptomatic men. Although serology may not capture all past infections in men, we have previously hypothesized that it may be better at detecting infections of possibly greater relevance for prostate carcinogenesis, such as repeat infections, infections of longer duration that might be more likely to ascend to the prostate, and those with complications, such as prostatitis, because detectable or higher antibody titers have been observed among individuals with HPV or HHV-8 infections of longer duration; individuals with Kaposi's sarcoma, a complication of HHV-8 infection; and women with chlamydial salpingitis, a complication of *C. trachomatis* infection (chlamydia), than among individuals with uncomplicated or transient infections, such as those limited to the lower genitourinary tract [[58] and references therein]. However, despite its possibly greater sensitivity for etiologically relevant histories of infection, serology may also falsely identify some men who have never been infected as seropositive, leading to non-differential misclassification of exposure and a possible bias of the results towards the null.

Human papillomavirus infection

Of the aforementioned STIs, the first to be extensively investigated in relation to prostate cancer was HPV infection, particularly types 16 and 18, because of their newly discovered causal associations with several anogenital cancers, including cervical, penile, and anal carcinomas [59]. This discovery led to a series of tissue-based and seroepidemiologic investigations of HPV

infection and prostate cancer beginning in the early 1990s. While the first of these studies observed suggestive positive findings [60-64], spurring additional research into this field, most subsequent studies have observed generally null results [[65] and references therein, [56, 58, 66-74]]. (Findings from most previous tissue-based studies have been expertly summarized in Strickler and Goedert's review article [65]; findings from seroepidemiologic studies are summarized in Table 4). Initially, investigators proposed that discrepancies between earlier and later seroepidemiologic findings might be due to differences in the timing of specimen collection relative to prostate cancer diagnosis, as earlier positive studies collected serum specimens decades before prostate cancer diagnosis, whereas later null studies generally collected specimens a few years before or at the time of diagnosis [65]. Therefore, antibody titers could have possibly waned since an earlier, causative "hit and run" HPV infection or related sexual factor [65], or during the process of invasive prostate cancer development [66]. However, as null findings have since been observed in more recent seroepidemiologic studies with early specimen collection [70, 73], and as minimal/no evidence of high-risk HPV DNA has been observed in most recent investigations of prostate cancer tissue [68, 69, 72, 75-79], these explanations seem less likely. Instead, it appears more likely that HPV infection does not influence prostate cancer risk, at least by biologic mechanisms proposed to date. Therefore, unless new biologic mechanisms are proposed, or radically new laboratory and/or epidemiologic methods are developed, further similar investigations are unlikely to yield additional insight.

Human herpesvirus type 8 infection

Although not as extensively studied as HPV infection, HHV-8 infection was also investigated in relation to prostate cancer because of its recently discovered causal relation with other cancers, namely Kaposi's sarcoma and primary effusion lymphoma [80]. Initially, studies

of HHV-8 infection and prostate cancer observed null associations [81, 82] or detected no evidence of HHV-8 infection when comparing cancerous to benign prostate tissue [83, 84] (Table 5). However, in 2004, Hoffman and colleagues [85] observed positive findings between HHV-8 seropositivity and prostate cancer in a series of case-control comparisons, most notably one conducted among men of African descent from Tobago, motivating several additional seroepidemiologic investigations. None of these subsequent investigations have, however, observed positive findings. Instead, most have observed findings more consistent with a null or even an inverse association [56, 58, 86, 87], leading the authors of the first positive study to propose that discrepancies between these null/inverse findings and their positive findings might be due to chance or possibly to an unknown environmental or genetic difference between Tobagan men and men from other study countries, as their positive association has reportedly remained significant after analysis of additional specimens from Tobago [87]. Therefore, more targeted investigations may be necessary to disentangle these two possibilities, and to explore a possible inverse association between HHV-8 infection and prostate cancer.

HSV-2, CMV and EBV infections

Although other herpesviruses, such as HSV-2, CMV, and EBV, were first investigated in relation to prostate cancer as early as the 1970s, only a handful of studies have been conducted on these viruses to date, most of which were conducted in the last few years after the introduction of new, considerably less cross-reactive serologic assays for HSV-2. However, despite use of these new, improved assays, most later studies of HSV-2 [56, 73, 86, 88], CMV [56, 88] and EBV seropositivity [88] have observed null or generally unstable associations with prostate cancer (Table 5). One exception to this statement is the recently observed positive association between HSV-2 seropositivity and prostate cancer risk in a U.S. military study using

serum specimens collected a mean of 94 months before diagnosis, but not using specimens collected a mean of 10 months before diagnosis [73]. However, as no association was observed in the only other study with early specimen collection [86], these findings may have been observed by chance. Finally, in a later tissue-based study, no association was observed for EBV DNA positivity, and no evidence of HSV-2 or CMV DNA was detected in prostate tissue [72]. Thus, taken together, findings from these few studies do not support an association between HSV-2, CMV or EBV infection and risk of prostate cancer. However, it is possible that these studies could have potentially missed an association if only certain types of herpesvirus infections, such as those acquired during a critical period of prostate development, are important for prostate carcinogenesis. In this case, new biomarkers or new types of epidemiologic studies would be necessary to more fully explore the possible roles of herpesviruses in prostate carcinogenesis.

Chlamydia trachomatis infection

Another STI that has recently been investigated in relation to prostate cancer risk is chlamydia, a common bacterial STI. Initially, this STI was included in investigations of prostate cancer risk as a marker of sexual activity [63]; however, it has since been investigated in relation to prostate cancer in its own right because of its known ability to cause chronic, persistent infections, and asymptomatic and symptomatic prostate inflammation in some men [[56, 58, 89] and references therein]. Despite this promising rationale, most studies to date have observed generally null or occasionally inverse associations between a history of chlamydia and prostate cancer, irrespective of the study design, method of assessment (serology or self-report), type of *C. trachomatis* antibody assay used (enzyme immunoassay or micro-immunofluorescence assay), and timing of specimen collection if assessed by serology [42, 56-58, 63, 73, 89] (Table

5).

