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ORIGINAL REPORT

Vasectomy and Risk of Aggressive Prostate Cancer: A 24-Year Follow-Up Study

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ABSTRACT

Purpose
Conflicting reports remain regarding the association between vasectomy, a common form of male contraception in the United States, and prostate cancer risk. We examined prospectively this association with extended follow-up and an emphasis on advanced and lethal disease.

Patients and Methods
Among 49,405 US men in the Health Professionals Follow-Up Study, age 40 to 75 years at baseline in 1986, 6,023 patients with prostate cancer were diagnosed during the follow-up to 2010, including 811 lethal cases. In total, 12,321 men (25%) had vasectomies. We used Cox proportional hazards models to estimate the relative risk (RR) and 95% CIs of total, advanced, high-grade, and lethal disease, with adjustment for a variety of possible confounders.

Results
Vasectomy was associated with a small increased risk of prostate cancer overall (RR, 1.10; 95% CI, 1.04 to 1.17). Risk was elevated for high-grade (Gleason score 8 to 10; RR, 1.22; 95% CI, 1.03 to 1.45) and lethal disease (death or distant metastasis; RR, 1.19; 95% CI, 1.00 to 1.43). Among a subcohort of men receiving regular prostate-specific antigen screening, the association with lethal cancer was stronger (RR, 1.56; 95% CI, 1.03 to 2.36). Vasectomy was not associated with the risk of low-grade or localized disease. Additional analyses suggested that the associations were not driven by differences in sex hormone levels, sexually transmitted infections, or cancer treatment.

Conclusion
Our data support the hypothesis that vasectomy is associated with a modest increased incidence of lethal prostate cancer. The results do not appear to be due to detection bias, and confounding by infections or cancer treatment is unlikely.

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INTRODUCTION

Vasectomy is a common form of contraception in the United States with a prevalence of 15%.[1,2] Two large cohort studies published in 1993, including the Health Professionals Follow-Up Study (HPFS), found an increased risk of prostate cancer among men with vasectomy[3,4]; other studies have not found an association.[5,6] A meta-analysis of 22 studies estimated a pooled relative risk (RR) for total prostate cancer of 1.37 (95% CI, 1.15 to 1.62) comparing men with and without vasectomy, although there was significant heterogeneity between studies. Among the five cohort studies included, the RR was 1.22 (95% CI, 0.90 to 1.64).[7] Since then, additional studies have been published. One prospective cohort of Maryland men reported an RR of 2.03 (95% CI, 1.24 to 3.32) for the association between vasectomy and incident prostate cancer.[8] However, two population-based case-control studies in Washington state[9] and New Zealand[10] and a hospital-based case-control study in China, Nepal, and the Republic of Korea[11] found no association.

Criticisms of the studies reporting positive associations of vasectomy with prostate cancer risk focus on bias and confounding. Detection bias may explain the positive results because men who opt for vasectomy may choose more medical care in general and see a urologist at an earlier age than do men who do not choose vasectomy.[10] This might lead to increased screening and increased diagnosis of early stage and low-grade prostate cancers. Publication bias has also been proposed given the small effect size noted in most studies.[12] Possible confounding by sexually transmitted infections (STIs)[7] has also been discussed.

In this study, we extend follow-up from the prospective HPFS cohort by two decades with more

than 6,000 patients with prostate cancer to investigate more comprehensively the association between vasectomy and prostate cancer risk,[3] including the risk of advanced, high-grade, and lethal cancers. To address previous criticisms, we controlled for intensity of prostate-specific antigen (PSA) screening and other possible confounders. To further reduce the potential for bias due to screening and to increased clinical relevance, we focus on the incidence of advanced and lethal prostate cancer, as well as the incidence of prostate cancer in a highly screened subgroup.

