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Sexually transmitted diseases and other urogenital conditions as risk factors for prostate cancer: a case–control study in Wayne County, Michigan

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Abstract

Objective: To investigate associations between prostate cancer and sexually transmitted diseases (STDs), prostatitis, benign prostatic hyperplasia (BPH), and vasectomy in a population-based case–control study in Wayne County, Michigan, among African American and white men aged 50–74 years.
Methods: Incident prostate cancer cases (n = 700) from 1996–1998 were identified from the Metropolitan Detroit Cancer Surveillance System. Controls (n = 604) were identified through random digit dialing and Medicare recipient lists, and frequency matched to cases on age and race. History of potential prostate cancer risk factors was ascertained through in-person interview.
Results: Prostate cancer was not associated with STD or vasectomy history. History of prostatitis was associated with prostate cancer among all subjects (odds ratio [OR] = 1.8, 95% confidence interval [CI]: 1.1, 2.9) and in African American men (OR = 2.2, 95% CI: 1.1, 4.6). History of BPH was associated with prostate cancer among all subjects (OR = 2.4, 95% CI: 1.8, 3.3); significant associations were observed in both African American (OR = 2.7, 95% CI: 1.6, 4.4) and white (OR = 2.3, 95% CI: 1.5, 3.4) men.
Conclusions: Among all subjects, prostate cancer was associated with prostatitis and BPH history, but not with STD or vasectomy history. Prevention efforts could be enhanced if inflammatory or infectious etiologies are found to be of importance in the subsequent development of prostate cancer.

Introduction

Prostate cancer is the most commonly diagnosed noncutaneous cancer and the second leading cause of cancer deaths in men in the United States [1]. It is estimated that one in every five American men will be affected by this disease [2]. Racial variations in incidence and mortality rates of prostate cancer are striking: African American men have the highest age-adjusted incidence rate of prostate cancer in the world (185.7 per 100,000), markedly higher than that of U.S. white men (110 per 100,000), with a mortality rate more than twice that of white men [3, 4].

Despite the considerable disease burden, relatively little is known about risk factors for prostate cancer or reasons for racial and ethnic differentials in risk. Epidemiologic studies of numerous putative risk factors for prostate cancer (including diet, body mass index (BMI), smoking, alcohol consumption, and physical activity) have been conducted, with inconsistent findings. The only well established risk factors for prostate cancer include age, race, and a family history of prostate cancer [5].

Recent studies have explored the contribution of sexually transmitted diseases (STDs) to the development

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of prostate malignancy. Specific STD agents have been associated inconsistently with prostate cancer, with positive associations reported with gonorrhea [6, 7], syphilis [7], and human papilloma virus (HPV) [8, 9]. Recent national data suggest that African Americans have substantially higher rates of STDs than other racial and ethnic groups in the United States [10, 11]. The possible influence of STDs has been suggested as a partial explanation for the higher rates of prostate cancer among African Americans [12], however, this relationship has not been well characterized.

Associations between urogenital conditions other than STDs and prostate cancer have also been studied, with inconsistent results. Prostatitis, a commonly occurring inflammation or infection of the prostate, is an important cause of morbidity in adult males [13–16]. Most previous case–control studies examining prostatitis and prostate cancer did not report significant associations [17–21]; however, Honda *et al.* reported an increased risk (OR = 2.2; 95% CI: 1.2, 4.3) [22]. Benign prostatic hyperplasia (BPH) is another highly prevalent condition among middle-aged and elderly men [23], but findings from epidemiologic studies of the association between BPH and prostate cancer have been inconsistent [24–27].

Men who have undergone vasectomy have been shown to have a moderately higher risk of prostate cancer in some studies [28–33], while other studies have reported no association [17, 20, 22, 34–39]. Because the prevalence of male sterilization (approximately 11%) has remained relatively stable in the U.S. since 1982 [40] and, worldwide, an estimated 42–60 million couples rely on vasectomy for contraception [38], any association of vasectomy with prostate cancer would be of importance.

This report is based on men in the metropolitan Detroit area who participated in a population-based case–control study of occupational risk factors for prostate cancer. The primary focus of this case–control study was to examine associations between occupational exposures and prostate cancer; the secondary analysis presented here considers associations of prostate cancer with a history of STD and other urogenital conditions, including prostatitis, BPH, and vasectomy.

Materials and methods

Case and control ascertainment

Cases were identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS), a population-based cancer registry established in the 1950s, and a founding member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program since 1973. Because of the large volume of prostate cancer cases reported in the MDCSS registry (exceeding sample size requirements), a random sample of half of all malignant prostate cancer cases diagnosed between April 1, 1996 and March 30, 1998 were identified. Eligible cases included those with histologically confirmed adenocarcinoma of the prostate (ICD-O topography code C61.9 [41]), aged 50–74 years, residing in Wayne County at the time of diagnosis, who spoke English and had a working telephone number. Wayne County, which includes the city of Detroit, was selected because of the high proportion of African American residents (over 40%). The physician of record for each case was sent a letter explaining the nature of the study and inquiring whether there was any medical reason not to contact the case. Each potential case not excluded by his physician was sent a letter explaining the nature of the study, and trained interviewers attempted to contact these cases within one week of the introductory letter. If the subject agreed to participate, arrangements were made for an in-person interview.