A few exceptions to this statement exist. In a recent study conducted in the U.S. military, a suggestive positive association was observed for *C. trachomatis* seropositivity using serum specimens collected at least five years before diagnosis, but not using specimens collected closer to diagnosis [73]. However, as null or inverse associations were observed in other studies with early specimen collection [63, 89], this recent sub-group finding may have been observed by chance. Other possible exceptions include the suggestive positive associations observed for self-reported history of chlamydia and prostate cancer among Asian-American and Latino men in the California Men's Health Study [57]. However, these self-reported associations are difficult to interpret because: 1) they were based on very few exposed cases; 2) chlamydia is frequently asymptomatic in men and thus difficult to assess by self-report; and 3) chlamydia diagnostics have only been available since 1985. Therefore, self-reported infections must have been acquired after 1985 when participants were older and must have been either symptomatic or diagnosed in participants' female partners, as men are rarely screened for chlamydia. A final exception to the overall generally null/inverse findings is the positive association observed for *C. trachomatis* IgA seropositivity, a marker of chronic chlamydial infection, among African-American participants in the PLCO study. However, no association was observed for another marker of chronic chlamydial infection, *C. trachomatis* heat shock protein 60 seropositivity [56], raising the possibility that these findings were observed by chance or that only certain chronic chlamydial infections (perhaps of a certain duration, or localized to the prostate) are associated with risk. Therefore, future investigations might benefit from novel biologic markers that can detect and distinguish between these different types of infection, and from examining men most likely to have had chronic infections.

Trichomonas vaginalis infection

Another STI gaining recent attention is *Trichomonas vaginalis* infection (trichomonosis). *T. vaginalis* is a common, sexually transmitted, extracellular protozoan known to cause vaginitis in 20-50% of infected women and non-gonococcal urethritis and/or prostatitis in a small percentage of infected men [90, 91]. To our knowledge, *T. vaginalis* was first proposed as an infectious agent "of interest" for prostate carcinogenesis by Wynder and colleagues [10], possibly because of its known ability to cause non-gonococcal prostatitis [13], and its common occurrence [92]. Gardner and colleagues [93, 94] further contributed to this hypothesis when they observed inflammatory infiltrates and focal areas of atypical epithelial hyperplasia near *T. vaginalis* organisms in prostate tissue from infected men, leading them to propose that *T. vaginalis* might contribute to prostate carcinogenesis via an IgE-mediated anti-trichomonad inflammatory immune mechanism.

Although *T. vaginalis* is known to cause clinical prostatitis and thus could potentially contribute to prostate carcinogenesis via symptomatic prostatic inflammation, it was not and still is not believed to be a major cause of clinical prostatitis. It may, however, be a frequent cause of asymptomatic prostatic inflammation. We have previously hypothesized that its frequently asymptomatic or non-specific presentation may allow it to persist undetected and untreated in the male urethra and thus possibly ascend to the prostate with greater frequency than other more symptomatic sexually transmitted infectious agents that are now readily detected and treated (e.g., *N. gonorrhoeae*) [95]. This hypothesis was based on the pre-antibiotic era observation of a 10-14 day delay between onset of gonorrhea and posterior urethral involvement [96], and the observed dramatic decline in gonococcal prostatitis following the introduction of antibiotics, from which we inferred that the longer an infection is left untreated, either due to lack of

effective treatment or symptoms, the more likely it is to involve the prostate. We further hypothesized that once/if *T. vaginalis* reaches the prostate, its frequent lack of symptoms may also allow it to persist within the prostate, where it may establish a chronic focus of infection [95]. This hypothesis is supported by findings from early, pre-antibiotic era studies of trichomonosis in which investigators frequently found evidence of *T. vaginalis* in prostate specimens from asymptomatic male partners of women with trichomonal vaginitis [97-102], some of whom were chronically infected [101].

In addition to eliciting inflammation within the prostate, another possible mechanism by which *T. vaginalis* may contribute to carcinogenesis is by directly damaging or lysing prostate epithelial cells [95]. In *in vitro* studies, *T. vaginalis* adherence to host urogenital epithelium has been observed to lead to epithelial cell death and disruption of epithelial monolayer integrity [103-106]. Epithelial cells damaged or lysed by *T. vaginalis* must then be regenerated, allowing for possible DNA replication errors (particularly if replication occurs in the face of a potentially genotoxic inflammatory immune response) and hyperproliferation if secretion of growth factors from inflammatory immune cells becomes dysregulated [95]. *T. vaginalis* adhesion to urogenital epithelium has also been observed to upregulate expression of anti-apoptotic genes [107], which may potentially prevent apoptosis and allow proliferation of prostate epithelial cells damaged but not lysed by infection. All of these insults - inflammation, cell injury/death and inhibition of apoptosis - may then potentially lead to the development of PIA lesions [95]. This hypothesis is supported by Gardner and colleagues' [93, 94] observation of focal areas of atypical prostatic epithelial hyperplasia near *T. vaginalis* organisms and associated inflammatory infiltrates, which, although not described as such, could possibly represent PIA lesions. Finally, as a further mechanism by which *T. vaginalis* may contribute to prostate carcinogenesis, *T. vaginalis* has

been observed to alter local polyamine concentrations, which have been found to be related to prostate cancer in some studies ([95] and references therein).