PATIENTS AND METHODS

The HPFS is a prospective cohort study of 51,529 male health professionals in the United States age 40 to 75 years at baseline in 1986. The men are sent biennial questionnaires collecting information on lifestyle and health outcomes. Men who reported a cancer diagnosis (except nonmelanoma skin cancer) before baseline were excluded, leaving 49,405 men who were observed prospectively until 2010. The HPFS is approved by the Human Subjects Committee at the Harvard School of Public Health.

Assessment of Vasectomy History

Men were asked on the 1986 questionnaire whether they had had a vasectomy and, if so, to identify the period: 1955 to 1964, 1965 to 1974, 1975 to 1979, or 1980 to 1986. Men were asked on each biennial questionnaire through 2000 if they had had a vasectomy since the previous questionnaire and, if so, in which year. By 2000, only 58 men (0.1%) reported a new vasectomy in the previous 2 years (the youngest age in the cohort in 2000 was 54 years), and the question was not asked in subsequent years.

In 1992, men were asked at what age they had had a vasectomy if it was before 1986. This more precise timing information was used to assign the date and age at vasectomy for 70% of the 11,113 men who had reported a vasectomy before 1986. Date and age at vasectomy for the remaining men were assigned by using the midpoint of the 10-year period categories from the 1986 questionnaire.

Ascertainment of Prostate Cancer Cases

Prostate cancer diagnoses were initially identified by self-reports from the participants or their next of kin and confirmed by review of medical records and pathology reports. Deaths were ascertained through reports from family members and searches of the National Death Index. An end points committee, which used all available data, assigned cause of death. Medical records confirmed approximately 90% of prostate cancer cases, and the remaining 10% were based on self-reports or death certificates. We observed men with prostate cancer by sending additional questionnaires every 2 years and collecting medical records to ascertain treatment, disease progression, and diagnosis of metastases.

We excluded men with stage T1a cancers. We defined advanced stage prostate cancer as stage T3b, T4, N1, or M1 at diagnosis; development of lymph node or distant metastasis; or death as a result of prostate cancer before the end of follow-up. Lethal cancers, a subset of advanced cancers, were those that caused death or metastasis to bone or other organs before the end of follow-up. Localized cancers were stage T1 or T2 and N0, M0 at diagnosis and did not progress to any metastasis or death during the follow-up period. Cancers were also categorized as high grade (Gleason score 8 to 10), Gleason grade 7, or low grade (Gleason score 2 to 6) at diagnosis based on prostatectomy or biopsy pathology reports; Gleason grade was not available for all men.

Statistical Analysis

Each participant contributed person-time from the date that he returned the baseline questionnaire in 1986 until prostate cancer diagnosis, death, or the end of follow-up, January 31, 2010. We used Cox proportional hazards regression to calculate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% CIs of total prostate cancer and lethal, advanced, localized, high-grade, Gleason grade 7, and low-grade prostate cancers. All models were stratified by age and calendar time.

Participants were classified according to vasectomy status in each period, comparing risk among men with and without vasectomy. In addition, we divided men with vasectomy into exposure groups based on median time since vasectomy ($< 23, \geq 23$ years) and median age at vasectomy ($< 38, \geq 38$ years).

Multivariable models were adjusted for race, height (quartiles), body mass index (six categories or missing), vigorous physical activity (quintiles), smoking (never, former smoker who quit ≥ 10 years ago, former smoker who quit < 10 years ago, current, or missing), type 2 diabetes mellitus (yes or no), family history of prostate cancer, history of PSA testing, multivitamin use (yes or no), and intakes of supplemental vitamin E and alcohol (quintiles) calculated from food frequency questionnaires. To account for diagnostic bias, we adjusted for PSA testing in the previous period (yes or no) and for higher intensity of past testing (yes for men reporting PSA tests in half or more of all questionnaires since 1994). All covariates except race and height were updated in each questionnaire cycle. Geographical region, religion, self-reported history of gonorrhea and syphilis, frequency of ejaculation, intakes of tomato sauce and α-linolenic acid, and body mass index at age 21 years were not included in the final models because they were not associated with vasectomy and had little effect on the RR estimates.

