Gonorrhea, Syphilis, Clinical Prostatitis, and the Risk of Prostate Cancer

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Abstract

Background: **Although previous case-control studies have observed positive associations among gonorrhea, syphilis, clinical prostatitis, and prostate cancer, many may have been susceptible to recall and interviewer biases due to their retrospective designs. Therefore, to investigate these associations without concerns of recall and interviewer biases, we conducted a large, prospective investigation in the Health Professionals Follow-up Study.**

Methods: **In 1992, participants were asked to report their histories of gonorrhea, syphilis, and clinical prostatitis by mailed questionnaire. Prostate cancer diagnoses were ascertained by self-report on the 1994 and each subsequent biennial follow-up questionnaire and confirmed by medical record review.**

Results: **Of the 36,033 participants in this analysis, 2,263 were diagnosed with prostate cancer between the date of return of the 1992 questionnaire and 2002. No association was observed between gonorrhea [adjusted relative risk (RR), 1.04; 95% confidence interval (95% CI), 0.79-1.36] or syphilis (RR, 1.06; 95% CI, 0.44-2.59) and prostate cancer. Overall null results were also observed between clinical prostatitis and prostate cancer (RR, 1.08; 95% CI, 0.96-1.20), although a significant positive association was observed among younger men (<59 years) screened for prostate cancer (RR, 1.49; 95% CI, 1.08-2.06; $P_{interaction}$ = 0.006).**

Conclusions: **Gonorrhea and syphilis do not seem to be risk factors for prostate cancer in this cohort of men with a lower burden of sexually transmitted infections. Clinical prostatitis is also unlikely to be a risk factor, although possible roles for prostatitis in younger men and asymptomatic prostatic infection and inflammation cannot be ruled out.** (Cancer Epidemiol Biomarkers Prev 2006;15(11):2160–6)

Introduction

As early as the 1950s, Ravich and Ravich (1) proposed that infections may contribute to later development of prostate cancer. Since that time, several epidemiologic studies have investigated this hypothesis, the results of which were summarized in two meta-analyses by Dennis et al.: relative risk (RR) of 1.44 [95% confidence interval (95% CI), 1.24-1.66] for self-reported history of any sexually transmitted infection (STI); RR of 1.36 (95% CI, 1.15-1.61) for gonorrhea; RR of 2.30 (95% CI, 1.34-3.94) for syphilis (2); and RR of 1.57 (95% CI, 1.01-2.45) for clinical prostatitis (3), one cause of which is urogenital infection. Despite the magnitude and statistical significance of these associations, limitations of the contributing studies should be considered. The majority were case-control studies with retrospective assessment of exposure, which may allow for differential recall and interviewer biases, and use of either hospital-based controls, who may have a different distribution of exposure than the underlying population from which cases were derived, or controls with benign prostatic hyperplasia, which may have shared etiology with prostate cancer. Furthermore, findings from studies of clinical prostatitis and prostate cancer may have been influenced by detection bias, whereby men with prostatitis may have been more likely to be examined for prostate cancer than men without prostatitis.

Recently, there has been renewed interest in the potential influence of infections on prostate carcinogenesis, due to the frequent observation of inflammation near putative prostate cancer precursor lesions (4), one source of which may be sexually transmitted or urogenital infection. Additionally, some epidemiologic studies published since the Dennis et al. meta-analyses (2, 3) have observed positive findings among STIs, clinical prostatitis, and prostate cancer using nested case-control or more rigorous, retrospective case-control study designs, and analytic strategies for assessing detection bias (5-9). To further investigate STIs, clinical prostatitis, and prostate cancer and to address some of the limitations of previous studies, we conducted a large, prospective investigation of self-reported histories of gonorrhea, syphilis, and clinical prostatitis in relation to subsequent development of prostate cancer. We selected this study design to avoid concerns of differential recall, interviewer, and control selection biases. We did our investigation in the Health Professionals Follow-up Study, a well-characterized cohort with extensive information on STI correlates, prostate cancer risk factors, and screening behaviors to allow for adjustment for potential confounders and to address the possibility of detection bias, particularly in the analysis of clinical prostatitis and prostate cancer. Gonorrhea and syphilis were assessed by self-report, due to a lack of a reliable serologic test for gonorrhea and a low expected cumulative incidence of both infections in this cohort. Relative to other STIs, gonorrhea and syphilis lend themselves well to assessment by self-report because of their traditional

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recognition as STIs, frequent symptomatic presentation in men, and routine investigation in men seeking STI care, thereby reducing misclassification. Clinical prostatitis was also assessed by self-report. This condition encompasses both infectious/inflammatory and noninfectious/inflammatory etiologies. To our knowledge, this study is one of the first to prospectively investigate gonorrhea, syphilis and clinical prostatitis in relation to prostate cancer.