To our knowledge, trichomonosis was first investigated in relation to prostate cancer in a small case-control study conducted in the late 1980s, the results of which were largely inconclusive because none of the participants reported a history of trichomonosis [45]. However, some participants likely did have a history of trichomonosis: 1) because trichomonosis tends to be asymptomatic in men and to be treated presumptively rather than specifically diagnosed in symptomatic men; and 2) because participants reported histories of other more symptomatic, well-known STIs, such as gonorrhea and syphilis [95]. To our knowledge, no further studies were conducted on trichomonosis and prostate cancer for almost two decades after this study, until we conducted a nested case-control study of trichomonosis and prostate cancer risk in the HPFS, using serology to ascertain a history of trichomonosis. In that study, we observed a positive association between *T. vaginalis* serostatus and overall prostate cancer risk (odds ratio (OR) =1.43, 95% CI: 1.00-2.03), and a suggestion of a more pronounced association for high-grade disease (OR=1.76, 95% CI: 0.97-3.18) [95]. We have since conducted two additional investigations of trichomonosis and prostate cancer risk, one in the Prostate Cancer Prevention Trial (PCPT) [108], and the other in the Physician's Health Study (PHS) [109]. While results in the PCPT were null, possibly due to the early stage of prostate cancer detected in that trial [108], results in the PHS were more consistent with our original findings. In that study, we observed a slight, non-significant positive association between *T. vaginalis* serostatus and overall prostate cancer risk (OR=1.23, 95% CI: 0.94-1.61), and significant, considerably more pronounced positive associations for risks of extraprostatic (OR=2.17, 95% CI: 1.08-4.37) and metastatic/fatal prostate cancer (OR=2.69, 95% CI: 1.37-5.28) [109]. Thus collectively, findings

from these initial studies suggest that trichomonosis may be associated with an increased risk of prostate cancer with the greatest potential for progression to fatal disease. However, additional investigations of high-grade and advanced stage prostate cancer will be necessary to rule out the possible role of chance, as well as additional epidemiologic and biologic studies to determine the validity of this possible association (e.g., studies to investigate possible confounding by other infectious agents).

CONCLUSION AND FUTURE PERSPECTIVE

Considering the literature on STIs and prostate cancer risk as a whole, particularly studies less susceptible to biases, a few hints exist to suggest an association between STIs and risk of prostate cancer. However, this possible association is not clear-cut, and may require more subtle investigations, both with respect to STI exposure and prostate cancer outcome, to elucidate its meaning. For instance, many STIs may have the potential to contribute to prostate carcinogenesis, as many are capable of infecting the prostate and eliciting inflammation or transforming prostate epithelial cells; however, their likelihood of contributing to prostate cancer risk may depend on additional characteristics, such as their typical duration of infection, likelihood of prostate infection, degree of inflammation elicited, degree of epithelial cell damage, and degree of other infectious agent-specific attribute(s). These characteristics may also vary in different settings, such as by calendar time (e.g., pre- versus current-antibiotic era), country (e.g., countries with access to timely STI treatment versus those without access), race, socio-economic status, or genetic background. Therefore, these characteristics (e.g., duration of infection) or markers of these characteristics (e.g., country) may need to be taken into consideration in interpreting previous study findings and in designing future studies. Future studies of STIs and prostate cancer would also benefit from the development of new biomarkers, such as those that

indicate chronicity of infection or prostate involvement.

In addition to considering various aspects of STI exposure, studies of STIs and prostate cancer may also need to consider aspects of prostate cancer outcome, as STI(s) may not contribute to risk of all prostate tumors. For instance, STI(s) could possibly contribute to risk of prostate tumors with the potential to progress to clinically manifest or life-threatening disease, but not to risk of indolent prostate tumors, such as possibly observed in the case of trichomonosis [95, 108, 109]. Therefore, prostate cancer characteristics may also need to be taken into consideration in interpreting previous study findings and in designing future studies.

Although this review has focused on infectious agents with known sexual routes of transmission, other genitourinary infectious agents not typically considered to be sexually transmitted may also be important for prostate carcinogenesis – for instance, infectious agents responsible for bacterial prostatitis. These organisms have been proposed to be sexually acquired, at least in some instances, based on their detection in the reproductive/genitourinary tract of both prostatitis patients and their sexual partners [110]. Therefore, these agents may be potential sexually transmitted infectious candidates for prostate carcinogenesis. New sexually transmitted infectious agents of possible relevance for prostate cancer are also likely to be discovered/recognized. For instance, xenotrophic murine leukemia virus-related virus (XMRV), a recently discovered virus in prostate tissue, has been proposed to be sexually transmitted based on its increased infectiousness in the presence of semen and its detection in prostate fluid, a component of semen [111]. This virus was initially identified in prostate tissue from men with prostate cancer and was found to be considerably more common in men homozygous for the R462Q variant allele of the ribonuclease L gene, an innate antiviral gene associated with prostate cancer risk in some studies, than in men carrying non-variant alleles [112]. XMRV has

subsequently been found to be positively associated with prostate cancer, particularly high grade prostate cancer, in a study of American men [113], but not in a study of German men [114], irrespective of R462Q variant status. Therefore, this virus may also be a potential sexually transmitted infectious candidate for prostate carcinogenesis.

In summary, given the hints of an association between STI(s) and prostate cancer risk from the literature to date, additional investigations of known, promising STI candidates, such as trichomonosis, are warranted, as well as investigations of the expanding pool of newly discovered/recognized STI candidates. However, before beginning these studies, investigators should carefully consider the relevance of their measured STI exposure (i.e., how likely it is to capture prostate infection, chronic infections, etc.), the relevance of their prostate cancer outcome, and the appropriateness of their choice of study population (i.e., how likely the study population is to have experienced the relevant exposure or outcome of interest), in addition to typical design considerations (e.g., information biases), to more fully inform possible associations.

