Ejaculation Frequency and Subsequent Risk of Prostate Cancer

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Context Sexual activity has been hypothesized to play a role in the development of prostate cancer, but epidemiological data are virtually limited to case-control studies, which may be prone to bias because recall among individuals with prostate cancer could be distorted as a consequence of prostate malignancy or ongoing therapy.

Objective To examine the association between ejaculation frequency, which includes sexual intercourse, nocturnal emission, and masturbation and risk of prostate cancer.

Design, Setting, and Participants Prospective study using follow-up data from the Health Professionals Follow-up Study (February 1, 1992, through January 31, 2000) of 29342 US men aged 46 to 81 years, who provided information on history of ejaculation frequency on a self-administered questionnaire in 1992 and responded to follow-up questionnaires every 2 years to 2000. Ejaculation frequency was assessed by asking participants to report the average number of ejaculations they had per month during the ages of 20 to 29 years, 40 to 49 years, and during the past year (1991).

Main Outcome Measure Incidence of total prostate cancer.

Results During 222426 person-years of follow-up, there were 1449 new cases of total prostate cancer, 953 organ-confined cases, and 147 advanced cases of prostate cancer. Most categories of ejaculation frequency were unrelated to risk of prostate cancer. However, high ejaculation frequency was related to decreased risk of total prostate cancer. The multivariate relative risks for men reporting 21 or more ejaculations per month compared with men reporting 4 to 7 ejaculations per month at ages 20 to 29 years were 0.89 (95% confidence interval [CI], 0.73-1.10); ages 40 to 49 years, 0.68 (95% CI, 0.53-0.86); previous year, 0.49 (95% CI, 0.27-0.88); and averaged across a lifetime, 0.67 (95% CI, 0.51-0.89). Similar associations were observed for organ-confined prostate cancer. Ejaculation frequency was not statistically significantly associated with risk of advanced prostate cancer.

Conclusions Our results suggest that ejaculation frequency is not related to increased risk of prostate cancer.

JAMA. 2004;291:1578-1586 www.jama.com

SEXUAL ACTIVITY IS HYPOTHesized to affect prostate carcinogenesis through numerous etiologic pathways. One of the most commonly postulated mechanisms implicates increased sexual activity as an indicator of higher androgenic activity and thus a marker for a high-risk population.[1] Another mechanism proposes that sexual activity represents a marker for opportunity for exposure to infectious agents, although no sexually transmitted infection has been consistently implicated in prostate cancer development.[2]

An alternative hypothesis suggests that a reduced ejaculatory output in otherwise normal men is an etiologic risk factor for prostate cancer. That proposition is based on the theory that infrequent ejaculation increases the risk of prostate cancer because of retained carcinogenic secretions in the prostatic acini.[3] A further hypothesis implicates repression of sexuality as a risk factor for prostate cancer and is derived from reports of greater sexual drive coupled with deprived sexual activity[4] and greater interest in more sexual intercourse than experienced[5] among prostate cancer cases compared with controls.

In the United States, 38% of married persons aged 60 years or older reportedly engage in sexual activity between 1 and 4 times per month, and 14% indicate being sexually active at least 5 times per month.[6] Although the libido declines with age, sexual activity is common among 70-, 80-, and even 90-year-old men.[7] Given that sexual activity is common, including in older men,[6,7] and that prostate cancer risk is high,[8] any association between these factors would have clinical and public health relevance. A recent meta-analysis[9] reported an increased risk of prostate cancer with greater sexual activity (odds ratio, 1.2; 95% confidence interval [CI], 1.1-1.3 for an increase in sexual activity of 3 times per week).

Epidemiological data on sexual activity and prostate cancer are almost entirely limited to case-control studies,[2,9,10] which may be particularly prone to methodological bias because infor-

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mation on prediagnosis sexual activity is collected after the diagnosis of cancer. Sexual function may diminish after the diagnosis of prostate cancer and its treatment,[11] and recall of past levels of sexual activity among individuals with prostate cancer could be distorted as a consequence of prostate malignancy or ongoing therapy.

Prospective data on self-reported sexual activity and prostate cancer are restricted to 2 investigations. These studies[12,13] considered age at first marriage, marital status, and number of children as measures of sexual activity and found no association between these factors and prostate cancer. Thus, the relationship between sexual activity and risk of prostate cancer is not clear.

To help resolve this issue, we prospectively examined the association between ejaculation frequency and risk of prostate cancer in the Health Professionals Follow-up Study, a large cohort of middle-aged US men. We focused on ejaculation frequency, capturing sexual intercourse, nocturnal emission, and masturbation. Thus, our exposure definition encompasses a wide range of variability in exposure to sexual activity. In addition, we reasoned that by examining ejaculation frequency, the effects of sexual function per se would be more readily distinguishable from effects related to exposure to sexually transmitted agents, which we do not consider in this article.

METHODS

Study Population

The Health Professionals Follow-up Study was initiated in 1986 when 51 529 US predominantly white male health professionals aged 40 to 75 years responded to a questionnaire concerning their medical history and known or suspected risk factors for cancer and other chronic diseases. Subsequently, follow-up questionnaires were mailed every 2 years to the entire cohort to update information on potential risk factors and to identify newly diagnosed illnesses. In 1992, the questionnaire included an assessment of frequency of ejaculation. Men were included if they did not have a diagnosis of cancer (6098 excluded); answered the 1992 questionnaire (8478 excluded); answered the question on ejaculation frequency (6862 excluded); and provided adequate dietary data (749 excluded). Men who had nonmelanoma skin cancer were allowed in the study. The analytic cohort consisted of 29 342 men, who were followed up to 2000. Participants provided informed consent. The Health Professionals Follow-up Study was approved by the human subjects committee of the Harvard School of Public Health, Boston, Mass.