To investigate the effects of PSA testing on the results, we did additional analyses within a highly screened subcohort of men who reported having PSA tests in 1994 (the first year PSA testing was asked) and 1996, with follow-up from 1996 through 2010. These results were also adjusted for intensity of PSA testing during follow-up.

We leveraged existing plasma biomarker data on a subset of men within the cohort. To further investigate possible confounding by STIs, we calculated the age-adjusted prevalence of seropositivity for *Chlamydia trachomatis*, *Trichomonas vaginalis*, human papillomavirus (HPV), and human herpesvirus type 8 (HHV-8) according to vasectomy status in a subset of 693 controls from a nested case-control study of prostate cancer. To explore possible mechanisms underlying associations with vasectomy, we compared age-adjusted plasma concentrations of sex hormones (testosterone, free testosterone, estradiol, and sex hormone–binding globulin) among 663 controls according to vasectomy status at the time of blood sample. Detailed methods describing the assays and analyses can be found in previous publications[13,14] and in the Appendix.

RESULTS

The cohort consisted of 49,405 men at baseline in 1986, at which time 22% reported having had a vasectomy. Vasectomy status was updated every 2 years until 2000. By 2000, 12,321 of the men (25%) in the entire cohort reported having had a vasectomy. Characteristics of the study population at baseline among men with and without a vasectomy by 2000 are shown in Table 1. Compared with those without a vasectomy, men reporting a vasectomy were more likely to be white, to consume alcohol, and to take multivitamins. Men with vasectomy reported more PSA testing than those without vasectomy. Among men with prostate cancer, those with vasectomy had lower PSA levels at diagnosis.

During 24 years of follow-up, 6,023 cases of prostate cancer were diagnosed, including 732 high-grade and 811 lethal cases. The multivariable-adjusted relative risk of total prostate cancer in men who had a vasectomy compared with those who did not was 1.10 (95% CI, 1.04 to 1.17; Table 2). Vasectomy was not significantly associated with the risk of low-grade cancer. However, men who had a vasectomy had an increased risk of both lethal (RR, 1.19; 95% CI, 1.00 to 1.43) and advanced stage disease (RR, 1.20; 95% CI, 1.03 to 1.40). The RR of developing high-grade cancer was also increased (RR, 1.22; 95% CI, 1.03 to 1.45) for men with a vasectomy. When we examined cases of prostate cancer diagnosed since our initial report in 1990,[3] findings were qualitatively similar.

Table 1. Age-Standardized Baseline Characteristics of the Study Population and Highly Screened Subcohort According to Vasectomy Status by 2000, Health Professionals Follow-Up Study

	Total Cohort, 1986, Vasectomy Status		Highly Screened Subcohort, 1996, Vasectomy Status	
	No	Yes	No	Yes
N	37,084	12,321	10,161	3,740
Age, years	55.5	51.8	66.8	63.1
Time since vasectomy, years	—	15.8	—	25.5
Age at vasectomy, years	—	38.6	—	39.4
Body mass index, kg/m^2	25.6	25.4	25.8	25.7
Height, inches	70	70	70	70
Race/ethnicity, %				
White	95	97	96	98
African American	1	< 1	1	< 1
Asian	2	1	1	< 1
Current smokers, %	10	10	4	5
Vigorous activity, % upper quintile	15	17	18	19
Diabetes, %	3	3	6	5
Family history of prostate cancer, %	12	12	15	16
Multivitamin use, %	41	43	51	51
Alcohol intake, g/day	10.8	12.9	10.4	12.5
Supplemental vitamin E, mg/day	37.6	39.8	55.5	55.5
PSA testing history, 2008				
PSA test from 2006-2008 (%)	59	67	74	80
No. of biennial questionnaires with PSA test, 1994-2008 (max = 8)	4.8	5.2	7.0	7.1
PSA test on at least half of all questionnaires, 1994-2008, %	69	75	97	97
Case characteristics*				
No. of prostate cancer cases	4,499	1,524	1,191	474
Age at diagnosis, years	70.7	68.1	73.0	70.2
Lethal cases, %†	15	12	8	9
Advanced cases, %†	20	16	11	12
Localized cases, %†	73	76	84	83
Gleason grade, %				
8-10	14	15	12	13
7	35	38	36	43
2-6	50	47	53	45
Median PSA at diagnosis, ng/mL‡	7.0	6.5	6.6	6.1
Mean PSA at diagnosis, ng/mL	18.5	11.1	11.7	9.3
Primary treatment, %				
Radical prostatectomy	45	47	37	40
Radiation	36	36	44	42
Hormonal therapy	8	7	8	8
Active surveillance	9	8	10	9
Other	2	2	2	2