EXECUTIVE SUMMARY

Early hypotheses for sexually transmitted infections (STIs) and prostate cancer

- A sexually transmitted etiology for prostate cancer was first proposed by Ravich and Ravich in the early 1950s to explain the higher observed prevalence of prostate cancer among mainly uncircumcised non-Jewish than circumcised Jewish men, similar to patterns for penile cancer and cervical cancer among female partners of these men. This hypothesis, together with other contemporary observations and hypotheses, led to a series of epidemiologic investigations on STIs and prostate cancer beginning in the 1970s.

Results for early studies of STIs and prostate cancer

- Early studies of STIs and prostate cancer (i.e., those conducted in men more likely to have been infected in the pre-antibiotic era) were primarily small case-control studies with retrospective, self-reported assessment of a narrow range of STIs, typically either any STIs, or gonorrhea and syphilis. In general, findings from these studies were supportive of a positive association between one or more of the more commonly reported STIs and prostate cancer.
- Based on their study design and analysis, early studies of STIs and prostate cancer may have been susceptible to recall bias, interviewer bias, and confounding by hormone-associated libido, all of which may have possibly led to false positive associations. On the other hand, greater STI exposure among men who passed through adolescence and early adulthood in the pre-antibiotic era, and later prostate cancer presentation among men diagnosed before the introduction of prostate specific antigen (PSA) testing may have possibly contributed to true positive associations between STIs and prostate cancer. Therefore, it is difficult to determine the relative contributions of possible biases in study design, confounding, greater STI

exposure, and later prostate cancer presentation to findings from early studies of STIs and prostate cancer.

Results for later studies of STIs and prostate cancer

STIs assessed by self-report, medical record abstraction, or registry query

- Similar to earlier case-control studies, several later case-control studies observed suggestive positive associations between histories of more commonly reported STIs and prostate cancer. These positive findings were observed in spite of several differences between earlier and later studies that might have served to reduce the likelihood of observing both true and false positive associations: less pre-antibiotic era STI exposure, earlier prostate cancer presentation, adjustment for correlates of libido, and lesser susceptibility to interviewer bias. However, one lingering concern for later case-control studies that may still have contributed to false positive associations is recall bias.
- Only a few prospective studies have investigated self-reported histories of gonorrhea and syphilis in relation to risk of prostate cancer to avoid concerns of recall bias. In general, these studies have observed null associations, although positive findings among foreign-born men leave open the possibility of associations with specific types of infection (e.g., infections with a longer duration, untreated infections) less likely to have been observed in American cohort study populations to date.

STIs assessed by serology and other laboratory methods

- Since the original hypothesis on STIs and prostate cancer was first proposed, several new STIs have been discovered or recognized as STIs (e.g., infections by oncogenic human papillomavirus (HPV) types, human herpesvirus type 8 (HHV-8) and *Chlamydia trachomatis*), and new and better tests to detect histories of other known STIs have been

developed (e.g., herpes simplex virus type 2 (HSV-2) and *Trichomonas vaginalis* infections). Several new resources for prostate cancer research have also been created (e.g., cohort studies with blood collection), allowing for prospective investigations of STIs and prostate cancer risk, and serologic detection of STI histories, both of which serve to reduce recall bias.

- In general, results for HPV, HHV-8, HSV-2, cytomegalovirus, Epstein-Barr virus, and *C. trachomatis* infection have been null. However, positive or inverse findings in some studies/sub-group analyses preclude firm conclusions. Therefore, more subtle investigations targeted at specific hypotheses (e.g., chronic prostate infections, infection during a critical period of prostate growth, etc.) may be necessary to elucidate possible associations between these STIs and prostate cancer.
- Another STI gaining recent attention is *Trichomonas vaginalis* infection, a common, but less well-known, protozoan infection. Results from three seroepidemiologic studies conducted to date suggest that *T. vaginalis* infection may be associated with risk of prostate cancer with the greatest potential to progress to fatal disease. However, additional studies will be necessary to rule out the possible role of chance, and to investigate the validity of this possible association.

Conclusion and future perspective

- Considering the STI and prostate cancer literature as a whole, a few hints exist to suggest that STIs may contribute to risk of prostate cancer. However, more subtle investigations, both with respect to STI exposure and prostate cancer outcome, will be necessary to elucidate the possible role(s) of known, promising STI candidates, as well as the expanding pool of newly discovered/recognized STI candidates.

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Table 1: Early* case-control studies of sexually transmitted infections (STIs) and prostate cancer