Materials and Methods

Study Population. The Health Professionals Follow-up Study is an ongoing, prospective study of 51,529 American male health professionals ages 40 to 75 years at enrollment in 1986. At that time, participants completed a baseline epidemiologic questionnaire on demographics, lifestyle, and medical history and a semiquantitative food frequency questionnaire. Since 1986, participants have completed questionnaires every 2 years to update exposure and disease status and every 4 years to update diet. The average response rate to follow-up questionnaires is 94% per follow-up cycle. Information on death was obtained from the National Death Index, U.S. Postal Service, or next of kin in response to follow-up questionnaires.

Included in this analysis were men who completed the baseline food frequency and 1992 follow-up questionnaires and who were free of a reported diagnosis of prostate and other cancers (except nonmelanoma skin cancer) as of the date of return of the 1992 questionnaire (n = 36,033). This study was approved by the Human Subjects Committee at the Harvard School of Public Health and the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health.

Assessment of Gonorrhea, Syphilis, and Clinical Prostatitis. On the 1992 follow-up questionnaire, participants were asked (*a*) did you ever have a diagnosis of syphilis, gonorrhea, neither; (*b*) have you ever had prostatitis or prostatic infection: no or yes; (*c*) how long did the symptoms persist: <1, 1 to 2, 3 to 5, 6 to 10, or >10 years; (*d*) were you ever treated for prostatitis: no or yes; and (*e*) if yes, at what age were you first treated: <30, 30 to 39, 40 to 49, 50 to 59, or ≥60. We categorized gonorrhea and syphilis separately as no, yes, or missing. Clinical prostatitis was explored as several different constructs, including ever prostatitis (no, yes, or missing), duration of prostatitis (<1, 1-2, ≥3 years, or missing), treatment for prostatitis (no, yes, or missing), and age at first treatment for prostatitis as a surrogate for age at first diagnosis of prostatitis (>30, 30-39, 40-49, 50-59, ≥60 years, or missing).

Identification of Prostate Cancer Cases. On each biennial follow-up questionnaire, participants were asked to report prostate cancer diagnoses within the past 2 years. Over 90% of these diagnoses were subsequently confirmed by medical record and/or pathology report review with permission from the participant or next of kin. Many of the remaining 10% provided supporting information for their diagnosis (e.g., evidence of treatment). Overall, we estimate that 96% of prostate cancer diagnoses have been ascertained in this cohort. Information on disease stage (tumor-node-metastasis classification) and Gleason sum was abstracted from medical records by study investigators.

For the present analysis, only men diagnosed with prostate cancer after the date of return of the 1992 questionnaire were included as cases. T_{1a} prostate cancers (n = 31, 1.4% of all prostate cancer cases) were not included as cases because these tumors comprise ≤5% of resected prostate tissue and may be especially prone to detection bias.

Statistical Analysis. To characterize exposed and unexposed participants, age-standardized means and proportions of covariates hypothesized or previously observed to be associated with gonorrhea, syphilis, prostatitis, and/or prostate cancer were calculated by each exposure. Factors hypothesized to be associated with gonorrhea, syphilis, and/or prostatitis included cigarette smoking before age 30 (pack-years), alcohol consumption from ages 18 to 22 (frequency per week), ejaculation frequency from ages 20 to 29 (frequency per month), and vigorous physical activity in high school and college. Factors previously observed to be associated with prostate cancer incidence or progression in the Health Professionals Follow-up Study cohort included race/ethnicity; body mass index at age 21 (kg/m^2); cumulative family history of prostate cancer; height (in.); updated cigarette smoking in the past 10 years (pack-years); intakes of total energy (kcal/d), alcohol (g/d), tomato sauce (servings/d), red meat (servings/d), fish (servings/d), fructose (g/d), calcium (mg/d), α-linolenic acid (g/d), and vitamin E (<15, ≥15 mg/d) in 1990; zinc (<101, ≥101 mg/d) supplementation in 1990; vigorous physical activity in 1992 (metabolic equivalent-hours/wk); and updated vasectomy and diabetes mellitus type 2 status. Cox proportional hazards regression was used to investigate age- and multivariable-adjusted associations between each exposure and prostate cancer. Participants contributed time at risk from the month of return of the 1992 questionnaire to the month of prostate cancer diagnosis, death, or end of the study period on January 31, 2002. Age (1-month intervals) and calendar time (2-year intervals) were controlled for as stratification variables in all regression models. Missing STI and prostatitis terms were also included in all models to investigate the effects of potential underreporting of exposure. This analysis was based on the assumption that participants reluctant to report their history of exposure would be more likely to leave sensitive questions blank rather than answer them untruthfully. None of the estimates for missing terms differed from null. Confounding was investigated by adding each covariate individually and in combination to the regression model and comparing with age-adjusted results. None of the point estimates from multivariable-adjusted analyses differed from age-adjusted estimates (<10% change). Therefore, for the purpose of succinct presentation and to allow for comparisons with previous Health Professionals Follow-up Study analyses, only age-adjusted estimates and estimates adjusted for factors previously observed to be associated with prostate cancer incidence or progression in the Health Professionals Follow-up Study cohort were presented.