Abbreviation: PSA, prostate-specific antigen.
*Incident cases, standardized to age distribution of cases overall and within the highly screened subcohort, respectively.
†Lethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up. Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.
‡Median PSA was not standardized to age at diagnosis.

Prostate-specific antigen testing is one of the strongest predictors of prostate cancer diagnosis and thus may act as an important confounder of the vasectomy association. To address this concern, we examined a subcohort of 13,901 highly screened men, of whom 27% reported a vasectomy by 2000. There were 1,665 incident cases of prostate cancer in this subcohort between 1996 and 2010, including 179 high-grade and 127 lethal cases. Characteristics of the highly screened subcohort at baseline by vasectomy status are shown in Table 1.

Vasectomy was not associated with total prostate cancer incidence or with risk of low-grade or localized prostate cancer in the highly screened subcohort (Table 2). However, vasectomy was associated with an increased risk of high-grade (RR, 1.28; 95% CI, 0.91 to 1.81) and grade 7 cancers (RR, 1.22; 95% CI, 1.02 to 1.47), although the association with high-grade cancers did not achieve statistical significance in this smaller cohort. Notably, men who had undergone vasectomy had a statistically significant 56% increased risk of lethal prostate cancer (RR, 1.56; 95% CI, 1.03 to 2.36) in the highly screened cohort.

The association between vasectomy and prostate cancer did not differ by time elapsed since vasectomy or by age at vasectomy (Table 3). The associations with lethal and advanced disease were similar by time elapsed since vasectomy, which was also true when we further divided time since vasectomy into 10-year categories (data not shown). There was a suggestion that the increased risk was more pronounced among men who were younger at the time of vasectomy (P value for difference = .08 for lethal, .09 for advanced); however, this pattern was not apparent when we examined age at vasectomy in quartiles (data not shown).

To examine the possibility of confounding by STIs, we compared the prevalence by vasectomy status of several pathogens measured serologically among 693 men without prostate cancer, of whom 185 (27%) had a vasectomy. Men who had undergone vasectomy had a significantly higher age-adjusted prevalence of HPV (22.2% *v* 14.3%, $P = .01$). However, there was no significant difference in age-adjusted prevalence of *Chlamydia* (4.7% *v* 2.7%, $P = .10$), *T vaginalis* (9.9% *v* 8.5%, $P = .28$), or HHV-8 infection (16.5% *v* 18.3%, $P = .56$) between men with and without vasectomy. Only *T vaginalis* and HHV-8 have been associated with prostate cancer risk in this cohort.[13-15]

We assessed whether treatment varied by vasectomy status. Age- and grade-adjusted distribution of active surveillance, radical prostatectomy, radiation, or hormonal treatment was similar between groups (Table 1).

To investigate the possible role of sex hormones as mediators of the association between vasectomy and prostate cancer, we analyzed levels of total testosterone, free testosterone, sex hormone–binding globulin, and estradiol among 663 men without prostate cancer at the time of blood draw. There were no significant differences in levels of any measured hormone between men with and without a vasectomy (data not shown).