STIs assessed by self-report, medical record abstraction, or registry query									
First author, year	Control definition	Sample size		Exposure	Results†				
		Cases	Controls		Any STIs	Gonorrhea	Syphilis	Other STIs	STIs among female partners
Steele, 1971 [6]	Hospital BPH	39	39 35	Self-report	12.8 vs 2.5% 12.8 vs 5.7%				
Krain, 1974 [7]	Hospital	221	221	Self-report	28 (12.7‡) vs 5 (2.3%‡), p=0.01				
Niijima, 1980 [22]	Hospital	187	200	Medical record	NS				
Mandel, 1987 [8]	Hospital Population	250	226 240	Self-report	OR=1.89 (0.84-4.24) OR=1.83 (0.91-3.70)				*Any STIs:* OR=2.71 (1.14-6.46) *Any STIs:* OR=2.09 (1.02-4.29)
Ross, 1987 [21]	Black population White population	142 142	142 142	Self-report	OR=1.7, p=0.03 OR=2.3, p=0.07				
Oishi, 1990 [25]	Hospital BPH	100	100 100	Self-report	OR=0.66 (0.26-1.67) OR=0.36 (0.16-0.83)				*Any STIs:* OR=1.81 (0.16-19.9) *Any STIs:* OR=1.07 (0.15-7.83)
Fincham, 1990 [24]	Population	382	625	Self-report	OR=1.02, NS				*Cervical cancer:* 1 vs 0%, OR=4.94, NS
Wynder, 1971 [10]	Black hospital White hospital	48 251	52 344	Self-report		26 vs 37%, NS 10 vs 8%, NS			
Heshmat, 1973 [11]	NA§	NA§	NA§	Registry		Coherence coefficient =0.990, p<0.05			
Heshmat, 1975 [9]	Hospital			Self-report		25 vs 12 discordant pairs‖, p<0.05			
Baker, 1981 [17]	BPH	44	90	Self-report		32 vs 22%	5 vs 8%	*"Recurrent genital sores":* 5 vs 0% *Pediculus pubis:* 5 vs 7%	
Mishina, 1985 [23]	Population	100	100	Self-report		OR=1.45, χ^2=0.59	OR=1.50, χ^2=0.10		*Gonorrhea:* OR=1.33, χ^2=0 *Syphilis:* OR=5.00, χ^2=0.50 *Colpitis/vaginitis:* OR=1.00, χ^2=1.00 *Cervical cancer:* OR=5.00, χ^2=0.50
Lees, 1985 [14]	Hospital BPH	83	83 83	Medical record		OR=0.72, NS OR=1, NS	OR=2.75, p<0.2 OR=5.5, p<0.05		
Feminella, 1975 [27]	BPH	101	101	Medical record					*Cervical cancer:*** 3 vs 0%, χ^2=3.04, NS relative to controls χ^2=207, p<<<0.01 relative to U.S.

							population
Greenwald, 1979 [28]	Widowers who died of any other cause†† Married men with any other cancer‡‡	151 541	411 497	Registry			*Cervical cancer:* OR=1.55 (0.65-3.86) *Cervical cancer:* OR=0.35 (0.12-0.98)
Jackson, 1981 [26]	Hospital	205	205	Self-report		*Urethritis:* reported "more frequently by [cases] than controls" OR<2, p<0.05	*Genital infection:* reported by "more [cases] than controls", "definite, although statistically not significant" *Genital cancer:* NS

STIs assessed by serology or other laboratory methods

First author, year	Control definition	Sample size		Exposure	Results†		
		Cases	Controls		HSV-2	CMV	EBV
Herbert, 1976 [16]	BPH	28	20	Antibody	71 vs 66%, NS		
Sanford, 1977 [19]	BPH Bladder cancer Non-genitourinary cancer	35	23 19 18	Antibody		95, 95, 80 vs 70, 53, 79%§§ 95, 95, 80 vs 78, 89, 84%§§ 95, 95, 80 vs 61, 78, 55%§§	
Baker, 1981 [17]	BPH	50	159	Antigen Antibody	2 (4.0‡) vs 4 (2.5%‡) 68 vs 51%, p<0.05		
Boldogh, 1983 [20]	Normal BPH	10	13 9	DNA, RNA or antigen	2 (20.0‡) vs 1 (7.7%‡) 2 (20.0‡) vs 0 (0.0%‡)	4 (40.0‡) vs 2 (15.4%‡) 4 (40.0‡) vs 3 (33.3%‡)	
Haid, 1984 [18]	BPH	27	33	Antigen	25.5 vs 24.2%, p>0.8		
Mandel, 1987 [8]	Hospital Population	250	226 240	Antibody	OR=0.27 (0.08-0.98) OR=0.46 (0.18-1.21)	OR=1.33 (0.56-3.16) OR=1.14 (0.41-3.15)	OR=0.50 (0.13-2.00) OR=0.86 (0.29-2.55)

BPH = benign prostatic hyperplasia; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV-2 = herpes simplex virus type 2; OR = odds ratio; NA = not applicable; NS = not statistically significant.

* Early was defined as a mean, median or midpoint age (depending on how the study population was described) of ≥25 years of age as of 1937, the approximate year when sulphonamide antibiotics were first introduced for treatment of gonorrhea.

† Raw results are provided exactly as described in each manuscript unless otherwise specified. These results are interpreted in the text. In the case in which two proportions or numbers are presented, the first refers to cases and the second to controls unless otherwise specified.

‡ Derived from data provided in the manuscript.

§ Ecologic study.

‖ The first number of pairs refers to discordant pairs in which the case was exposed and the control was unexposed, and the second number of pairs refers to discordant pairs in which the case was unexposed and the control was exposed.

** Results for cervicitis, vaginitis and syphilis are not presented because the timing of these diagnoses with respect to their husbands' prostate cancer or BPH diagnosis is unclear.

†† Cases were widowers who died of prostate cancer.

‡‡ Cases were married men with prostate cancer.
§§ Three different serologic assays were used.