Controls were initially identified through a random-digit dialing (RDD) telephone sample of Wayne County residents, aged 50–74 years, who spoke English and had a working telephone number. Controls were selected by stratified random sampling using Waksberg's two-stage RDD method [42] and were frequency matched to the cases by race (white, African American, and other) and age (in five-year intervals). To include sufficient numbers of controls in older age groups, a random sample of Medicare recipients aged 65–74 years with working telephone numbers obtained from a Health Care Financing Administration (HCFA) listing was also used. Potential controls were sent introductory letters similar to those sent to potential cases requesting participation. The study protocol and consent form were approved by the Wayne State University Human Investigation Committee and all subjects provided written informed consent prior to the interview.

Interview

Trained interviewers asked cases and controls about demographics, medical history, family medical history, physical activity, lifestyle factors, household exposures, and occupational history using a structured questionnaire. Within the medical history section, subjects were asked to self-report their past history of four specific STDs (gonorrhea, syphilis, chancroid, genital herpes) or "other" STDs, and urogenital conditions other than STDs, including prostatitis, BPH, and vasectomy. Subjects were also asked to report their past history of

transurethral resection of the prostate (TURP), a common surgical treatment for BPH. Exposures were assessed for the period before a specified reference date, which was the date of diagnosis for cases and the date of study entry for controls.

Cases were compared to controls to determine whether the two groups differed according to matching variables, subject characteristics (including marital status, education, current BMI, cigarette use prior to reference date, average weekly number of alcoholic drinks in the previous year, and family history of prostate cancer), and risk factors of interest. A positive family history of prostate cancer (in first degree relatives only) was defined as self-reported history of prostate cancer in the subject's father and/or brother(s). History of specific STDs was based on self-report; in addition, a positive history of "any STD" was defined by self-reported history of at least one of the four specific STDs or "other" STD. For cases, tumor stage and grade were ascertained through linkage with the MDCSS database. Tumor stage was categorized as localized, regional (regional direct extension; regional lymph nodes; regional direct extension and regional lymph nodes; or regional, not otherwise specified), distant, or unknown. MDCSS records tumor grade as well differentiated (Gleason score 2–4), moderately differentiated (Gleason score 5–7), poorly differentiated (Gleason score 8–10), or unknown.

Statistical analysis

Comparisons of categorical variables between cases and controls were made using two-tailed χ^2 tests in the entire study sample and within African American and white men (stratified). p-Values < 0.05 were considered statistically significant. Unconditional logistic regression analyses were conducted to explore relationships between urogenital conditions and prostate cancer by estimating odds ratios (OR) and 95% confidence intervals (CI). These analyses were first conducted in the entire sample and then were repeated after stratifying by race to examine potential interactions between race and each urogenital condition. Additionally, interaction terms between race and each urogenital condition were added to the appropriate multivariable models and assessed for statistical significance. Adjustments for age (as a continuous variable), education level, family history of prostate cancer (in first degree relatives only) and, where appropriate, race were included in all logistic regression models, because these variables were associated with either prostate cancer or the risk factor of interest. The potential for confounding and effect modification by other subject characteristics was also investigated, including marital status, current BMI, cigarette use prior to the reference date, and average weekly number of alcoholic drinks in the previous year; however, because the effects were not statistically significant, these variables were not included in the multivariable models.

We examined associations between BPH, TURP and prostate cancer because TURP may increase the detection rate for prostate cancer. Because of the potential for reporting bias for topics of a sensitive nature, analyses for the associations between prostate cancer and history of STD, prostatitis and BPH were repeated after excluding participants who had another individual present during their interview. Data analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA) [43].

Results

Study sample

Of the 1287 men with prostate cancer who were eligible to be cases, 730 (56.7%) completed the interview (Table 1). Of the 557 individuals not interviewed, 78 (14.0%) died before contact could be made, 8 (1.4%) were not contacted because their physician refused, 257 (46.1%) refused to participate, 40 (7.2%) were too ill or hard of hearing, and 174 (31.2%) were unable to be contacted. Analyses were limited to 700 African American and white cases; the 30 cases (4.1%) that identified "other" race or did not provide race information were excluded. The average time interval between date of diagnosis of cases and date of interview was 16.1 months (range: 3.1–42.2; standard deviation: 7.8).