DISCUSSION

With 24 years of follow-up and more than 6,000 cases of prostate cancer, our updated analysis in the HPFS supports a positive association between vasectomy and the risk of advanced or lethal prostate cancer. After accounting for differences in PSA screening, vasectomy was not associated with the risk of low-grade or localized disease.

There have been mixed findings from other cohort and case-control studies.[4,5,8,16] Our analysis represents the largest cohort study with the longest follow-up to date to examine the relationship of

Table 2. Relative Risk and 95% CIs of Prostate Cancer by Vasectomy Status Among the Full Study Population and Highly Screened Subcohort, Health Professionals Follow-Up Study

	Total Cohort, 1986-2010				Highly Screened Subcohort, 1996-2010			
	Vasectomy Status				Vasectomy Status			
		Yes				Yes		
	No	RR	95% CI	*P*	No	RR	95% CI	*P*
Total prostate cancer								
No. of patients	4,499	1,524			1,191	474		
Age-adjusted RR*	1.00	1.14	1.08 to 1.21	< .001	1.00	1.05	0.94 to 1.18	.37
Fully adjusted RR*	1.00	1.10	1.04 to 1.17	.001	1.00	1.05	0.94 to 1.17	.41
Grade 8-10 prostate cancer								
No. of patients	544	188			126	53		
Age-adjusted RR*	1.00	1.24	1.04 to 1.46	.02	1.00	1.23	0.88 to 1.72	.23
Fully adjusted RR*	1.00	1.22	1.03 to 1.45	.02	1.00	1.28	0.91 to 1.81	.15
Grade 7 prostate cancer								
No. of patients	1,303	524			374	187		
Age-adjusted RR*	1.00	1.23	1.11 to 1.37	< .001	1.00	1.22	1.02 to 1.47	.03
Fully adjusted RR*	1.00	1.18	1.06 to 1.31	.002	1.00	1.22	1.02 to 1.47	.03
Grade 2-6 prostate cancer								
No. of patients	1,870	656			545	201		
Age-adjusted RR*	1.00	1.14	1.04 to 1.25	.004	1.00	0.96	0.81 to 1.13	.62
Fully adjusted RR*	1.00	1.08	0.99 to 1.19	.09	1.00	0.95	0.80 to 1.12	.52
Lethal prostate cancer†								
No. of patients	644	167			90	37		
Age-adjusted RR*	1.00	1.20	1.00 to 1.43	.05	1.00	1.48	0.99 to 2.22	.06
Fully adjusted RR*	1.00	1.19	1.00 to 1.43	.05	1.00	1.56	1.03 to 2.36	.04
Advanced prostate cancer†								
No. of patients	821	231			119	49		
Age-adjusted RR*	1.00	1.21	1.04 to 1.41	.01	1.00	1.32	0.93 to 1.87	.12
Fully adjusted RR*	1.00	1.20	1.03 to 1.40	.02	1.00	1.35	0.95 to 1.93	.10
Localized prostate cancer†								
No. of patients	2,996	1,082			905	368		
Age-adjusted RR*	1.00	1.14	1.06 to 1.23	< .001	1.00	1.05	0.92 to 1.19	.46
Fully adjusted RR*	1.00	1.09	1.02 to 1.17	.02	1.00	1.04	0.92 to 1.18	.55

Abbreviation: RR, relative risk.

*Age-adjusted model adjusted for age in months and calendar time. Multivariable model also adjusted for race, height (quartiles), current body mass index (six categories), vigorous physical activity (quintiles), smoking (never, former smoker who quit ≥ 10 years ago, former smoker who quit < 10 years ago, or current), diabetes, family history of prostate cancer, multivitamin use (yes or no), intake of supplemental vitamin E and alcohol (both quintiles), and history of prostate-specific antigen testing.

†Lethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up. Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

vasectomy to total and lethal prostate cancer.[7,9,10] Three previous cohort studies have examined the association of vasectomy with advanced stage disease, with all finding increased but not statistically significant RRs ranging from 1.4 to 2.1.[3,4,8] In contrast, the six case-control studies that have examined the association of vasectomy with advanced stage disease found no statistically significant associations (RR range, 0.73 to 1.1).[10,16-20] Only one cohort study has investigated the risk of high-grade prostate cancer with vasectomy and did not find an association.[8] However, a retrospective review of 522 consecutive patients who underwent prostate biopsy found a statistically significant higher mean Gleason score in patients with a history of vasectomy.[21]

A criticism of previous studies is that individuals who elect vasectomy have closer medical follow-up, resulting in increased screening for and detection of prostate cancer. Indeed, in the total cohort, we noticed a trend toward more intensive screening among men with a history of vasectomy, and PSA at diagnosis was higher in men without vasectomy, suggesting that they were potentially diagnosed with more advanced disease. Thus, although detection bias might explain an increased risk of screen-detected localized cancer among men with vasectomy, it cannot explain our findings of the higher risk of lethal or advanced disease among this group. In addition, in our subcohort of highly screened men reporting early adoption of PSA screening, and with adjustment for ongoing PSA testing, we still noted increased risks of high-grade and lethal prostate cancer, further suggesting that detection bias does not explain the observed associations.

We explored relationships between vasectomy and serologic evidence of STIs, because some STIs may be associated with both vasectomy and prostate cancer risk. In this cohort, however, vasectomy was associated only with HPV, whereas prostate cancer risk was positively associated only with *T vaginalis* and HHV-8 infections.[13,22] Thus, confounding by STIs does not seem to explain our findings, although we cannot rule out differences in an unidentified, unmeasured STI. In addition, treatment choices do not explain the association as the groups elected similar treatments when age and grade at diagnosis were controlled.

Table 3. Relative Risk and 95% CIs of Prostate Cancer by Time Since Vasectomy and Age at Vasectomy Among the Full Study Population, Health Professionals Follow-Up Study, 1986-2010

	Time Since Vasectomy							Age at Vasectomy						
		< 23 years			≥ 23 years				< 38 years			≥ 38 years		
	None	RR	95% CI	*P*	RR	95% CI	*P*	None	RR	95% CI	*P*	RR	95% CI	*P*
Total prostate cancer														
No. of cases	4,499	378			1,118			4,499	615			881		
Age-adjusted RR*	1.00	1.15	1.03 to 1.29	.01	1.14	1.06 to 1.22	< .001	1.00	1.19	1.09 to 1.29	< .001	1.12	1.04 to 1.20	.004
Fully adjusted RR*	1.00	1.12	1.01 to 1.25	.04	1.10	1.02 to 1.17	.008	1.00	1.14	1.04 to 1.24	.003	1.08	1.00 to 1.16	.05
Grade 8-10 prostate cancer														
No. of cases	544	41			144			544	72			113		
Age-adjusted RR*	1.00	1.24	0.89 to 1.72	.21	1.24	1.03 to 1.50	.03	1.00	1.27	0.99 to 1.64	.06	1.22	0.99 to 1.50	.06
Fully adjusted RR*	1.00	1.22	0.88 to 1.71	.23	1.22	1.01 to 1.48	.04	1.00	1.27	0.98 to 1.64	.07	1.20	0.97 to 1.48	.09
Grade 7 prostate cancer														
No. of cases	1,303	123			387			1,303	220			290		
Age-adjusted RR*	1.00	1.18	0.97 to 1.43	.10	1.24	1.10 to 1.39	< .001	1.00	1.27	1.10 to 1.48	.001	1.19	1.04 to 1.35	.01
Fully adjusted RR*	1.00	1.14	0.94 to 1.38	.19	1.18	1.05 to 1.32	.01	1.00	1.21	1.04 to 1.40	.01	1.14	1.00 to 1.30	.05
Grade 2-6 prostate cancer														
No. of cases	1,870	176			472			1,870	269			379		
Age-adjusted RR*	1.00	1.24	1.06 to 1.46	.01	1.12	1.01 to 1.24	.03	1.00	1.18	1.04 to 1.35	.01	1.13	1.01 to 1.26	.03
Fully adjusted RR*	1.00	1.18	1.00 to 1.39	.05	1.06	0.95 to 1.17	.30	1.00	1.11	0.97 to 1.27	.11	1.07	0.96 to 1.20	.23
Lethal prostate cancer†														
No. of cases	644	50			114			644	55			109		
Age-adjusted RR*	1.00	1.18	0.88 to 1.60	.27	1.20	0.98 to 1.48	.08	1.00	1.29	0.97 to 1.71	.08	1.16	0.94 to 1.43	.16
Fully adjusted RR*	1.00	1.18	0.87 to 1.60	.28	1.20	0.98 to 1.48	.08	1.00	1.29	0.97 to 1.72	.08	1.16	0.94 to 1.42	.17
Advanced prostate cancer†														
No. of cases	821	65			161			821	89			137		
Age-adjusted RR*	1.00	1.12	0.86 to 1.46	.40	1.25	1.05 to 1.48	.01	1.00	1.42	1.13 to 1.78	.003	1.11	0.92 to 1.33	.28
Fully adjusted RR*	1.00	1.11	0.85 to 1.44	.44	1.23	1.04 to 1.47	.02	1.00	1.40	1.11 to 1.76	.004	1.10	0.91 to 1.32	.32
Localized prostate cancer†														
No. of cases	2,996	268			796			2,996	436			628		
Age-adjusted RR*	1.00	1.23	1.08 to 1.40	.002	1.12	1.04 to 1.22	.005	1.00	1.15	1.04 to 1.28	.01	1.14	1.05 to 1.25	.003
Fully adjusted RR*	1.00	1.18	1.04 to 1.35	.01	1.07	0.98 to 1.16	.12	1.00	1.09	0.99 to 1.21	.09	1.09	1.00 to 1.19	.05