The primary outcome for each analysis was total prostate cancer. Additional outcomes considered were organ-confined ($\leq T_2$ and N_0M_0), advanced (T_{3b} or worse), low-grade (Gleason sum <7), and high-grade (Gleason sum ≥7) prostate cancer. Detection bias was investigated by performing analyses stratified by routine prostate cancer screening (digital rectal examination and/or prostate-specific antigen test as a time-dependent factor). Digital rectal examinations and prostate-specific antigen tests done for symptoms were not considered routine screening. Additional stratified analyses were limited to screened men to allow for comparisons among men with equal opportunity for prostate cancer detection. These included analyses stratified by surrogates of underlying prostate cancer susceptibility (age at prostate cancer diagnosis and family history of prostate cancer) and by factors hypothesized to influence prostatic inflammation earlier or later in life [aspirin use from ages 20-29, age (<70, ≥70 years) as a surrogate for opportunity to have acquired a genitourinary infection in the pre-antibiotic era before 1937, ejaculation frequency from ages 20-29, race/ethnicity, and current nonsteroidal anti-inflammatory drug use, cigarette smoking, diabetes, body mass index, and intakes of tomato sauce, alcohol, vitamin E, zinc and α-linolenic acid]. The statistical significance of any observed stratum-specific differences was assessed by including an additional cross-product term in regression models. All statistical analyses were done using SAS version 8.2 (SAS Institute, Cary, NC).

A priori power calculations indicated that the main analysis had 80% power to detect a relative risk of 1.40 for gonorrhea (similar to the summary estimate presented in the Dennis and Dawson meta-analysis; ref. 2), 2.68 for syphilis, and 1.17 for clinical prostatitis. The main analysis had 62% power to detect a relative risk of 2.30 for syphilis and 99% power to detect a relative risk of 1.57 for clinical prostatitis, similar to the summary estimates presented in the Dennis et al. meta-analyses (2, 3).

Results

Of the 36,033 eligible participants, 2,263 were diagnosed with prostate cancer between the date of return of the 1992 questionnaire and 2002, 231 of whom were diagnosed with advanced-stage disease. Three percent of participants reported a history of gonorrhea, 0.2% reported a history of syphilis, and 15.9% reported a history of clinical prostatitis, the majority of which was treated and lasted <1 year. In general, men who reported histories of gonorrhea (Table 1) or syphilis (data not shown) were more likely to be African American and to report higher levels of cigarette smoking and alcohol consumption in 1992 and early adulthood, higher frequencies of ejaculation in early adulthood, and a history of the other STI. Men who reported a history of clinical prostatitis were more likely to report regular nonsteroidal anti-inflammatory drug use, having had a vasectomy and prostate cancer screening, cigarette smoking in early adulthood, and a history of gonorrhea (Table 1).

Gonorrhea and Syphilis. No association was observed between a history of gonorrhea and prostate cancer overall or by stage and grade in age-adjusted and various multivariable-adjusted analyses (Tables 2 and 3; data not shown). Similar null associations were observed across strata of prostate cancer screening and surrogates of prostate cancer susceptibility and prostatic inflammation (data not shown).

Five cases of prostate cancer (person-years = 706) were reported among men with a history of syphilis, and 2,049 cases (person-years = 299,582) were reported among men without such a history (age-adjusted RR, 1.06; 95% CI, 0.44-2.59). The reported cumulative incidence of syphilis was too low to perform additional analyses.