Assessment of Ejaculation Frequency

Ejaculation frequency was assessed in 1992 by asking participants to report the average number of ejaculations they had per month during the ages of 20 to 29 years, 40 to 49 years, and during the past year (1991). There were 6 possible response categories for each age period (none, 1-3, 4-7, 8-12, 13-20, and ≥21 ejaculations per month). We collapsed the none and 1 to 3 ejaculation categories because of insufficient numbers of participants in the none category.

Case Ascertainment

On each follow-up questionnaire, we asked participants whether they had received a diagnosis of prostate cancer during the prior 2 years. For men who reported a diagnosis of prostate cancer (or next of kin for decedents), we requested permission to obtain medical records and pathological reports to confirm the diagnosis and obtain further details. Most deaths in the cohort were ascertained through reports from family members and searches of the National Death Index. A study investigator who was unaware of questionnaire data used the information received from any procedures or tests conducted during the initial diagnosis, including staging prostatectomy and bone scans, to stage prostate cancer. The major end point was total prostate cancer incidence. We also considered organ-confined prostate cancer and advanced cancer as separate groups. The latter was defined as cancer extending regionally to the seminal vesicle or other adjacent organs, metastasis to pelvic lymph nodes or distant organs (usually bone) at the time of diagnosis, or that was fatal by the end of follow-up (C2 or D or fatal; T3b or T4 or N1 or M1, or fatal). Because stage T1a lesions are typically indolent and are especially prone to detection bias, we excluded these (3% of the total) from our primary analyses.

Data Analysis

Person-time of follow-up for each participant was calculated from the date of return of the 1992 questionnaire to the date of prostate cancer, death, or the end of the study period in 2000. The relative risk (RR) was calculated as the incidence rate of prostate cancer among men in a specific category of ejaculation frequency divided by the rate among a common reference group with adjustment for age. We used the category of 4 to 7 ejaculations per month as the common reference group to achieve meaningful comparisons between increasingly extreme ejaculation frequencies and to ensure stability of the RR estimates. Multivariate RRs were computed using the Cox proportional hazards model.[14] The basic multivariate model included covariates that were previously observed to be associated with risk of total or advanced prostate cancer or that have been associated with risk in the literature. Covariates were racial group; family history of prostate cancer; history of vasectomy; body mass index at age 21 years, which was calculated as weight in kilograms divided by square height in meters; height; pack-years of smoking in the previous decade; history of type 2 diabetes; vigorous physical activity; and intake of total energy, calcium, fructose, supplemental vitamin E, supplemental zinc, red meat, tomato-based foods, fish, α-linolenic acid, and alcohol. To account for lack of proportionality in the hazards across follow-up, we fit separate baseline hazards for groups defined by age and calendar period. Because the relationships be-

tween age-specific ejaculation frequencies and prostate cancer could potentially confound each other, we entered terms representing ejaculation frequency at ages 20 to 29 years, 40 to 49 years, and during the year prior to the 1992 questionnaire simultaneously in our models. We also considered ejaculation frequency across a lifetime, which was calculated as the average of the ejaculation frequencies at ages 20 to 29 years, 40 to 49 years, and during the prior year. All reported *P* values are 2-tailed and $P<.05$ was considered significant. All analyses were performed using SAS statistical software (release 8.02, SAS Institute Inc, Cary, NC).

RESULTS

During 222426 person-years of follow-up between 1992 and 2000, there were 1449 cases of total prostate cancer, 953 cases of organ-confined prostate cancer, and 147 cases of advanced prostate cancer. The mean (SD) ejaculations per month at ages 20 to 29 years were 15.1 [6.9]; 40 to 49 years, 11.3 [6.1]; 50 to 59 years, 9.4 [6.1]; and 60 years or older, 5.0 [4.5]. Fifty-eight percent of men reported an ejaculation frequency of more than 3 times per week at ages 20 to 29 years, whereas the proportion of men having more than 3 ejaculations per week decreased to 32% at ages 40 to 49 years, and further declined to 22% at ages 50 to 59 years and to 5% at ages 60 years or older. Ejaculation frequency at ages 20 to 29 years showed positive correlations with ejaculation frequency at ages 40 to 49 years ($r=0.70$); 50 to 59 years ($r=0.54$); and 60 years or older ($r=0.39$); all $P<.001$. The number of ejaculations at ages 40 to 49 years was positively correlated with those at ages 50 to 59 years ($r=0.81$) and 60 years or older ($r=0.53$); all $P<.001$.

Age-standardized lifetime ejaculation frequency was evaluated in relation to various risk factors for prostate cancer to assess the potential for confounding (TABLE 1). Men with greater lifetime ejaculation frequency tended to be physically more active and were more likely to have a history of syphilis or gonorrhea, prostatitis, and vasectomy than men with lower ejaculation frequency. In addition, men with greater ejaculation frequency were more likely to be currently divorced or separated and consumed more total energy, lycopene, fish, alcohol, supplemental vitamin E, and supplemental zinc. Men in the highest category of average lifetime ejaculation frequency were less likely to have a family history of prostate cancer and a history of surgery for enlarged prostate than men in the lower categories of ejaculation frequency. Men in the highest and lowest categories had a lower prevalence of prostate-specific antigen (PSA) screening relative to men in the intermediate categories of ejaculation frequency.