NOTE. Totals by time since vasectomy and age at vasectomy do not sum to total number of men with vasectomy because of missing data on year of vasectomy.
Abbreviation: RR, relative risk.

*Age-adjusted model adjusted for age in months and calendar time. Multivariable model also adjusted for race, height (quartiles), current body mass index (six categories), vigorous physical activity (quintiles), smoking (never, former smoker who quit > 10 years ago, former smoker quit who < 10 years ago, or current), diabetes, family history of prostate cancer, multivitamin use (yes or no), intake of supplemental vitamin E and alcohol (both quintiles), and history of prostate-specific antigen testing.

†Lethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up. Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

The biologic mechanisms behind the association between vasectomy and lethal prostate cancer are not clear. Physiologic changes in men after vasectomy are well known and range from local effects on the testis to effects that have potential systemic implications.[23] Studies to understand a potential causative association of vasectomy with prostate cancer incidence have focused on bridging these observed physiologic changes with mechanisms that may ultimately lead to the development of prostate cancer.[24] The challenge lies in the fact that there is usually a 20- to 30-year interval between vasectomy and detection of prostate cancer. Previous theories as to the mechanism of increased prostate cancer incidence have included immunologic effects,[25] cellular proliferative changes,[26] and hormonal imbalances[27] secondary to vasectomy. We observed no significant differences in circulating levels of sex hormones by vasectomy status in this cohort. However, we have only a single blood measurement and cannot assess levels over time or changes after vasectomy.

Some semen proteins are upregulated, whereas others are lost after vasectomy,[28] which may affect prostate carcinogenesis. For example, decreased expression of TGFBI and TGFBIII proteins in the semen of men after vasectomy versus controls has been observed.[28] Transforming growth factor-β signaling has been implicated in an inhibitory role in prostate tumorigenesis.[29] Last, infertile men have been reported to have a 2.6-fold higher risk of high-grade prostate cancer.[30] It is feasible that an overlapping mechanism leads to high-grade prostate cancer in men after vasectomy and men who are otherwise infertile.