Table 1. Age-standardized characteristics by histories of gonorrhea and clinical prostatitis in the Health Professionals Follow-up Study, 1992

	Gonorrhea*		Clinical prostatitis*	
	No (n = 31,966)	Yes (n = 966)	No (n = 29,854)	Yes (n = 5,732)
Mean age (y)	59.3	57.5	59.2	60.7
Race/ethnicity (%)				
Caucasian	91.8	86.0	91.4	92.2
African American	0.6	7.0	0.8	0.8
Asian	1.6	1.1	1.8	0.5
Other	6.0	5.9	6.1	6.4
Family history of prostate cancer† (%)	13.6	13.6	13.3	14.5
Mean height in 1986 (in.)	70.2	70.1	70.2	70.2
Smoked cigarettes in the past 10 y (%)	20.1	28.3	20.1	20.3
Mean intakes of				
Total energy (kcal/d)‡	1,930	1,921	1,927	1,924
Alcohol (g/d)‡	10.2	14.3	10.4	10.0
Tomato sauce (servings per day)§	0.2	0.2	0.2	0.2
Red meat (servings per day)§	1.0	1.0	1.0	1.0
Fish (servings per day)§	0.3	0.4	0.3	0.4
Fructose (g/d)‡,‖	49.7	48.5	49.7	49.9
Calcium (mg/d)‡	874	845	871	867
α-Linolenic acid (g/d)‡,‖	1.0	1.0	1.0	1.1
Vitamin E intake (≥15 mg/d, %)‡	40.0	42.3	39.4	42.4
Zinc supplementation (≥101 mg/d, %)‡	0.4	0.2	0.3	0.5
Regular (≥2 times per week) use of nonsteroidal anti-inflammatory drugs (%)	41.0	41.8	40.4	44.3
Any vigorous leisure time physical activity (%)	60.3	62.9	60.1	61.4
Vasectomy (%)	24.9	26.1	24.4	27.4
Diabetes mellitus type 2 (%)	4.8	3.7	4.9	3.8
Screening prostate specific antigen test (%)¶	88.1	87.9	87.5	91.3
Screening digital rectal examination (%)¶	85.8	84.1	85.5	86.9
Smoked cigarettes before age 30 (%)**	46.9	59.4	46.6	49.6
Consumed alcohol, ages 18 to 22 (%)††	65.1	76.3	64.8	66.4
Mean monthly ejaculation frequency, ages 20-29	14.0	15.3	14.0	14.2
History of (%)				
Gonorrhea	—	—	2.4	4.3
Syphilis	0.2	2.3	0.2	0.2
Clinical prostatitis	15.5	24.3	—	—
Mean body mass index at age 21 (kg/m^2)**	23.0	22.8	23.0	22.9
Any vigorous physical activity (%) in				
High school	88.4	87.1	88.3	88.3
College	80.0	76.4	80.0	79.3

*Numbers do not sum to 36,033 due to missing participant responses.
†Assessed in 1990 through 1996.
‡Assessed in 1990.
§Cumulative mean intake between 1986 and 1990.
‖Adjusted for total energy intake.
¶Assessed through 2002.
**Assessed in 1986.
††Assessed in 1988.

Table 2. RRs and 95% CIs of total prostate cancer for histories of gonorrhea and clinical prostatitis in the Health Professionals Follow-up Study, 1992-2002

	Cases/person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR* (95% CI)	Multivariable-adjusted RR* among men screened for prostate cancer (95% CI)
History of gonorrhea [†]				
No	1,999/291,519	1.00	1.00	1.00
Yes	55/8,770	1.05 (0.80-1.38)	1.04 (0.79-1.36)	0.99 (0.72-1.38)
History of clinical prostatitis [‡]				
No	1,809/272,289	1.00	1.00	1.00
Yes	421/51,964	1.09 (0.98-1.22)	1.08 (0.96-1.20)	0.94 (0.82-1.07)
Duration of clinical prostatitis (y) [‡]				
<1	303/39,041	1.10 (0.97-1.24)	1.08 (0.95-1.22)	0.92 (0.79-1.07)
1-2	41/4,180	1.27 (0.93-1.74)	1.27 (0.92-1.74)	1.11 (0.75-1.64)
≥3	44/5,788	0.89 (0.65-1.20)	0.88 (0.65-1.20)	0.75 (0.52-1.10)
Treatment for clinical prostatitis [‡]				
Untreated	22/2,686	1.22 (0.80-1.86)	1.18 (0.77-1.81)	1.10 (0.65-1.84)
Treated	382/46,415	1.11 (0.99-1.24)	1.10 (0.98-1.23)	0.95 (0.83-1.09)
Age at first treatment for clinical prostatitis (y) [‡]				
<30	52/8,686	1.06 (0.80-1.40)	1.06 (0.80-1.41)	1.03 (0.74-1.44)
30-39	81/9,923	1.33 (1.06-1.66)	1.30 (1.04-1.62)	1.23 (0.94-1.60)
40-49	68/11,426	0.93 (0.73-1.19)	0.93 (0.73-1.19)	0.78 (0.57-1.06)
50-59	97/9,122	1.22 (1.00-1.51)	1.20 (0.98-1.48)	0.99 (0.76-1.28)
≥60	82/7,012	1.03 (0.82-1.29)	1.00 (0.80-1.26)	0.82 (0.62-1.10)