Table 1. Potentially eligible prostate cancer cases and controls. Wayne County, Michigan, April 1996–March 1998

	Cases		Controls	
	n	%	n	%
Total potentially eligible men	1287		1457	
Not interviewed	557	43.3	771	52.9
Physician refused (cases only)	8	1.4	[a]	[a]
Subject/Family member refused	257	46.1	396	51.4
Too ill/Hard of hearing	40	7.2	45	5.8
Deceased	78	14.0	29	3.8
Unable to contact	174	31.2	301	39.0
Interviewed	730	56.7	686	47.1
Did not complete interview	0	0.0	2	0.3
Excluded after interview				
History of prostate cancer (controls only)	[a]		[a] 46	6.7
Race other than African American or White/Did not provide race information	30	4.1	34	5.0
Eligible	700	95.9	604	88.0

[a]Not applicable.

Of the 1457 total potentially eligible controls, 686 (47.1%) were interviewed (Table 1). Of the 771 individuals not interviewed, 29 (3.8%) died before contact could be made, 396 (51.4%) refused to participate, 45 (5.8%) were too ill or hard of hearing, and 301 (39.0%) were unable to be contacted. Of the 686 individuals who were interviewed, 2 (0.3%) did not complete the interview, 46 (6.7%) were excluded because of a prior diagnosis of prostate cancer, and 34 (5.0%) were excluded because they identified "other" race or did not provide race information. Analyses were thus limited to the 604 African American and white controls who completed an interview. Of the participating controls, 46% were selected through RDD and 54% through HCFA. Telephone numbers were not available for 185 (28.4%) of the 651 randomly selected HCFA controls; 63 (34.1%) of these were contacted door-to-door and the remaining 122 (66.0%) were excluded. The average time interval between date of study entry and interview of controls was 4.5 months (range: 0–35.8; standard deviation: 4.8).

Subject characteristics

Overall, 700 eligible prostate cancer cases diagnosed between April 1996 and March 1998 and 604 controls were included in the analyses (Table 2). Cases and controls were similar with respect to marital status, current BMI, smoking history, average weekly number of alcoholic drinks in the previous year, and the presence of anyone else during the interview. Overall, a greater proportion of cases was older ($p = 0.04$), African American ($p = 0.005$), had attained less education ($p = 0.03$), and had a family history of prostate cancer in first degree relatives ($p = 0.0004$) compared to controls. A smaller proportion of cases had a history of vasectomy ($p = 0.007$) compared to controls. Among the 610 African American subjects, there were no significant differences between cases and controls for any of the characteristics presented in Table 2. Among the 694 white subjects, a greater proportion of cases was older ($p = 0.04$) and had a family history of prostate cancer in first degree relatives ($p = 0.0012$) compared to controls.

Table 2. Characteristics of prostate cancer cases and controls. Wayne County, Michigan, April 1996–March 1998.

Characteristic	African Americans (n = 610)				Whites (n = 694)				Total (n = 1304)			
	Cases (n = 353)		Controls (n = 257)		Cases (n = 347)		Controls (n = 347)		Cases (n = 700)		Controls (n = 604)	
	n	%	n	%	n	%	n	%	n	%	n	%
Age[a,b,c]												
50–54	35	9.9	30	11.7	24	6.9	43	12.4	59	8.4	73	12.1
55–59	39	11.1	27	10.5	54	15.6	70	20.1	93	13.3	97	16.1
60–64	73	20.7	39	15.2	62	17.9	54	15.6	135	19.3	93	15.4
65–69	98	27.8	85	33.1	107	30.8	94	27.1	205	29.3	179	29.6
70–74	108	30.6	76	29.6	100	28.8	86	24.8	208	29.7	162	26.8
Race[b]												
African American									353	50.4	257	42.6
White									347	49.6	347	57.5
Marital status												
Single	34	9.7	26	10.2	20	5.8	20	5.8	54	7.7	46	7.6
Married/living together	240	68.2	166	64.8	286	82.4	283	81.6	526	75.3	449	74.5
Divorced/separated	51	14.5	42	16.4	20	5.8	34	9.8	71	10.2	76	12.6
Widowed	27	7.7	22	8.6	21	6.1	10	2.9	48	6.9	32	5.3
Refused	1		1		0		0		1		1	
Education[b]												
0–8th grade	0	0	0	0	2	0.6	0	0	2	0.3	0	0
9–11th grade	92	26.1	58	22.6	24	6.9	22	6.3	116	16.6	80	13.3
H.S. graduate	110	31.2	59	23.0	90	25.9	90	25.9	200	28.6	149	24.7
At least some college	151	42.8	140	54.5	231	66.6	235	67.7	382	54.6	375	62.1
Current body mass index												
<18.5	3	0.9	1	0.4	3	0.9	2	0.6	6	0.9	3	0.5
18.5–24.9	79	22.6	60	23.4	75	21.6	91	26.4	154	22.1	151	25.1
25.0–29.9	173	49.4	123	48.1	170	49.0	160	46.4	343	49.2	283	47.1
≥30.0	95	27.1	72	28.1	99	28.5	92	26.7	194	27.8	164	27.3
Don't know/refused	3		1		0		2		3		3	

Table 2. (Continued)