Because this was an observational study, one limitation was that the decision to undergo vasectomy was a matter of preference, introducing the possibility of confounding. However, the cohort is rich in covariate data, and we have adjusted for and considered a broad range of risk factors, minimizing the chance for residual confounding. In addition, most men had a vasectomy before baseline was reported, so there may be some inaccuracies in reporting the timing of vasectomy, which could affect the associations for time since vasectomy and age at vasectomy. Information on grade of prostate cancer was abstracted from the original medical records, and there have been shifts in Gleason grading over time. Thus, there may be some misclassification of Gleason grading in the cohort.

Our study found that men with a history of vasectomy had a 10% increased risk of prostate cancer, with a 19% higher risk of lethal

disease. Among highly screened men, the risk of lethal disease was 56% higher for those with vasectomy. The cumulative incidence of lethal prostate cancer during a 24-year follow-up was 1.6%; thus, these relative risks translate to small increases in absolute risk. The decision to opt for a vasectomy remains a highly personal one in which the potential risks and benefits must be considered. The findings of this study warrant continued epidemiologic and experimental research into clarifying the association of vasectomy with prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

We examined associations between vasectomy status and several plasma biomarkers among men without cancer to explore whether these were potential confounders or mediators of the association. Between 1993 and 1995, participants in the cohort were asked to provide a blood sample for research purposes. Chilled, EDTA-preserved blood specimens were returned to the Harvard School of Public Health via overnight courier by 18,225 participants. Among 2,077 men without a diagnosis of prostate cancer at the time of blood collection, plasma concentrations of sex steroid hormones and sex hormone–binding globulin (SHBG) were measured in the laboratory of Nader Rifai, PhD, at the Children's Hospital, Boston, MA, by using the following methods: total testosterone, a chemiluminescent immunoassay[26] (Elecsys autoanalyzer; Roche Diagnostics, Indianapolis, IN); free testosterone, an enzyme immunoassay[27] (Diagnostic Systems Laboratories, Webster, TX); estradiol, a third-generation radioimmunoassay (Diagnostic Systems Laboratory); and SHBG, a coated tube noncompetitive immunoradiometric assay (Diagnostic Systems Laboratory).

Mean circulating sex hormone levels were compared between men with and without a vasectomy at the time of blood draw by one-way analysis of variance adjusted for age at diagnosis, smoking, body mass index, fasting status at blood draw, time of day at blood draw, and laboratory batch. Testosterone, free testosterone, and estradiol were log-transformed to improve normality, and levels of SHBG were normalized through the calculation of a batch-specific *z* score because of between-batch variation.

Plasma antibodies to the sexually transmitted infections *Chlamydia trachomatis*, *Trichomonas vaginalis*, human papillomavirus (HPV), and human herpesvirus type 8 (HHV-8) were measured in a nested case-control study of prostate cancer, including 632 controls, as described elsewhere.[12,13] Antibody serostatus for *C trachomatis* was assessed with the *C trachomatis* IgG enzyme immunoassay (Ani Labsystems, Helsinki, Finland). Antibody serostatus for *T vaginalis* was assessed by enzyme-linked immunosorbent assay in the laboratory of John Alderete, MD. HPV-16, HPV-18, and HPV-33 IgG antibody serostatus were assessed by three in-house enzyme-linked immunosorbent assays in the laboratory of Raphael Viscidi, MD. Antibody serostatus for HHV-8 was assessed by an in-house monoclonal antibody–enhanced immunofluorescent assay against multiple lytic HHV-8 antigens in the laboratory of Frank Jenkins.

To investigate potential confounding by sexually transmitted infections, the age-adjusted prevalence of seropositivity for several sexually transmitted infections was compared between men with and without vasectomy at blood draw among men without prostate cancer. Logistic regression was used to calculate age-adjusted *P* values for differences in the prevalence of the infections.