*Adjusted for race/ethnicity (Southern European, Scandinavian, other Caucasian, African American, Asian, and other); body mass index at age 21 (kg/m^2); cumulative family history of prostate cancer through 1996 (no/yes); height (in., continuous); updated cigarette smoking in the past 10 years (none, 1-5, 6-10, 11-20, and >20 pack-years); intakes of total energy (kcal/d, quintiles), alcohol (none, 1-4, 5-14, 15-29, 30-49, and ≥50 g/d), tomato sauce (servings per day, quintiles), red meat (servings per day, quintiles), fish (servings per day, quartiles), energy-adjusted fructose (g/d, quintiles), calcium (mg/d, quintiles), energy-adjusted α-linolenic acid (g/d, quintiles), and vitamin E (<15, ≥15 mg/d) in 1990; zinc (<101, ≥101 mg/d) supplementation in 1990; vigorous physical activity in 1992 (metabolic equivalent-hours/wk, quintiles); updated vasectomy (no/yes) and diabetes mellitus type 2 (no/yes) status; age (one-month intervals); and calendar time (2-year intervals).

[†]Participants with missing gonorrhea (cases = 209, 27,705 person-years) or clinical prostatitis information (missing history of prostatitis, missing duration of prostatitis, missing treatment for prostatitis, and missing age at first treatment information, cases = 33, 3,741 person-years) were included in the analyses (data not shown).

[‡]The reference category was no history of clinical prostatitis.

Clinical Prostatitis. No association was observed between a history of clinical prostatitis and prostate cancer in age-adjusted and various multivariable-adjusted analyses (Table 2; data not shown). Similar null results were observed for clinical prostatitis of varying duration and for treated and untreated prostatitis. No patterns of association were observed by age at first treatment for clinical prostatitis, although a slight, significant positive association was observed for prostatitis first treated between the ages of 30 and 39 (Table 2; data not shown). When the data were stratified by routine prostate cancer screening to investigate detection bias, a significant positive association was observed between prostatitis and prostate cancer among nonscreened men (multivariable-adjusted RR, 1.60; 95% CI, 1.26-2.04), whereas no association was observed among screened men ($P_{interaction} < 0.0001$; Table 2). Similar patterns of association were observed for prostatitis of varying duration, treated and untreated prostatitis, and prostatitis first treated at varying ages. Of note, the positive association observed for prostatitis first treated between the ages of 30 and 39 diminished among men screened for prostate cancer (Table 2).

No associations were observed between clinical prostatitis and prostate cancer of varying stage and grade, with the exception of a slight significant positive association between prostatitis and low-grade prostate cancer (Table 3). This positive association was largely confined to nonscreened men (multivariable-adjusted RR, 1.83; 95% CI, 1.32-2.55); among screened men, no association was observed. Similar patterns were observed for high-grade, organ-confined, and advanced-stage disease (Table 3).

To allow for comparisons among men with equal opportunity for prostate cancer detection, additional stratified analyses were limited to men screened for prostate cancer. In analyses stratified by age at prostate cancer diagnosis, a significant positive association was observed between prostatitis and prostate cancer in the youngest men [<10th percentile of age at prostate cancer diagnosis (59 years)], no association was observed in middle-aged men [10th percentile to median age (59-68 years)], and a slight inverse association was observed in the oldest men [≥ median age (69 years); Table 4]. Similar patterns of association were observed for organ-confined and low-grade prostate cancer (data not shown). Too few younger men were diagnosed with advanced or high-grade prostate cancer to explore whether associations varied by age at diagnosis. No effect modification was observed by family history of prostate cancer or by surrogates of prostatic inflammation (all $P_{interaction} > 0.10$).

Discussion

No association was observed between a history of gonorrhea and prostate cancer in this large prospective study of health professionals. Suggestive null results were also observed for a history of syphilis and prostate cancer. Additionally, the low cumulative incidence of syphilis precludes anything but a very minor role for syphilis in the burden of prostate cancer in this study population and in similar populations with low incidences of syphilis. Overall null results were also observed for a history of clinical prostatitis and prostate cancer, although significant positive associations were observed for men not routinely screened for prostate cancer and younger screened men.