Ejaculation frequency was examined in relation to risk of total prostate cancer (TABLE 2). In age- and multivariate-adjusted analyses, most categories of ejaculation frequency were unrelated to risk of total prostate cancer. However, a lower risk was observed in the highest category of ejaculation frequency. The multivariate RR for men reporting 21 or more ejaculations per month compared with men reporting between 4 and 7 ejaculations per month at ages 20 to 29 years was 0.89 (95% CI, 0.73-1.10); 40 to 49 years, 0.68 (95% CI, 0.53-0.86); in the prior year, 0.49 (95% CI, 0.27-0.88); and across a lifetime, 0.67 (95% CI, 0.51-0.89). When the entire range of ejaculation frequency was analyzed as a continuous variable in the multivariate model, each increment of 3 ejaculations per week across a lifetime was associated with a 15% (95% CI, 4%-24%) decrease in risk of total prostate cancer. However, there was a suggestive decreased risk of total prostate cancer observed among men in the lowest category of ejaculation frequency at ages 40 to 49 years and across a lifetime. The multivariate RR for men reporting 3 or less ejaculations per month compared with men reporting between 4 and 7 ejaculations per month across a lifetime was 0.89 (95% CI, 0.69-1.15).

Restricting the outcomes to organ-confined prostate cancer, the relationships were similar to those for total prostate cancer, albeit somewhat stronger (TABLE 3). Each increment of 3 ejaculations per week across a lifetime was associated with a 19% (95% CI, 7%-30%) decrease in risk of organ-confined prostate cancer. Again, a suggestive decreased risk of organ-confined prostate cancer was observed among men in the lowest category of ejaculation frequency at ages 20 to 29 years, 40 to 49 years, and across a lifetime. The multivariate RR for men reporting 3 or fewer ejaculations per month compared with men reporting between 4 and 7 ejaculations per month across a lifetime was 0.72 (95% CI, 0.51-1.01).

In contrast to the results for total and organ-confined prostate cancer, the intermediate categories of ejaculation frequency at ages 40 to 49 years were associated with a lower risk of advanced prostate cancer (TABLE 4). High ejaculation frequencies during the previous year and across a lifetime were associated with a suggestive increase in risk of advanced prostate cancer. The multivariate RR for men reporting 21 or more ejaculations per month compared with men reporting between 4 and 7 ejaculations per month across a lifetime was 1.76 (95% CI, 0.81-3.80).

The consistency among ejaculation frequencies at ages 20 to 29 years, 40 to 49 years, and during the previous year was examined. Compared with men who were consistently in the lowest 4 categories of ejaculation frequency, men who were consistently in the highest category of frequency of ejaculations showed a markedly reduced risk of total prostate cancer (RR, 0.25; 95% CI, 0.12-0.54) and organ-confined prostate cancer (RR, 0.15; 95% CI, 0.05-0.47). There was not a sufficient number of cases to examine patterns of ejaculation frequency over time in relation to advanced prostate cancer risk.

The results regarding the relationship of ejaculation frequency with prostate cancer were not materially altered after controlling for history of syphilis or gonorrhea or limiting the study population to men (1) younger than 60 years; (2) 60 years or older; (3) married; (4) without a history of prostatitis, a previ-

ous diagnosis of enlarged prostate, or surgery for enlarged prostate; (5) with a PSA test by 2000. The results also were not altered when either the first 2 or 4 years of follow-up were excluded and the 1992 reporting of ejaculation frequency was related to incidence of prostate cancer from 1994 to 2000 or 1996 to 2000, respectively (TABLE 5).

Table 1. Baseline Characteristics of Participants in the Health Professionals Follow-up Study (N = 29 342)*