Characteristic	African Americans (n = 610)				Whites (n = 694)				Total (n = 1304)			
	Cases (n = 353)		Controls (n = 257)		Cases (n = 347)		Controls (n = 347)		Cases (n = 700)		Controls (n = 604)	
	n	%	n	%	n	%	n	%	n	%	n	%
Smoked > 100 cigarettes in lifetime												
No	96	27.3	69	26.9	81	23.3	87	25.1	177	25.3	156	25.8
Yes	256	72.7	188	73.2	266	76.7	260	74.9	522	74.7	448	74.2
Don't know	1		0		0		0		1		0	
Alcohol use												
Never	170	48.2	118	45.9	114	32.9	105	30.3	284	40.6	223	36.9
Ever	183	51.8	139	54.1	233	67.2	242	69.7	416	59.4	381	63.1
≤7[d]	131	72.0	86	63.7	180	78.3	190	79.8	311	75.5	276	74.0
8–21[d]	38	20.9	30	22.2	41	17.8	40	16.8	79	19.2	70	18.8
22–56[d]	13	7.1	14	10.4	9	3.9	8	3.4	22	5.3	22	5.9
≥57[d]	0	0	5	3.7	0	0	0	0	0	0	5	1.3
Amount unknown[d]	1		4		3		4		4		8	
Family history of prostate cancer in first degree relatives[b,c,e]												
No	201	81.7	148	88.1	217	76.7	213	87.7	418	79.0	361	87.8
Yes	45	18.3	20	11.9	66	23.3	30	12.3	111	21.0	50	12.2
Don't know	107		89		64		104		171		193	
Vasectomy history[b]												
No	350	99.2	254	98.8	277	80.1	258	74.4	627	89.7	512	84.8
Yes	3	0.9	3	1.2	69	19.9	89	25.7	72	10.3	92	15.2
Don't know	0		0		1		0		1		0	
Tumor stage												
Localized	281	79.6			273	78.7			554	79.1		
Regional	55	15.6			62	17.9			117	16.7		
Distant	10	2.8			4	1.2			14	2.0		
Unknown	7	2.0			8	2.3			15	2.1		
Tumor grade[f]												
Well differentiated	19	5.4			10	2.9			29	4.1		
Moderately differentiated	248	70.3			260	74.9			508	72.6		
Poorly differentiated	63	17.9			59	17.0			122	17.4		
Unknown	23	6.5			18	5.2			41	5.9		
Anyone else present during interview												
No	275	80.9	190	76.6	237	71.4	255	76.6	512	76.2	445	76.6
Yes	65	19.1	58	23.4	95	28.6	78	23.4	160	23.8	136	23.4
Not recorded by interviewer	13		9		15		14		28		23	

[a]Age at diagnosis for cases; Age at study entry for controls.
[b]Chi-squared $p < 0.05$ among all cases and controls combined (does not include don't know or not asked).
[c]Chi-squared $p < 0.05$ among white cases and controls (does not include don't know or not asked).
[d]Average weekly number of alcoholic drinks in the year before diagnosis (cases) or interview (controls).
[e]Defined as self-reported history of prostate cancer in subject's father and/or brother(s).
[f]Well differentiated (Gleason score 2–4); moderately differentiated (Gleason score 5–7); poorly differentiated (Gleason score 8–10).

Among cases, African Americans and whites had similar distributions of tumor stage ($p = 0.37$) and grade ($p = 0.29$) at diagnosis, with the majority having tumors of localized stage (79.1%) and moderately differentiated grade (72.6%).

Associations of STDs with prostate cancer

Overall, 25.4% of cases and 21.4% of controls reported a history of at least one episode of STD. Among all subjects, 42.1% of African Americans and 7.2% of whites reported a history of at least one episode of STD. After adjusting for age, race, education, and family history of prostate cancer in first degree relatives, prostate cancer was not associated with a history of any STD, gonorrhea, genital herpes, chancroid, syphilis or other STDs in the entire sample (Table 3). Similarly, no significant associations between STD history and prostate cancer were observed among African American men or white men. No interaction between race and

Table 3. Adjusted odds of prostate cancer by race and history of sexually transmitted disease (STD), prostatitis, and benign prostate hyperplasia (BPH). Wayne County, Michigan, April 1996–March 1998[a]