Table 2: Later* case-control studies of sexually transmitted infections (STIs) assessed primarily by self-report and prostate cancer

First author, year	Control definition	Sample size			Results†				
		Cases	Controls	Exposure	Any STIs	Gonorrhea	Syphilis	Other STIs	STIs among female partners
Hayes, 1992 [46]	Hospital	100	113	Self-report	NS (low prevalence)				
Ewings, 1996 [47]	Hospital and BPH	159	325	Self-report	OR=2.06 (0.38-11.22)				*Cervical cancer:* OR=0.56 (0.06-2.98)
Lightfoot, 2004 [38]	Population	760	1,632	Self-report	OR=2.12 (1.27-3.53)				
Fernandez, 2004 [39]	Hospital	273	254	Self-report	OR=1.7 (1.1-2.5)				
Checkoway, 1987 [45]	BPH	40	64	Self-report		10.0 vs 7.8%	5.0 vs 4.7%	*Genital herpes:* 0.0 vs 0.0%‡ *Other STI:* 0.0 vs 0.0%	
Honda, 1988 [44]	Population	216	216	Self-report		OR=1.4 (0.8-2.6)	OR=6.0 (0.7-276.0)		
Ilic, 1996 [40]	Hospital	101	202	Self-report		4.0 vs 0.0%, p>0.10§			
Hsieh, 1999 [36]	Hospital	320	246	Self-report		χ for contrast or trend=0.73, p=0.47		*Other STI:* χ for contrast or trend= -0.31, p=0.76	
Hayes, 2000 [41]	Black population	479	594	Self-report Antibody		OR=1.6 (1.2-2.2)	OR=2.4 (1.2-4.9) OR=2.2 (1.0-4.6)‖		
	White population	502	721	Self-report Antibody		OR=1.4 (0.7-2.9)	OR=2.8 (0.2-49.1) OR=0.8 (0.2-3.5)‖		
Rosenblatt, 2001 [42]	Population	753	703	Self-report		OR=1.50 (1.02-2.18)	OR=1.60 (0.51-5.02)	*Urethritis:* OR=0.80 (0.38-1.68) *Genital herpes:* OR=1.65 (0.69-3.99) *Genital warts:* OR=0.88 (0.38-2.08) **	
Patel, 2005 [37]	Black population	353	257	Self-report		OR=1.0 (0.7-1.6)	OR=1.3 (0.5-3.2)	*Genital herpes:* Could not be estimated *Chancroid:* OR=0.2 (0.02-1.9) *Other STIs:* OR=1.8 (0.3-9.6)	
	White population	347	347			OR=1.1 (0.5-2.5)	Could not be estimated	*Genital herpes:* OR=1.2 (0.3-5.5) *Chancroid:* OR=0.8 (0.05-13.0)	

							Other STIs: OR=0.7 (0.1-3.9)	
Pelucchi, 2006 [48] and La Vecchia, 1993 [49]	Hospital	280	689	Self-report	OR=0.64 (0.20-2.03)	OR=1.75 (0.10-31.44)	*Genital herpes:* NS (low number exposed) *Genital warts:* Could not be estimated	
Sarma, 2006 [43]	Population	129	703	Self-report	OR=1.78 (1.13-2.79)	OR=1.54 (0.55-4.34)	*Herpes:* OR=0.89 (0.11-7.70) *Other STIs:* OR=1.12 (0.23-5.47)	*Cervical cancer:* OR=2.06 (0.41-10.45)
Newell, 1989 [50]	Other cancer	110	220				*Genital warts:* NS	

BPH = benign prostatic hyperplasia; OR = odds ratio; NS = not statistically significant.

* Later was defined as a mean, median or midpoint age (depending on how the study population was described) of <25 years of age as of 1937, the approximate year when sulphonamide antibiotics were first introduced for treatment of gonorrhea.

† Raw results are provided exactly as described in each manuscript unless otherwise specified. These results are interpreted in the text. In the case in which two proportions or numbers are presented, the first refers to cases and the second to controls unless otherwise specified.

‡ Results for *Trichomonas vaginalis* infection are described later in the text in the section on *T. vaginalis* infection.

§ Recalculated using Fisher's exact test as p=0.01.

‖ Serologic testing was performed on a subset of the study population: 125 Black cases, 131 Black controls, 146 White cases and 155 White controls.

** Results for *Chlamydia trachomatis* infection are described later in Table 5.

Table 3: Prospective studies of sexually transmitted infections (STIs) assessed by self-report, medical record abstraction, or registry query and prostate cancer

First author, year	Study design	Sample size	Exposure	Results*		
				Gonorrhea	Syphilis	Other STIs
Hiatt, 1994 [51]	Nested case-control	238 cases, 238 controls	Medical record	OR=1.5 (0.5-4.2)		
Michalek, 1994 [52]	Cohort	Approximately 10,262 exposed†	Registry		SIR=58 (37-86)	
Sutcliffe, 2006 [55]	Cohort	32,932	Self-report	RR=1.04 (0.79-1.36)	RR=1.06 (0.44-2.59)	
Huang, 2008 [56]	Nested case-control	*Black:* 103 cases, 368 controls *White:* 765 cases, 915 controls	Self-report	OR=1.0 (0.6-1.6) OR=1.4 (0.8-2.2)	OR=0.8 (0.3-2.4) OR=0.4 (0.1-1.9)	
	Cohort	*Black:* 1,516‡ *White:* 29,995‡		RR=0.9 (0.6-1.4) RR=1.0 (0.8-1.3)	RR=0.7 (0.3-1.8) RR=0.4 (0.1-1.3)	
Cheng, 2010 [57]	Cohort	*Black:* 5,784	Self-report	RR=1.12 (0.88-1.44)	RR=1.32 (0.80-2.17)	*Genital herpes:* RR=0.91 (0.57-1.46) *Genital warts:* RR=0.55 (0.28-1.07)§
		White: 42,409		RR=0.94 (0.78-1.14)	RR=0.93 (0.54-1.61)	*Genital herpes:* RR=0.78 (0.58-1.06) *Genital warts:* RR=0.93 (0.70-1.25)§
		Asian: 6,024		RR=1.16 (0.56-2.41)	RR=3.72 (1.35-10.26)	*Genital herpes:* RR=1.20 (0.38-3.81) *Genital warts:* RR=Could not be estimated§
		Latino: 11,213		RR=1.39 (1.01-1.91)	RR=1.38 (0.64-2.93)	*Genital herpes:* RR=1.16 (0.63-2.13) *Genital warts:* RR=0.44 (0.16-1.19)§
		Other: 3,245		RR=1.43 (0.70-2.92)	RR=0.91 (0.12-6.66)	*Genital herpes:* RR=0.75 (0.10-5.54) *Genital warts:* RR=0.58 (0.08-4.25)§

OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio.