Characteristic	Lifetime No. of Ejaculations/mo				
	0-3 (n = 1327)	4-7 (n = 6523)	8-12 (n = 9107)	13-20 (n = 10 362)	≥21 (n = 2023)
	Mean (SD)				
Age, y	62.1 (10.3)	59.8 (9.6)	61.0 (9.0)	56.7 (8.6)	55.6 (7.6)
Living children†	2.2 (1.0)	2.2 (1.0)	2.2 (1.0)	2.2 (1.1)	2.1 (1.1)
Ejaculations per month					
Ages 20-29 y	3.7 (2.0)	8.4 (2.6)	13.4 (3.8)	20.5 (4.8)	24.9 (1.9)
Ages 40-49 y	1.9 (1.3)	5.6 (1.6)	9.8 (2.4)	15.0 (4.1)	25.1 (0.98)
Previous year (1991)	1.6 (0.5)	3.5 (2.1)	5.3 (3.1)	9.6 (4.6)	19.0 (5.9)
Body mass index‡	25.4 (3.4)	25.5 (3.3)	25.8 (3.4)	26.0 (3.5)	26.1 (3.4)
Height in 1986, in	70.1 (2.8)	70.2 (2.6)	70.2 (2.7)	70.2 (2.6)	70.1 (2.6)
Vigorous physical activity, MET hours/wk	12.0 (22.0)	13.6 (25.1)	14.1 (24.8)	16.2 (29.9)	18.2 (31.2)
Daily intake§					
Total energy, kcal	1836 (578)	1892 (574)	1918 (582)	1972 (603)	2056 (638)
Lycopene, µg‖	9325 (5625)	9662 (6017)	9872 (5994)	10 288 (6317)	10 897 (6910)
α-Linolenic acid, g‖	1.05 (0.3)	1.06 (0.3)	1.07 (0.3)	1.06 (0.3)	1.04 (0.3)
Calcium, mg‖	914 (397)	907 (357)	901 (371)	906 (366)	917 (386)
Fructose, g‖	50.9 (17.9)	49.2 (17.0)	48.7 (16.9)	48.5 (17.1)	48.6 (17.4)
Alcohol, g	8.2 (12.7)	9.7 (13.2)	10.9 (14.6)	11.7 (14.5)	13.6 (17.9)
Servings per week					
Red meat	6.8 (4.5)	6.9 (4.6)	6.9 (4.6)	7.1 (4.9)	7.0 (4.9)
Fish	2.0 (1.8)	2.2 (1.8)	2.3 (1.9)	2.5 (1.9)	2.7 (2.0)
	No. (%)				
Supplement use					
Vitamin E	552 (41.6)	2792 (42.8)	4053 (44.5)	4673 (45.1)	975 (48.2)
Zinc	268 (20.2)	1376 (21.1)	1931 (21.2)	2259 (21.8)	479 (23.7)
Marital status					
Married	1182 (89.1)	6021 (92.3)	8296 (91.1)	9191 (88.7)	1665 (82.3)
Divorced or separated	54 (4.1)	267 (4.1)	474 (5.2)	746 (7.2)	247 (12.2)
Widowed	32 (2.4)	117 (1.8)	182 (2.0)	197 (1.9)	42 (2.1)
Never married	46 (3.5)	91 (1.4)	100 (1.1)	176 (1.7)	61 (3.0)
Smoked in past 10 years	224 (16.9)	1318 (20.2)	1831 (20.1)	2217 (21.4)	413 (20.4)
Family history of prostate cancer	131 (9.9)	646 (9.9)	874 (9.6)	1026 (9.9)	184 (9.1)
History of diseases and procedures					
Routine screening for PSA by 2000	1109 (83.6)	5675 (87.0)	7932 (87.1)	8901 (85.9)	1697 (83.9)
Elevated PSA by 2000	187 (14.1)	1155 (17.7)	1521 (16.7)	1534 (14.8)	318 (15.7)
Prostate biopsy¶	170 (12.8)	920 (14.1)	1321 (14.5)	1399 (13.5)	259 (12.8)
Venereal disease#	16 (1.2)	176 (2.7)	255 (2.8)	404 (3.9)	95 (4.7)
Prostatitis**	179 (13.5)	1102 (16.9)	1557 (17.1)	1772 (17.1)	332 (16.4)
Benign prostatic hyperplasia††	289 (21.8)	1611 (24.7)	2377 (26.1)	2508 (24.2)	429 (21.2)
Diabetes	54 (4.1)	313 (4.8)	446 (4.9)	528 (5.1)	103 (5.1)
Vasectomy	239 (18.0)	1592 (24.4)	2450 (26.9)	2818 (27.2)	544 (26.9)
Transurethral resection of prostate	74 (5.6)	404 (6.2)	537 (5.9)	560 (5.4)	85 (4.2)

Abbreviations: MET, metabolic equivalent task; PSA, prostate-specific antigen.
*All values (except age) are standardized to the age distribution of the study population. All variables were assessed in 1992, unless indicated otherwise. Percentages may not equal 100 due to rounding.
†Assessed in 1988.
‡Calculated as weight in kilograms divided by the square height in meters.
§Nutrients and foods were assessed in the 1990 questionnaire.
‖Adjusted for total energy intake using residuals analysis.
¶Assessed in 1994.
#Indicates syphilis or gonorrhea.
**Based on a report of symptoms and/or treatment for prostatitis or prostatic infection.
††Includes history of enlarged prostate and history of transurethral resection of the prostate.

The associations between ejaculation frequency and risk of prostate cancer were not modified by subgroups defined by current body mass index, family history of prostate cancer, history of smoking, history of prostatitis, history of syphilis or gonorrhea, or marital status (all P for interaction $>.05$).

COMMENT

In this prospective cohort study among predominantly white men, higher ejaculation frequency was not related to increased risk of prostate cancer. Our results suggest that high ejaculation frequency possibly may be associated with a lower risk of total and organ-confined prostate cancer. These associations were

Table 2. Relative Risk of Total Prostate Cancer (n = 1449 Cases) Among 29 342 Men in the Health Professionals Follow-up Study*