Characteristic	African Americans (n = 610)				Whites (n = 694)				Total (n = 1304)			
	Cases (n = 353)	Controls (n = 257)	OR[b]	95% CI	Cases (n = 347)	Controls (n = 347)	OR[b]	95% CI	Cases (n = 700)	Controls (n = 604)	OR[c]	95% CI
Any STD history												
Never	196	149	1.0		320	320	1.0		516	469	1.0	
Ever	155	102	1.1	0.7, 1.6	23	27	0.9	0.5, 1.8	178	129	1.0	0.7, 1.5
(%) Ever	(43.9)	(39.7)			(6.7)	(7.8)			(25.4)	(21.4)		
(Missing)	(2)	(6)			(4)	(0)			(6)	(6)		
Frequency of any STD												
1 (referent: Never)	85	57	1.0	0.6, 1.6	17	18	1.0	0.5, 2.3	102	75	1.0	0.7, 1.6
2	36	22	1.2	0.8, 1.7	5	5	1.2	0.5, 2.5	41	27	1.2	0.8, 1.6
≥3	31	22	1.0	0.8, 1.3	1	2	0.8	0.3, 1.7	32	24	1.0	0.8, 1.2
(missing)	(3)	(1)			(0)	(2)			(3)	(3)		
Gonorrhea history												
Never	211	158	1.0		329	329	1.0		540	487	1.0	
Ever	139	94	1.0	0.7, 1.6	16	18	1.1	0.5, 2.5	155	112	1.0	0.7, 1.5
(%) Ever	(39.7)	(37.3)			(4.6)	(5.2)			(22.3)	(18.7)		
(Missing)	(3)	(5)			(2)	(0)			(5)	(5)		
Frequency of gonorrhea												
1 (referent: Never)	78	53	1.0	0.6, 1.6	15	13	1.5	0.6, 3.6	93	66	1.1	0.7, 1.6
2	31	20	1.1	0.7, 1.7	1	4	[d]		32	24	1.1	0.7, 1.6
≥3	27	21	1.0	0.7, 1.3	0	1	[d]		27	22	1.0	0.7, 1.2
(Missing)	(3)	(0)			(0)	(0)			(3)	(0)		
Genital herpes (HSV-1 or HSV-2) history												
Never	351	251	1.0		343	344	1.0		694	595	1.0	
Ever	0	1	[d]		4	3	1.2	0.3, 5.5	4	4	1.1	0.3, 5.2
(%) Ever	(0)	(0.4)			(1.2)	(0.9)			(0.6)	(0.7)		
(Missing)	(2)	(5)			(0)	(0)			(2)	(5)		
Chancroid history												
Never	348	251	1.0		345	346	1.0		693	597	1.0	
Ever	3	3	0.2	0.02, 1.9	1	1	0.8	0.05, 13.0	4	4	0.3	0.1, 1.7
(%) Ever	(0.9)	(1.2)			(0.3)	(0.3)			(0.6)	(0.7)		
(Missing)	(2)	(3)			(1)	(0)			(3)	(3)		
Syphilis history												
Never	325	242	1.0		346	344	1.0		671	586	1.0	
Ever	24	12	1.3	0.5, 3.2	1	3	[d]		25	15	1.1	0.5, 2.4
(%) Ever	(6.9)	(4.7)			(0.3)	(0.9)			(3.6)	(2.5)		
(Missing)	(4)	(3)			(0)	(0)			(4)	(3)		
Other STDs history												
Never	343	252	1.0		344	344	1.0		687	596	1.0	
Ever	8	2	1.8	0.3, 9.6	2	3	0.7	0.1, 3.9	10	5	1.2	0.4, 3.8
(%) Ever	(2.3)	(0.8)			(0.6)	(0.9)			(1.4)	(0.8)		
(Missing)	(2)	(3)			(1)	(0)			(3)	(3)		
Prostatitis history												
Never	295	238	1.0		288	320	1.0		583	558	1.0	
Ever	43	15	2.2	1.1, 4.6	43	23	1.6	0.8, 2.9	86	38	1.8	1.1, 2.9
(%) Ever	(12.7)	(5.9)			(13.0)	(6.7)			(12.9)	(6.4)		
(Missing)	(15)	(4)			(16)	(4)			(31)	(8)		
BPH history												
Never	235	211	1.0		205	281	1.0		440	492	1.0	
Ever	109	39	2.7	1.6, 4.4	137	62	2.3	1.5, 3.4	246	101	2.4	1.8, 3.3
(%) Ever	(31.7)	(15.6)			(40.1)	(18.1)			(35.9)	(17.0)		
(Missing)	(9)	(7)			(5)	(4)			(14)	(11)		

[a]Table adapted from Hayes *et al.* [7].

[b]Odds ratio (OR) and 95% confidence interval (CI); ORs are adjusted for age (as a continuous variable), education, and family history of prostate cancer (first degree relatives), and do not include subjects with missing covariate data.

[c]ORs are adjusted for age (as a continuous variable), race, education, and family history of prostate cancer in first degree relatives, and do not include subjects with missing covariate data.

[d]Could not estimate OR and 95% CI.

history of any STD was observed (p for interaction term = 0.59).

Because most men with a history of STD reported only one episode of infection (with the exception of gonorrhea), frequency of infection is only presented for any STD and for gonorrhea. Both overall and within African Americans or whites, men with one, two, or three or more episodes of any STD did not demonstrate higher odds of prostate cancer compared to those without a history of any STD, after adjusting for covariates. Similarly, no significant associations were observed between men with one, two, or three or more episodes of gonorrhea compared to those without a history of gonorrhea, either overall or within African Americans or whites.