* Raw results are provided exactly as described in each manuscript unless otherwise specified. These results are interpreted in the text.
† Derived from data provided in the manuscript.
‡ Provided by authors.
§ Results for *Chlamydia trachomatis* infection are described later in Table 5.

Table 4: Seroepidemiologic studies of human papillomavirus (HPV) infection and prostate cancer

First author, year	Study design	Sample size	Result*		
			HPV-16	HPV-18	Other HPV types
Strickler, 1998 [115]	Case-control	63 cases, 144 BPH controls	p=0.54 for geometric mean comparison 1.6 vs 4.9%, p=0.44		*HPV-11:* p=0.64 for geometric mean comparison
Strickler, 1998 [116]	Case-control	47 cases, 48 endocrine disorder controls	6 vs 4%		
Dillner, 1998 [63]	Nested case-control	165 cases, 290 controls	OR=2.58 (0.77-8.56)	OR=2.88 (1.27-6.56)	*HPV-33:* OR=0.66 (0.26-1.66)† *HPV-11:* OR=0.61 (0.27-1.39)†
Hisada, 2000 [64]	Nested case-control	48 cases, 63 controls	OR=2.7 (0.9-7.9)		
Rosenblatt, 2003 [66]	Case-control	642 cases, 570 population controls	OR=1.06 (0.71-1.57)	OR=1.36 (0.69-2.69)	
Adami, 2003 [67]	Case-control	238 cases, 210 population controls	OR=0.7 (0.4-1.3)	OR=0.9 (0.5-1.9)	*HPV-33:* OR=1.6 (1.0-2.7)
Korodi, 2005 [70]	Nested case-control	*Finland:* 136 cases, 498 controls *Sweden:* 87 cases, 346 controls *Norway:* 577 cases, 1,752 controls *Total:* 800 cases, 2,596 controls	OR=0.44 (0.15-1.26) OR=1.18 (0.53-2.66) OR=0.97 (0.64-1.46) OR=0.90 (0.64-1.26)	OR=0.55 (0.19-1.60) OR=2.00 (0.37-10.92) OR=0.81 (0.47-1.40) OR=0.79 (0.49-1.26)	*HPV-33:* OR=1.04 (0.45-2.44) *HPV-33:* OR=0.89 (0.36-2.22) *HPV-33:* OR=1.00 (0.69-1.47) *HPV-33:* OR=0.99 (0.72-1.38)
Sitas, 2007 [71]	Case-control	205 cases, 673 other cancer and cardiovascular disease controls	*Medium:*‡ OR=1.33 (0.87-2.04) *High:*‡ OR=1.22 (0.77-1.93)		
Sutcliffe, 2007 [58]	Nested case-control	691 cases, 691 controls	OR=0.83 (0.57-1.23)	OR=1.04 (0.66-1.64)	*HPV-33:* OR=1.14 (0.76-1.72)
Huang, 2008 [56]	Nested case-control	*Black:* 103 cases, 368 controls *White:* 765 cases, 915 controls	OR=1.0 (0.7-1.6) OR=0.9 (0.7-1.3)	OR=0.9 (0.6-1.5) OR=1.2 (0.8-1.7)	
Dennis, 2009 [73]	Nested case-control	267 cases, 267 controls	*Mean 10 mo§, HPV-16 or -18:* OR=0.92 (0.59-1.45), *HPV-16,-18,-6 or -11:* OR=1.07 (0.75-1.52) *Mean 94 mo§, HPV-16 or -18:* OR=1.13 (0.73-1.75), *HPV-16,-18,-6 or -11:* OR=0.98 (0.69-1.40) *>60 mo§, HPV-16 or -18:* OR=1.20 (0.74-1.95), *HPV-16,-18,-6 or -11:* OR=1.00 (0.67-1.50)		
Sutcliffe, 2010 [74]	Nested case-control	616 cases, 616 controls	*Weak:*‡ OR=0.94 (0.53-1.64) *Strong:*‡ OR=1.07 (0.77-1.48)	*Weak:*‡ OR=0.75 (0.27-2.04) *Strong:*‡ OR=0.87 (0.47-1.63)	*HPV-31, weak:*‡ OR=0.76 (0.45-1.28) *HPV-31, strong:*‡ OR=1.15 (0.80-1.64)

BPH = benign prostatic hyperplasia; OR = odds ratio.

* Raw results are provided exactly as described in each manuscript unless otherwise specified. These results are interpreted in the text. In the case in which two proportions or numbers are presented, the first refers to cases and the second to controls unless otherwise specified.

† Crude OR. Other ORs presented for Diller, 1998 [63] are adjusted.

‡ Seropositivity.

§ Collection of serum before prostate cancer diagnosis.