	No. of Ejaculations/mo				
	0-3	4-7	8-12	13-20	≥21
Ages 20-29 y					
No. of cases	62	165	459	489	274
Age-adjusted RR (95% CI)	1.06 (0.78-1.43)	1.00	1.06 (0.88-1.28)	0.94 (0.77-1.14)	0.88 (0.71-1.08)
Multivariate RR (95% CI)†	1.09 (0.80-1.47)	1.00	1.06 (0.88-1.29)	0.95 (0.78-1.16)	0.89 (0.73-1.10)
Ages 40-49 y					
No. of cases	78	410	560	304	97
Age-adjusted RR (95% CI)	0.82 (0.63-1.08)	1.00	0.96 (0.79-1.15)	0.97 (0.78-1.21)	0.66 (0.52-0.85)
Multivariate RR (95% CI)†	0.83 (0.64-1.09)	1.00	0.96 (0.80-1.16)	0.98 (0.79-1.23)	0.68 (0.53-0.86)
Previous year (1991)					
No. of cases	606	476	260	94	13
Age-adjusted RR (95% CI)	1.06 (0.93-1.21)	1.00	1.06 (0.89-1.26)	1.06 (0.83-1.36)	0.48 (0.27-0.86)
Multivariate RR (95% CI)†	1.06 (0.93-1.21)	1.00	1.06 (0.89-1.26)	1.07 (0.83-1.37)	0.49 (0.27-0.88)
Lifetime‡					
No. of cases	75	383	513	419	59
Age-adjusted RR (95% CI)	0.88 (0.68-1.13)	1.00	0.88 (0.77-1.00)	0.84 (0.73-0.97)	0.66 (0.49-0.87)
Multivariate RR (95% CI)†	0.89 (0.69-1.15)	1.00	0.89 (0.77-1.01)	0.86 (0.74-0.99)	0.67 (0.51-0.89)

Abbreviations: CI, confidence interval; RR, relative risk.
*Excludes stage T1a lesions (3% of the total) because stage T1a lesions are typically indolent and are especially prone to detection bias.
†Adjusted for current age; period; racial group; family history of prostate cancer; history of vasectomy; body mass index at age 21 years; height; pack-years of smoking in the previous decade; history of type 2 diabetes; vigorous physical activity; intake of total energy, calcium, fructose, supplemental vitamin E, supplemental zinc, red meat, tomato-based foods, fish, α-linolenic acid, and alcohol. Ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the past year were mutually adjusted for each other using residuals analysis.
‡Calculated as the average of the ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the previous year (1991).

Table 3. Relative Risk of Organ-Confined Prostate Cancer (n = 953 Cases) Among 29 342 Men in the Health Professionals Follow-up Study*

	No. of Ejaculations/mo				
	0-3	4-7	8-12	13-20	≥21
Ages 20-29 y					
No. of cases	27	111	311	324	180
Age-adjusted RR (95% CI)	0.70 (0.45-1.07)	1.00	1.00 (0.79-1.26)	0.85 (0.67-1.08)	0.81 (0.63-1.04)
Multivariate RR (95% CI)†	0.72 (0.47-1.11)	1.00	1.00 (0.79-1.26)	0.84 (0.66-1.07)	0.81 (0.63-1.05)
Ages 40-49 y					
No. of cases	48	276	366	208	55
Age-adjusted RR (95% CI)	0.80 (0.57-1.12)	1.00	0.96 (0.76-1.21)	1.06 (0.80-1.39)	0.53 (0.39-0.73)
Multivariate RR (95% CI)†	0.83 (0.59-1.16)	1.00	0.96 (0.76-1.21)	1.06 (0.81-1.40)	0.53 (0.38-0.72)
Previous year (1991)					
No. of cases	382	315	185	63	8
Age-adjusted RR (95% CI)	1.08 (0.92-1.28)	1.00	1.19 (0.97-1.47)	1.02 (0.75-1.38)	0.39 (0.19-0.82)
Multivariate RR (95% CI)†	1.10 (0.93-1.30)	1.00	1.19 (0.96-1.47)	1.02 (0.75-1.39)	0.39 (0.18-0.81)
Lifetime‡					
No. of cases	40	268	320	293	32
Age-adjusted RR (95% CI)	0.69 (0.49-0.96)	1.00	0.78 (0.66-0.92)	0.81 (0.69-0.96)	0.48 (0.33-0.69)
Multivariate RR (95% CI)†	0.72 (0.51-1.01)	1.00	0.78 (0.66-0.92)	0.82 (0.69-0.97)	0.48 (0.33-0.69)

Abbreviations: CI, confidence interval; RR, relative risk.
*Defined as A_2 or B; or T1b or T1c or T2 and N0M0. Men with T3a or worse disease or men with missing information on stage were censored at their date of diagnosis but were not counted as cases.
†Adjusted for current age; period; racial group; family history of prostate cancer; history of vasectomy; body mass index at age 21 years; height; pack-years of smoking in the previous decade; history of type 2 diabetes; vigorous physical activity; intake of total energy, calcium, fructose, supplemental vitamin E, supplemental zinc, red meat, tomato-based foods, fish, α-linolenic acid, and alcohol. Ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the past year were mutually adjusted for each other using residuals analysis.
‡Calculated as the average of the ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the previous year (1991).

not explained by potential risk factors for prostate cancer, such as age, family history of prostate cancer, history of syphilis or gonorrhea, smoking, and diet. Although we cannot exclude a possibly greater risk of advanced prostate cancer with higher recent ejaculation frequency, we did not observe a higher risk of advanced prostate cancer for high ejaculation frequency earlier in life.