We analyzed history of any STD by tumor stage and grade among cases, but did not find significant differences in the distribution of STD history by early (localized) versus advanced (regional plus distant) stage tumors (excluding unknown, $p = 0.49$) or by grade (excluding unknown, $p = 0.28$).

Associations of prostatitis and BPH with prostate cancer

After adjusting for age, race, education, and family history of prostate cancer in first degree relatives, the odds of prostate cancer among men with a history of prostatitis were nearly twice that of men without a history of prostatitis in the entire sample (OR = 1.8, 95% CI: 1.1, 2.9) (Table 3). After stratifying by race, the odds of prostate cancer among men with a history of prostatitis were twice the odds of those without a history of prostatitis in African American men (OR = 2.2, 95% CI: 1.1, 4.6). There was no evidence for interaction between race and history of prostatitis (p for interaction term = 0.57).

The odds of prostate cancer among men with a history of BPH were over twice the odds of men without a history of BPH (OR = 2.4, 95% CI: 1.8, 3.3), after adjusting for age, race, education, and family history of prostate cancer in first degree relatives (Table 3). After stratifying by race, the odds of prostate cancer among men with a history of BPH were more than twice the odds of those without a history of BPH in both African American (OR = 2.7, 95% CI: 1.6, 4.4) and white (OR = 2.3, 95% CI: 1.5, 3.4) men. There was no evidence for interaction between race and history of BPH (p for interaction term = 0.84).

Men in this study with a history of BPH were over six times as likely to have undergone TURP compared to those without a history of BPH (OR = 6.4, 95% CI: 4.0, 10.1) (data not shown). Among the 342 men with a history of BPH there was no significant association between TURP and prostate cancer (OR = 0.9, 95% CI: 0.5, 1.6)

For a considerable proportion of cases (22.9%) and controls (22.5%), at least one other individual was present during their interview. The analyses were repeated after excluding 296 subjects who had someone else present during their interview and 51 subjects for whom this information was not recorded by the interviewer. For all odds ratios presented in Table 3, the estimates did not differ by more than 10%, and the directions of the effects were unchanged (data not shown).

Associations of vasectomy with prostate cancer

Odds ratios for history of vasectomy, age at vasectomy, and interval since vasectomy are shown in Table 4. Because only six African American subjects (three cases, three controls) reported a history of vasectomy, these analyses combined African American and white subjects. All odds ratios were adjusted for age, race, education, and family history of prostate cancer in first degree relatives. A history of vasectomy was reported by 72 cases (10.3%) and 92 controls (15.2%). There was no significant association between vasectomy history and

Table 4. Odds of prostate cancer by age at and interval since vasectomy. Wayne County, Michigan, April 1996–March 1998[a]

Vasectomy	Cases (n = 700)	Controls (n = 604)	OR[b]	95% CI[c]
Never (referent)	627	512	1.0	
Ever	72	92	1.0	0.7, 1.5
(Don't know)	(1)	(0)		
Age at vasectomy (years)				
≤34 (referent: never)	32	31	1.2	0.6, 2.3
35–39	10	25	0.6	0.4, 0.9
40–44	8	18	0.9	0.6, 1.3
≥45	21	17	1.2	1.0, 1.5
(Missing[d])	(1)	(1)		
Interval since vasectomy (years)				
≤14 (referent: never)	7	14	1.3	0.4, 4.1
15–19	9	11	1.0	0.6, 1.7
20–24	25	30	1.1	0.9, 1.3
≥25	27	33	0.9	0.8, 1.1
(Missing[e])	(4)	(4)		

[a]Table adapted from Lesko *et al.* [37] and Cox *et al.* [38].

[b]Odds ratios (OR) are adjusted for age (as a continuous variable), race, education, and family history of prostate cancer (first degree relatives), and do not include subjects with missing covariate data.

[c]CI, confidence interval.

[d]Not enough information to calculate age at vasectomy for these individuals.

[e]Not enough information to calculate interval since vasectomy for these individuals.

prostate cancer (OR = 1.0, 95% CI: 0.7, 1.5), after adjusting for covariates in the model. Age at vasectomy was not significantly associated with prostate cancer with the exception that men who had a vasectomy between ages 35 and 39 had lower odds of prostate cancer as compared to men without a history of vasectomy (OR = 0.6, 95% CI: 0.4, 0.9). Interval since vasectomy was not significantly associated with prostate cancer. No trend of increasing prostate cancer odds with successively younger ages at or longer intervals since vasectomy was observed.