Gonorrhea. In the United States, incidence rates of gonorrhea have fluctuated dramatically over the course of the 20th century. Rates were high immediately following the Second World War, with a peak incidence of 275.0/100,000. This peak was followed by a decline in incidence in the 1950s and a subsequent increase in the 1960s and 1970s to a second peak incidence of 467.7/100,000 at the height of the sexual revolution. Since that time, rates of gonorrhea gradually declined to 113.5/100,000 in 2004 (10). Among population-based controls in more recent studies of gonorrhea and prostate cancer, cumulative incidences of gonorrhea range from 2.5% among Caucasian men from Georgia, Michigan, and New Jersey (11) and men enrolled in the Kaiser Permanente

Table 3. RRs and 95% CIs of prostate cancer for histories of gonorrhea and clinical prostatitis in the Health Professionals Follow-up Study, 1992-2002

	Cases/person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR* (95% CI)	Multivariable-adjusted RR* among men screened for prostate cancer (95% CI)
Organ-confined ($\leq T_2$ and N_0M_0) prostate cancer				
History of gonorrhea†				
No	1,386/292,149	1.00	1.00	1.00
Yes	36/8,786	0.99 (0.71-1.38)	0.96 (0.68-1.34)	0.85 (0.56-1.29)
History of clinical prostatitis†				
No	1,251/272,861	1.00	1.00	1.00
Yes	289/52,098	1.09 (0.96-1.24)	1.07 (0.94-1.22)	0.97 (0.83-1.13)
Advanced (T_{3b} or worse) prostate cancer				
History of gonorrhea†				
No	206/293,219	1.00	1.00	1.00
Yes	7/8,814	1.37 (0.64-2.95)	—‡	—‡
History of clinical prostatitis†				
No	189/273,814	1.00	1.00	1.00
Yes	41/52,325	1.01 (0.72-1.42)	1.01 (0.72-1.43)	0.81 (0.50-1.30)
Low-grade (Gleason sum < 7) prostate cancer				
History of gonorrhea†				
No	1,002/292,486	1.00	1.00	1.00
Yes	28/8,795	1.05 (0.72-1.54)	1.04 (0.70-1.52)	1.03 (0.66-1.63)
History of clinical prostatitis†				
No	882/273,179	1.00	1.00	1.00
Yes	234/52,147	1.26 (1.09-1.46)	1.24 (1.08-1.44)	1.11 (0.94-1.32)
High-grade (Gleason sum $\geq$ 7) prostate cancer				
History of gonorrhea†				
No	706/292,773	1.00	1.00	1.00
Yes	18/8,805	1.00 (0.62-1.60)	0.97 (0.60-1.57)	0.76 (0.41-1.40)
History of clinical prostatitis†				
No	650/273,413	1.00	1.00	1.00
Yes	136/52,239	0.98 (0.81-1.18)	0.97 (0.80-1.17)	0.87 (0.69-1.10)

*Adjusted for race/ethnicity (Southern European, Scandinavian, other Caucasian, African American, Asian, and other); body mass index at age 21 (kg/m^2); cumulative family history of prostate cancer through 1996 (no/yes); height (in.); updated cigarette smoking in the past 10 years (none, 1-5, 6-10, 11-20, and >20 pack-years); intakes of total energy (kcal/d, quintiles), alcohol (none, 1-4, 5-14, 15-29, 30-49, and $\geq$50 g/d), tomato sauce (servings per day, quintiles), red meat (servings per day, quintiles), fish (servings per day, quartiles), energy-adjusted fructose (g/d, quintiles), calcium (mg/d, quintiles), energy-adjusted α-linolenic acid (g/d, quintiles), and vitamin E (<15, $\geq$15 mg/d) in 1990; zinc (<101, $\geq$101 mg/d) supplementation in 1990; vigorous physical activity in 1992 (metabolic equivalent-hours/week, quintiles); updated vasectomy (no/yes) and diabetes mellitus type 2 (no/yes) status; age (1-month intervals); and calendar time (2-years intervals).
†Participants with missing gonorrhea or prostatitis information were included in the analyses (data not shown).
‡Too few prostate cancer cases among men with a history of gonorrhea to estimate a multivariable-adjusted RR.

Medical Care Program in northern California (12) to 37.3% among African-American men from Michigan (13). The lower estimate of 2.5% is similar to our observed cumulative incidence of 2.7% in our cohort of predominantly Caucasian men. To our knowledge, no nationally representative estimates of the cumulative incidence of gonorrhea exist.