Although each of several analytic approaches indicated that high ejaculation frequency was related to decreased risk of total and organ-confined prostate cancer, there are several plausible alternative explanations for our results. We were concerned about the possibility that the observed inverse relationships were due to avoidance of ejaculation among men with early symptoms related to prostate cancer. However, diminished ejaculation frequency as a preclinical consequence of prostate cancer would be expected to be more pronounced among men with advanced prostate cancer than among men with organ-confined prostate cancer, a circumstance that was not supported by our data. In addition, our findings were es-

Table 4. Relative Risk of Advanced Prostate Cancer (n = 147 Cases) Among 29 342 Men in the Health Professionals Follow-up Study*

	No. of Ejaculations/mo				
	0-3	4-7	8-12	13-20	≥21
Ages 20-29 y					
No. of cases	10	16	38	52	31
Age-adjusted RR (95% CI)	1.79 (0.78-4.11)	1.00	1.04 (0.56-1.94)	1.09 (0.59-2.00)	1.00 (0.52-1.90)
Multivariate RR (95% CI)†	1.83 (0.78-4.32)	1.00	1.07 (0.56-2.02)	1.13 (0.60-2.11)	1.04 (0.54-2.02)
Ages 40-49 y					
No. of cases	9	42	51	34	11
Age-adjusted RR (95% CI)	0.70 (0.32-1.56)	1.00	0.52 (0.29-0.89)	0.52 (0.28-0.96)	0.69 (0.33-1.46)
Multivariate RR (95% CI)†	0.70 (0.31-1.59)	1.00	0.53 (0.30-0.94)	0.53 (0.28-1.01)	0.73 (0.34-1.55)
Previous year (1991)					
No. of cases	74	37	21	12	3
Age-adjusted RR (95% CI)	1.34 (0.86-2.07)	1.00	0.98 (0.53-1.78)	2.08 (0.99-4.34)	1.73 (0.48-6.27)
Multivariate RR (95% CI)†	1.28 (0.83-1.99)	1.00	0.98 (0.53-1.79)	2.12 (1.01-4.47)	1.79 (0.49-6.60)
Lifetime‡					
No. of cases	10	33	52	43	9
Age-adjusted RR (95% CI)	1.26 (0.61-2.58)	1.00	1.04 (0.67-1.61)	1.12 (0.71-1.78)	1.45 (0.68-3.06)
Multivariate RR (95% CI)†	1.31 (0.62-2.74)	1.00	1.11 (0.71-1.73)	1.20 (0.75-1.92)	1.76 (0.81-3.80)

Abbreviations: CI, confidence interval; RR, relative risk.
*Defined as cancer extending regionally to the seminal vesicle or other adjacent organs, metastasis to pelvic lymph nodes or distant organs (usually bone) at the time of diagnosis, or that was fatal by the end of follow-up (C2 or D or fatal; T3b or T4 or N1 or M1 or fatal). Men with organ-confined disease, men with T3aN0M0 disease, or men with missing information on stage were censored at their date of diagnosis but were not counted as cases.
†Adjusted for current age; period; racial group; family history of prostate cancer; history of vasectomy; body mass index at age 21 years; height; pack-years of smoking in the previous decade; history of type 2 diabetes; vigorous physical activity, intake of total energy, calcium, fructose, supplemental vitamin E, supplemental zinc, red meat, tomato-based foods, fish, α-linolenic acid, and alcohol. Ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the past year were mutually adjusted for each other using residuals analysis.
‡Calculated as the average of the ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the previous year (1991).

Table 5. Multivariate Relative Risk of Total Prostate Cancer in the Health Professionals Follow-up Study*

Variable	No. of Cases	Lifetime No. of Ejaculations/mo†				
		0-3	4-7	8-12	13-20	≥21
Age, y						
<60	388	0.68 (0.35-1.32)	1.00	0.83 (0.62-1.10)	0.84 (0.65-1.09)	0.63 (0.39-0.99)
≥60	1061	0.94 (0.72-1.24)	1.00	0.90 (0.77-1.05)	0.85 (0.72-1.01)	0.70 (0.49-1.00)
Married men	1228	0.87 (0.66-1.15)	1.00	0.87 (0.75-1.00)	0.85 (0.72-0.99)	0.70 (0.52-0.95)
Controlled for history of venereal disease‡	1449	0.90 (0.70-1.15)	1.00	0.89 (0.77-1.01)	0.86 (0.74-0.99)	0.67 (0.51-0.89)
Excluding men with history of prostatitis, BPH, or TURP	1397	0.85 (0.66-1.10)	1.00	0.87 (0.76-1.00)	0.83 (0.72-0.96)	0.67 (0.50-0.89)
Excluding noncase subjects with no PSA test by 2000	1449	0.93 (0.72-1.19)	1.00	0.88 (0.77-1.01)	0.86 (0.75-0.99)	0.69 (0.52-0.91)
Excluding first 2 years of follow-up	1019	0.74 (0.53-1.02)	1.00	0.87 (0.74-1.02)	0.83 (0.71-0.99)	0.68 (0.49-0.93)
Excluding first 4 years of follow-up	673	0.66 (0.43-1.01)	1.00	0.91 (0.74-1.10)	0.81 (0.66-0.99)	0.63 (0.42-0.94)

Abbreviations: BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen; TURP, transurethral resection of prostate.
*Values expressed as multivariate relative risk (95% confidence interval). Excluded stage T1a lesions (3% of the total) because stage T1a lesions are typically indolent and are especially prone to detection bias. Relative risk adjusted for current age; period; racial group; family history of prostate cancer; history of vasectomy; body mass index at age 21 years; height; pack-years of smoking in the previous decade; history of type 2 diabetes; vigorous physical activity; intake of total energy, calcium, fructose, supplemental vitamin E, supplemental zinc, red meat, tomato-based foods, fish, α-linolenic acid, and alcohol.
†Calculated as the average of the ejaculation frequencies at ages 20 to 29 years, ages 40 to 49 years, and during the previous year (1991).
‡Indicates syphilis or gonorrhea.

sentially unaltered when we excluded cases diagnosed in the early years of follow-up. Hence, our results suggest that reverse causation may have accounted for very little, if any of the observed inverse association between high ejaculation frequency and total and organ-confined prostate cancer risk.