Discussion

In this study we examined associations between prostate cancer and STDs, prostatitis, BPH, and vasectomy. A strength of the study was the inclusion of a large number of African American prostate cancer cases and population-based controls, which enabled us to assess the effects of potential risk factors both in the entire study sample and among African American and white men. A number of studies have examined STD history in relation to risk of prostate cancer, reporting mixed findings. Research has focused primarily on gonorrhea, syphilis, chlamydia, herpes simplex virus (HSV), and HPV. Hayes *et al.* conducted one of the largest population-based case–control investigations of STDs and prostate cancer to date, and found that cases were more likely to report a history of gonorrhea or syphilis (OR = 1.6, 95% CI: 1.2, 2.1), to show serological evidence of syphilis (OR = 1.8, 95% CI: 1.0, 3.5), and to have a higher frequency of gonorrhea episodes (p for trend = 0.009) [7]. Another population-based case–control study reported a borderline significant increased risk of prostate cancer among men with prior gonorrhea infection (OR = 1.5, 95% CI: 1.02, 2.18) [6], whereas no evidence for gonorrhea as a risk factor for prostate cancer was found in a hospital-based case–control study conducted among men in Greece [44]. Two population-based case–control studies examining the relationship between chlamydia infection and prostate cancer did not report significant associations [6, 8]. HPV, in particular, has generated interest due to its strong association with other genitourinary cancers; associations of HPV with prostate cancer have been reported in some studies [8, 9] but not others [6, 45–47].

In the late 1980s Ross *et al.* conducted case–control studies of prostate cancer risk factors among African American and white men in California to elucidate reasons for the differential in prostate cancer risk in these two racial groups [20]. The authors found an elevated risk of prostate cancer in both African American (relative risk (RR) = 1.7) and white (RR = 2.3) men with a history of STD, with the RR achieving statistical significance in African American men. Significant differences in sexual activity factors, including frequency of sexual intercourse, age at first sexual intercourse, and number of spouse's pregnancies, were also proposed as possible explanations for the increased risk of prostate cancer among African American men. More recently, it has been suggested that the higher incidence rate of prostate cancer in African Americans may be partially due to a greater prevalence of oncogenic viral DNA in prostatic tissues [47].

Our results do not indicate an important role for sexually transmitted agents in the etiology of prostate cancer; however, there are several potential limitations that should be considered in the interpretation our findings. It is conceivable that stronger associations between STD history and prostate cancer may exist among men with an advanced stage of disease at diagnosis. However, the majority of cases in our study had localized tumors (79.1%), so we were not able to conduct a complete analysis of the men with advanced tumors. We did not have information on timing of infections; thus, if the relevant window of exposure is either earlier or later in life, our study may have attenuated the true associations between these infections and prostate cancer. We relied on self-report of past history of STD, which is difficult to validate and may be limited by a subject's ability to recognize asymptomatic infection or recall the event, reluctance to admit a stigmatic condition, or lack of awareness of a specific diagnosis made in the past. Moreover, information on STD history is subject to social desirability bias, that is, subjects may be inclined to provide answers they believe are more socially acceptable to others present at interview. To address the potential for bias in STD reporting, we repeated the analyses after excluding subjects who had someone else present during their interview. Though the absence of another person during the interview does not preclude misclassification of exposures with in-person interviews, it was useful to note that the associations between prostate cancer and history of STD, prostatitis and BPH were essentially unchanged after the exclusions.

The high non-participation rate (ratio of interviewed to total potentially eligible men) may limit the generalizability of the results obtained from the final study sample. We note that there is some evidence for different participation rates in our cases and controls by age and race. Although we adjusted for these variables in our analyses, nevertheless the adjustment may not completely account for this potential bias or other uncontrolled selection forces which may have affected our

study findings. In order to enrich our study population with older controls, a random sample of Medicare recipients aged 65–74 years with working telephone numbers obtained from a HCFA listing was used in addition to RDD controls. We cannot exclude the potential for a selection bias if those HCFA controls with working telephone numbers that we were able to contact and interview somehow differed from potential controls without working telephone numbers. The interval between identification of cases through the rapid reporting system and date of interview was substantial, for several reasons. Our study population included older, urban men, a group that may be more difficult to reach for interviews. Additionally, obtaining physician consent prior to contacting cases for interview and errors in initial contact information obtained through the rapid reporting system contributed to delays in interviewing cases. Several measures to enhance the quality of the study were instituted, including the use of rapid reporting data updates and reverse telephone directories to correct errors in contact information.