Table 5: Later* case-control studies of other sexually transmitted infections (STIs) typically assessed by serology or other laboratory methods and prostate cancer

First author, year	Study design	Sample size	Exposure	Result†		
				HHV-8	HSV-2, CMV or EBV	*C. trachomatis*
Monini, 1996 [81]	Case-control	8 cases, 8 BPH controls	DNA	25 vs 63%		
Tasaka, 1997 [83]	Case-control	32 cases, 20 BPH controls	DNA	No DNA detected		
Lebbe, 1997 [84]	Case-control	6 cases, 13 BPH controls, 3 normal controls	DNA	No DNA detected		
Sitas, 1999 [82]	Cross-sectional survey of cancer patients	3,293 patients (202 prostate cancer, 3,091 other cancer)	Antibody	NS		
Hoffman, 2004 [85]	Case-control	*Caribbean:* 138 Tobago cases, 140 Tobago controls 174 Trinidad controls *United States:* 100 cases, 99 other cancer controls 177 blood donor controls	Antibody	OR=2.24 (1.29-3.90) OR=2.63 (1.54-4.50) OR=1.65 (0.77-3.54) OR=4.67 (1.9-11.65)		
Korodi, 2005 [86]	Nested case-control	163 cases, 288 controls	Antibody	OR=0.74 (0.19-2.88)	*HSV-2:* OR=0.93 (0.44-1.96)	
Jenkins, 2007 [87]	Case-control	*Italy:* 10 cases, 34 BPH controls	Antibody	*Lytic IFA:* OR=1.08 (0.27-4.33) *K8.1 ELISA:* OR=0.813 (0.17-4.21) *ORF73 ELISA:* OR=0.60 (0.12-3.03)		
		United States:				
		Black: 41 cases, 98 BPH controls		*Lytic IFA:* OR=0.88 (0.35-2.24) *K8.1 ELISA:* OR=0.328 (0.10-1.11) *ORF73 ELISA:* OR=0.43 (0.16-1.18)		
		Black: 95 cases, 75 population controls		*Lytic IFA:* OR=0.56 (0.28-1.14) *K8.1 ELISA:* OR=0.52 (0.10-2.66) *ORF73 ELISA:* OR=0.62 (0.17-2.20)		
		White: 104 cases, 80 population controls		*Lytic IFA:* OR=0.71 (0.36-1.43) *K8.1 ELISA:* OR=0.76 (0.17-3.40) *ORF73 ELISA:* OR=0.77 (0.13-4.44)		
Sutcliffe, 2007 [58]	Nested case-control	691 cases, 691 controls	Antibody	OR=0.70 (0.52-0.95)		OR=1.13 (0.65-1.96)
Huang, 2008 [56]	Nested case-control	*Black:* 103 cases, 368 controls	Antibody	OR=0.3 (0.1-1.4)	*HSV-2:* OR=1.3 (0.8-2.0) *CMV:* OR=0.9 (0.4-1.7)	*IgG:* OR=1.1 (0.7-1.7) *IgA:* OR=2.1 (1.2-3.6)
		White: 765 cases, 915 controls		OR=1.3 (0.9-1.7)	*HSV-2:* OR=0.9 (0.7-1.3) *CMV:* OR=1.1 (0.9-1.3)	*IgG:* OR=1.2 (0.9-1.6) *IgA:* OR=0.7 (0.4-1.1)
Berrington de Gonzalez, 2006 [88]	Case-control	66 cases, 95 other cancer controls, 101 cardiovascular disease controls	Antibody		*HSV-2:* NS *CMV:* NS	
Bergh, 2007 [72]	Nested case-control	159 cases, 159 controls	DNA		*HSV-2:* No DNA detected	

				CMV: No DNA detected *EBV:* 9.4 vs 8.8%	
Dennis, 2009 [73]	Nested case-control	267 cases, 267 controls	Antibody	*HSV-2, mean 10 mo‡:* OR=1.17 (0.79-1.73) *HSV-2, mean 94 mo‡:* OR=1.60 (1.05-2.44) *HSV-2, >60 mo‡:* OR=2.04 (1.26-3.29)	*Mean 10 mo‡:* OR=1.07 (0.64-1.81) *Mean 94 mo‡:* OR=1.35 (0.79-2.31) *>60 mo‡:* OR=1.80 (0.96-3.38)
Dillner, 1998 [63]	Nested case-control	165 cases, 290 controls	Antibody		OR=1.04 (0.54-2.00)
Rosenblatt, 2001 [42]	Case-control	753 cases, 703 population controls	Self-report		OR=0.43 (0.12-1.48)
Anttila, 2005 [89]	Nested case-control	*Finland:* 138 cases, 497 controls *Sweden:* 86 cases, 341 controls *Norway:* 514 cases, 1,433 controls *Total:* 738 cases, 2,271 controls	Antibody		OR=0.71 (0.40-1.29) OR=0.52 (0.15-1.79) OR=0.70 (0.48-1.03) OR=0.69 (0.51-0.94)
Cheng, 2010 [57]	Cohort	*Black:* 5,784 *White:* 42,409 *Asian:* 6,024 *Latino:* 11,213 *Other:* 3,245	Self-report		RR=1.00 (0.62-1.63) RR=0.88 (0.59-1.32) RR=5.55 (1.70 -18.09) RR=1.82 (0.80-4.15) RR=1.39 (0.19-0.18)

BPH = benign prostatic hyperplasia; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ELISA = enzyme-linked immunosorbent assay; HSV-2 = herpes simplex virus type 2; HHV-8 = human herpesvirus type 8; OR = odds ratio; IFA = immunofluorescence assay; NS = not statistically significant; RR = relative risk.

* Later was defined as a mean, median or midpoint age (depending on how the study population was described) of <25 years of age as of 1937, the approximate year when sulphonamide antibiotics were first introduced for treatment of gonorrhea.

† Raw results are provided exactly as described in each manuscript unless otherwise specified. These results are interpreted in the text. In the case in which two proportions or numbers are presented, the first refers to cases and the second to controls unless otherwise specified.

‡ Collection of serum before prostate cancer diagnosis.