A further potential explanation for our results is that men with high ejaculation frequency may wish to preserve their sexual function and, thus, undergo less screening tests for prostate cancer, leading to less diagnosis of organ-confined prostate cancer among these men. The fact that men in the highest category of ejaculation frequency underwent slightly fewer PSA screening tests and less prostate biopsies than most men with lower ejaculation frequencies suggests the possibility of modest detection bias. In contrast to this possible explanation, the inverse relationship with total and organ-confined prostate cancer persisted when the analysis was restricted to men with the opportunity to have prostate cancer detected by PSA. Thus, decreased prostate cancer detection among men with greater ejaculation frequency is unlikely to entirely account for our results.

Because factors such as diet, smoking, physical activity, and the quality of personal relationships are strong determinants of sexual function,[15-18] a further potential concern was the possibility that the apparent beneficial effect of greater ejaculation frequency on risk for total and organ-confined prostate cancer was due to the existence of a healthy lifestyle related both to ejaculation frequency and to prostate cancer. We observed similar results before and after controlling for a broad range of lifestyle and dietary factors potentially related to prostate cancer risk. In addition, the fact that the age-adjusted and multivariate-adjusted RRs were almost identical makes it unlikely that an unconsidered factor that correlates with these lifestyle and dietary factors could produce such strong confounding. Thus, our results are probably not due to confounding by purported lifestyle or dietary risk factors for prostate cancer.

Our results are not likely to be explained by differential measurement error in our assessment of ejaculation frequency between cases and noncases. Notwithstanding, self-reported ejaculation frequency may have contained some inaccuracy because of its sensitive nature and the need for individuals to recall ejaculation frequency in the distant past. It is possible that the oldest men in our cohort (men aged 81 years in 1992) may not have accurately recalled their average monthly ejaculation frequency from ages 20 to 29 years. Moreover, recall of past levels of ejaculation frequency may have been more accurate among men who had the highest ejaculation frequencies than among those with lower ejaculation frequencies. Reported ejaculation frequency rates among men in our study are largely consistent with survey data on sexual activity among US adults.[6,19] Furthermore, our mailed questionnaire on ejaculation frequency was identifiable only by study identification number and not by name, which may have resulted in a more accurate report than in-person interviews. Because these data were collected prior to the occurrence of prostate cancer, the accuracy of reported ejaculation frequency should not differ between men with and without subsequent prostate cancer. Thus, error in the measurement of ejaculation frequency would tend to dampen the results, but would not produce an inverse association. In addition, reporting of other lifestyle factors in this cohort of health professionals has been found to be reasonably accurate.[20,21]

We noted a suggestive decrease in risk of total and organ-confined prostate cancer among men in the lowest category of ejaculation frequency across a lifetime. Whether that finding was due to lower androgenicity among these men remains unknown. The apparent decrease in risk of total and organ-confined prostate cancer among men with a low ejaculation frequency was not due to low prevalence of sexually transmitted infections among these men because adjustment for history of syphilis or gonorrhea did not alter the results.

We only evaluated ejaculation frequency during adulthood, but not during adolescence. The peripubertal period may be of etiologic significance with respect to prostate carcinogenesis because prostate epithelial cell differentiation occurs at this critical period.[22] If ejaculation frequency during puberty was most important for prostate carcinogenesis, measuring adult ejaculation frequency would fail to capture the relevant period of exposure. However, our findings suggest that ejaculation frequency during mid and late adulthood rather than in early adulthood are etiologically relevant periods for influencing prostate tumors. Because the inverse relation was observed for organ-confined cases but not advanced cases, sexual activity may be hypothesized only to affect slow-growing, early stage prostate cancers. Our results are generalizable to white US men aged 46 years or older.

Previous investigations on reported ejaculation frequencies or sexual intercourse and prostate cancer are limited to studies of retrospective design and results are mixed. Nine studies observed a statistically significant[1,23-27] or nonsignificant[28-30] positive association; 3 studies[27,31,32] reported no association; 7 studies found a statistically significant[4,5,10,33] or nonsignificant[34-36] inverse relationship; and 1 study[37] found a U-shaped relationship.

Nine[4,24,25,27,30-32,35,36] of the aforementioned studies found little or no variation in prostate cancer risk according to sexual activity during different ages. However, 1 study[35] observed a nonsignificant inverse association between sexual activity before the age of 30 years and prostate cancer, and no relationship with sexual activity in later life. In contrast, 2 other studies[38,39] reported a positive association between frequency of sexual intercourse before ages 50 to 60 years and prostate cancer and an inverse relationship for frequency of sexual intercourse after age 60 years. A recent

meta-analysis[9] of these studies[1,4,5,23-39] reported RRs for sexual activity at 3 times per week of 1.14 (95% CI, 0.98-1.31) during the third decade of life, 1.24 (95% CI, 1.05-1.46) during the fifth decade, and 0.68 (95% CI, 0.51-0.91) during the seventh decade. That meta-analysis[9] noted the somewhat inconsistent association between frequency of sexual activity and risk of prostate cancer in previous studies.