Our null finding for gonorrhea is consistent with the results from eight previous case-control studies (12-19) but differs from those from an additional six case-control studies and meta-analysis findings (2, 7, 11, 20-23). Profound nondifferential misclassification of gonorrhea due to poor recall or a reluctance to report stigmatizing diseases is unlikely to explain our null result for several reasons. First, covariate patterns for men with and without a history of gonorrhea were consistent with expected patterns. Second, the association between missing information for gonorrhea and prostate cancer was null, indicating that associations were not missed because truly exposed participants skipped questions on STIs. Finally,

Table 4. RRs and 95% CIs of total prostate cancer for a history of clinical prostatitis by percentile of age at prostate cancer diagnosis among men screened for prostate cancer in the Health Professionals Follow-up Study, 1992-2002

	Total		Stratified by age at prostate cancer diagnosis					
	No prostatitis	Prostatitis*	<10th percentile (<59 y)		10th to 49th percentile (59-68 y)		≥50th percentile (≥69 y)	
			No prostatitis	Prostatitis*	No prostatitis	Prostatitis*	No prostatitis	Prostatitis*
Cases/person-years	1,313/186,820	275/38,138	183/73,900	49/12,737	549/63,406	116/13,613	581/49,514	110/11,788
Age-adjusted RR (95% CI)	1.00	0.95(0.83-1.08)	1.00	1.58† (1.14-2.17)	1.00	0.96 (0.78-1.17)	1.00	0.79 (0.64-0.97)
Multivariable-adjusted RR‡ (95% CI)	1.00	0.94 (0.82-1.07)	1.00	1.49§ (1.08-2.06)	1.00	0.94 (0.76-1.14)	1.00	0.79(0.64-0.98)

*Participants with missing prostatitis information were included in the analyses (data not shown).
†$P_{\text{interaction with age}} = 0.005$.
‡Adjusted for race/ethnicity (Southern European, Scandinavian, other Caucasian, African-American, Asian, and other); body mass index at age 21 (kg/m^2); cumulative family history of prostate cancer through 1996 (no/yes); height (in.); updated cigarette smoking in the past 10 years (none, 1-5, 6-10, 11-20, and >20 pack-years); intakes of total energy (kcal/d, quintiles), alcohol (none, 1-4, 5-14, 15-29, 30-49, and $\geq$50 g/d), tomato sauce (servings per day, quintiles), red meat (servings per day, quintiles), fish (servings per day, quartiles), energy-adjusted fructose (g/day, quintiles), and calcium (mg/d, quintiles), energy-adjusted α-linolenic acid (g/d, quintiles), and vitamin E (<15, $\geq$15 mg/d) in 1990; zinc (<101, $\geq$101 mg/d) supplementation in 1990; vigorous physical activity in 1992 (metabolic equivalent-hours/week, quintiles); updated vasectomy (no/yes) and diabetes mellitus type 2 (no/yes) status; age (1-month intervals); and calendar time (2-year intervals).
§$P_{\text{interaction with age}} = 0.006$.

we have previously observed a positive association between gonorrhea and benign prostatic hyperplasia in this cohort (24), indicating a sufficient degree of correct exposure classification to detect statistical associations between gonorrhea and chronic disease end points. Differential loss to follow-up is also unlikely to explain our null result because men who reported a history of gonorrhea completed a similar number of follow-up questionnaires as men who did not report a history of gonorrhea. Finally, although our observed cumulative incidence of gonorrhea was low, insufficient statistical power is also unlikely to explain our null result because sufficient exposed time at risk existed to detect a relative risk as low as 1.40 (similar to the summary estimate presented in the Dennis and Dawson meta-analysis; ref. 2) with 80% power. Rather, we believe that differences between our prospective study findings and some of the previous case-control study findings are more likely explained by methodologic differences, such as pre-diagnostic versus post-diagnostic assessment of gonorrhea and use of mailed questionnaires rather than interviewer-administered questionnaires to reduce differential recall and interviewer biases.

Another possible explanation for differences in study findings is differences in the spectrum and frequency of STIs across study populations. For instance, among men born earlier in calendar time, a history of gonorrhea may be more likely to reflect a longer duration of non–antibiotic-treated infection, which frequently resulted in prostatitis (25). As a further example, among men of different race/ethnicity, socioeconomic, or educational status, a history of gonorrhea may be more likely to represent multiple episodes of gonorrhea (or possibly coinfections), which were more strongly associated with prostate cancer than single episodes of gonorrhea in a case-control study by Hayes et al. (11). Therefore, although our null study findings are likely generalizable to most men in developed countries who are unlikely to experience more than a few episodes of treated gonorrhea, we cannot rule out possible associations between repeated episodes of gonorrhea (or coinfections) and prostate cancer and between untreated or delayed-treated gonorrhea and prostate cancer in populations with a higher burden of STIs.

Clinical Prostatitis. Between 1990 and 1994, there were an estimated 2,000,000 outpatient visits for prostatitis per year in the United States (26). Among select American male populations, estimates of the cumulative incidence of prostatitis range from ~5% among National Guardsmen ages 20 to 49 years (27) to 25% among male participants ages ≥65 years in the MrOS study, a community-based study of six clinical centers throughout the United States (28). This range encompasses our observed cumulative incidence of 15.9%, with individual differences likely due to differences in the ages of study populations and the definitions of clinical prostatitis used.