Our study demonstrated that prostate cancer cases were nearly twice as likely to have a history of prostatitis compared to controls, and a similar, significant association was also evident in African American men. No interaction between race and history of prostatitis was observed. The observed positive association between prostatitis and prostate cancer in our study (OR = 1.8, 95% CI: 1.1, 2.9) was consistent with results of a recent study by Roberts *et al*. (OR = 1.7, 95% CI: 1.1, 2.6) [21]. A potential mechanism of carcinogenesis involving repeated tissue damage and regeneration in the presence of highly reactive oxygen and nitrogen species lends biological plausibility to the association between prostatitis and prostate cancer [48]. Our results could reflect either an etiological connection between prostatitis and prostate cancer or could reflect a detection bias; many men with elevated serum prostate-specific antigen levels undergo prostate biopsy for evaluation for possible prostate cancer; based on histological criteria, prostatitis is the most common noncancer diagnosis [49]. The epidemiological literature on the association between chronic prostatitis and risk of prostate cancer is limited, largely due to the difficulty in characterizing this clinical entity and the lack of a valid practical definition [50]. It is also unclear whether chronic inflammation influences prostate cancer initiation, promotion, or both processes [51]. In our study, we are not aware if men with prostatitis were diagnosed by a urologist or primary care physician, and there may be differences in the diagnostic approach used by these types of physicians [15]. Furthermore, self-reported prostatitis information was not adequate to determine whether the prostatitis episodes were acute or chronic, bacterial or nonbacterial, so we were limited to the broad classification of "prostatitis" as a covariate of interest for prostate cancer. There is some potential for misclassification of exposure status due to the lack of clear-cut diagnostic criteria and the overlap between symptoms of prostatitis and BPH. However, identifiable correlates of prostatitis do exist (such as age, severe lower urinary tract symptoms, high stress, and history of vasectomy and STD), and their inclusion in future studies should enhance recognition of this condition and help distinguish it from BPH. Using data from the Health Professionals Follow-Up Study, Collins *et al*. reported that men with a history of BPH had 7.7-fold greater odds (95% CI: 7.2, 8.3) of prostatitis compared to men without BPH history [15]. Studies that distinguish between acute bacterial, chronic bacterial, and nonbacterial prostatitis, though difficult and expensive to undertake, could enhance our understanding of the potential infectious and inflammatory roles for prostatitis in prostate cancer risk.

Our study also suggested that prostate cancer cases were more than twice as likely to have a past history of BPH, both overall (OR = 2.4, 95% CI: 1.8, 3.3) and within African American (OR = 2.7, 95% CI: 1.6, 4.4) and white (OR = 2.3, 95% CI: 1.5, 3.4) men. No interaction between race and history of BPH was observed. As discussed above in relation to prostatitis, the observed association could be a result of referral bias or detection bias. Men seen by urologists may be screened more vigilantly and, thus, may be more likely to be diagnosed with another urological condition. Men who are diagnosed with BPH may be subject to additional medical care and may be more closely followed up for other prostate problems, including prostate cancer. TURP is a common surgical treatment for BPH and could explain the observed association between BPH and prostate cancer. Incidental detection of prostate cancer through TURP is thought to explain slightly less than ten percent of all detected cases [52]. In the current study, we did not find a significant association between TURP and prostate cancer among men with a history of BPH. A recent review of the epidemiologic literature found no relationship between BPH and prostatic adenocarcinomas arising in the peripheral zone and weak evidence between BPH and prostatic adenocarcinomas originating in the transition zone [53]; a much more likely explanation for our findings is that BPH and prostate cancer share common predisposing factors.

Overall, we found no significant association between history of vasectomy and prostate cancer, with the exception that men who had a vasectomy between 35

and 39 years of age had decreased odds of prostate cancer (OR = 0.6, 95% CI: 0.4, 0.9). Previous studies have suggested an elevated risk of prostate cancer among men who underwent vasectomies at younger ages, but the observed effects were not statistically significant [36, 39]. It would be expected that differential surveillance for and/or detection of prostate cancer among men who have undergone vasectomy would increase the odds of prostate cancer: men who have seen a urologist for a vasectomy may have subsequently been exposed to more digital rectal examinations or invasive procedures used to diagnose prostate cancer [54]. We were unable to examine associations of vasectomy with prostate cancer by race because only six African American men (1%) reported a history of vasectomy in this study; this is consistent with previously reported vasectomy rates of 1–2% among African Americans in the U.S. [40]. The underlying mechanisms by which this sterilization procedure could influence prostate carcinogenesis remain unclear, but commonly offered biological explanations include the potential for this surgery to alter endocrine function and plasma hormone levels [55] or a permanent reduction in prostatic secretions following vasectomy resulting in prolonged exposure of prostatic glands to carcinogenic factors present in prostatic fluid [31]. As prostate cancer is a hormonally-related cancer, it is biologically plausible that clinical syndromes that influence hormone levels may affect risk of prostate cancer [50].

A body of evidence for an infectious component to prostate cancer development has begun to emerge; however, the inconsistent results of previously conducted studies suggest the need for additional research in this area. As the carcinogenic effects of chronic inflammation have been considered in organs including the liver, esophagus, large bowel, urinary bladder and gastric mucosa [13, 56], the study of prostatitis in relation to prostate cancer could shed light on a potential inflammatory etiology of prostate cancer. Observed associations between BPH and prostate cancer may reflect common predisposing factors. Questions remain as to whether men with a history of prostatitis or BPH have an increased risk of prostate cancer, whether the observed association is due to some degree of recall bias, or whether these men simply undergo more vigilant prostate cancer screening; future studies should take into account screening patterns to examine the potential role of detection and recall bias. The lack of association between vasectomy and prostate cancer in this study should be assuring in light of the limited contraceptive options for men and the widespread practice of vasectomy throughout the world. Prevention efforts could be enhanced if inflammatory or infectious etiologies are found to be of importance in the subsequent development of prostate cancer.

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