Our overall null study finding for clinical prostatitis is consistent with findings from eight previous case-control studies of clinical prostatitis and prostate cancer (7, 12, 15, 19, 29-32) but differs from those from an additional nine case-control studies and meta-analysis results (3, 8, 9, 13, 17, 22, 23, 28). One methodologic concern for positive studies is detection bias, whereby men with a history of prostatitis may be followed more closely for prostate cancer than men without such a history, due to ongoing investigations for chronic prostatitis or closer medical contact following a diagnosis of prostatitis. With the exception of one study (9), none of the positive studies took, to our knowledge, frequency of urologic investigation into consideration in their analyses. Therefore, these studies' findings may have been influenced by detection bias. In our study, we observed a significant positive association between prostatitis and prostate cancer among nonscreened men, but no overall association among screened men, suggesting that the results among nonscreened men may have been due to detection bias (i.e., increased rates of incidental prostate cancer detection among men being investigated for prostatitis). To avoid this concern, all subsequent analyses were stratified by prostate cancer screening, and only those among screened men are considered etiologically relevant.

Although no association was observed between clinical prostatitis and prostate cancer overall among screened men, we do not believe that this rules out possible associations between prostatic infection or inflammation and prostate cancer for the following reasons. First, although the current definition of prostatitis includes conditions with a clear infectious and inflammatory component (e.g., acute and chronic bacterial prostatitis), it also includes conditions less clearly associated with prostatic inflammation, such as chronic nonbacterial prostatitis/chronic pelvic pain syndrome. This latter condition accounts for 90% of clinical prostatitis and is comprised of inflammatory and non-inflammatory chronic nonbacterial prostatitis (33), the relative contributions of which are largely unknown. Second, clinical prostatitis may be difficult for patients and their physicians to distinguish from other prostatic conditions with similar symptoms, such as benign prostatic hyperplasia (34-36). This difficulty may lead to nondifferential misclassification of prostatitis exposure and possible attenuation of study findings. Finally, prostatic inflammation may not necessarily produce symptoms. The prevalence of asymptomatic inflammatory prostatitis, defined as inflammation in prostatic secretions or tissue from men without symptoms of prostatitis (37), is largely unknown but may range from 32% to 44% (38, 39). Given all of these factors, the general definition of clinical prostatitis may not be sensitive or specific enough for prostatic inflammation to explore its potential influence on prostate carcinogenesis.

Despite these limitations, we did observe a significant positive association between prostatitis and prostate cancer among younger men (<59 years) screened for prostate cancer. Similar findings were also observed in the one study that restricted participants to ≤60 years of age (23). Possible explanations for our findings include (*a*) chance; (*b*) an increased relative proportion of bacterial and/or inflammatory prostatitis and a lesser proportion of benign prostatic hyperplasia in younger than in older men; (*c*) a lesser and less varied accumulation of carcinogenic prostatic exposures in younger than in older men, making potential associations easier to detect in younger men; or (*d*) a greater degree of incidentally detected prostate cancer in younger than in older men due to greater prostatitis-mediated prostate-specific antigen elevations, particularly if a higher relative proportion of younger men have bacterial or inflammatory prostatitis. Our findings are unlikely to be explained by increased prostate cancer work-up in younger men because rates of prostate biopsy were similar in younger and older men who reported elevated prostate-specific antigen. In the present study, we also observed a significant inverse association between prostatitis and prostate cancer among older men, the reason for which is unclear.

Several methodologic strengths distinguish this study from previously conducted studies. First, it is one of the largest studies of gonorrhea, clinical prostatitis, and prostate cancer conducted to date to allow for detection of potentially modest associations. Second, it is one of the first studies, to our knowledge, to prospectively investigate associations among gonorrhea, syphilis clinical prostatitis, and prostate cancer to minimize potential differential ascertainment biases. Finally, it was conducted in an extremely well-characterized cohort with information on early life factors that might be associated with STI acquisition, purported risk factors for prostate cancer, and prostate cancer screening to allow for adjustment for potential confounders and to address the possibility of detection bias.

In conclusion, no associations were observed among gonorrhea, syphilis, and prostate cancer in this population of men with a lower burden of reported STIs. Null results were also observed for clinical prostatitis and prostate cancer in the full study cohort, although a significant positive association was observed among younger men screened for prostate cancer. Additional prospective studies are warranted to investigate the effect of multiple episodes of infection and coinfection on the risk of prostate cancer among men with a higher burden of STIs and the effect of prostatitis on prostate cancer risk in younger men. Novel methods are also needed to investigate asymptomatic prostatic infection and inflammation in relation to prostate cancer.

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