Several features distinguish our analysis from previous reports on sexual activity and prostate cancer. First, the prospective study design precluded bias attributable to differential recall of sexual activity by men with and without prostate cancer. Second, we focused on ejaculation frequency rather than on frequency of sexual intercourse, which enhanced exposure variability and allowed us to explore the physiological effects of sexual function per se. Third, our analysis included nearly 50% more cases than the number of cases included in any of the previous studies reporting on sexual activity and prostate cancer. Fourth, our study had data on PSA tests, which allowed us to address the possibility of detection bias. Finally, because we controlled for a wide range of medical, lifestyle, and dietary factors, potential confounding by these factors was likely minimized.

Our finding of no association or a possibly inverse association between high ejaculation frequency and prostate cancer is difficult to reconcile with the commonly proposed concept that androgenic stimulation is related both to enhanced libido and to increased risk of prostate cancer. In some studies, circulating testosterone levels are positively associated with prostate cancer risk.[40] Limited evidence shows that circulating levels of testosterone or its major metabolite dihydrotestosterone correlate positively with sexual desire,[41] erectile function,[42] and frequency of orgasms.[43]

However, sexual activity is a complex physiological function, which may relate to prostate cancer risk through several nonandrogenic pathways. For example, frequency of ejaculations may modulate prostate carcinogenesis by altering the composition of prostatic fluid. Frequent ejaculations may decrease the intraprostatic concentration of xenobiotic compounds and chemical carcinogens, which readily accumulate in prostatic fluid.[44,45] Frequent ejaculations may also reduce the development of intraluminal prostatic crystalloids,[46] which have been associated with prostate cancer in some,[47,48] but not all pathology studies.[49] Because seminal plasma locally reduces host responsiveness[50-52] (possibly by factors produced by the prostate gland[53]), retained prostatic fluid may diminish intraprostatic immune surveillance against tumor cells.

A more speculative possibility linking increased ejaculation frequency with decreased prostate cancer risk is that ejaculation is accompanied by a release of psychological tension during the emission phase,[54] which may lower central sympathetic nervous activity when repeated frequently. Prostate epithelial cell division is stimulated by the release of growth factors from adjacent stromal cells that are heavily innervated with α_1 adrenergic receptors.[55,56]

In summary, our results among predominantly white men suggest that ejaculation frequency is not related to increased risk of prostate cancer. High ejaculation frequency may possibly be associated with a lower risk of total and organ-confined prostate cancer. It is unlikely that reverse causation, differences in prostate cancer screening behavior, or confounding are entirely responsible for the observed results. Mechanisms other than the link between androgenicity and ejaculation frequency should be evaluated as potential etiological factors underlying the inverse association between ejaculation frequency and prostate cancer.

Author Contributions: Dr Leitzmann had full access to all of the data in this study and takes responsibility for the integrity of the data, and the accuracy of the data analysis.
Study concept and design: Leitzmann, Platz, Willett, Giovannucci.
Acquisition of data: Platz, Stampfer, Willett, Giovannucci.
Analysis and interpretation of data: Leitzmann, Platz, Stampfer, Willett, Giovannucci.
Drafting of the manuscript: Leitzmann, Platz.
Critical revision of the manuscript for important intellectual content: Leitzmann, Platz, Stampfer, Willett, Giovannucci.
Statistical expertise: Leitzmann, Platz, Stampfer, Willett, Giovannucci.
Obtained funding: Willett, Giovannucci.
Administrative, technical, or material support: Willett.
Funding/Support: This work was supported by research grants CA055075 and HL035464 to Dr Willett from the National Institutes of Health and by Cancer Epidemiology Training grant 5T32 CA09001-26 to Dr Leitzmann from the National Cancer Institute.
Role of the Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Acknowledgment: We are indebted to the participants in the Health Professionals Follow-up Study for their continuing cooperation and to Jill Arnold, Elizabeth Frost-Hawes, Mira Kaufman, Mildred Wolff, Barbara Vericker, Alvin Wing, and Laura Sampson for expert help.

REFERENCES

1. Krain LS. Some epidemiologic variables in prostatic carcinoma in California. *Prev Med.* 1974;3:154-159.
2. Strickler HD, Goedert JJ. Sexual behavior and evidence for an infectious cause of prostate cancer. *Epidemiol Rev.* 2001;23:144-151.
3. Isaacs JT. Prostatic structure and function in relation to the etiology of prostatic cancer. *Prostate.* 1983;4:351-366.
4. Rotkin ID. Studies in the epidemiology of prostatic cancer: expanded sampling. *Cancer Treat Rep.* 1977;61:173-180.
5. Steele R, Lees RE, Kraus AS, Rao C. Sexual factors in the epidemiology of cancer of the prostate. *J Chronic Dis.* 1971;24:29-37.
6. Marsiglio W, Donnelly D. Sexual relations in later life: a national study of married persons. *J Gerontol.* 1991;46:S338-S344.
7. Bortz WM II, Wallace DH, Wiley D. Sexual function in 1,202 aging males: differentiating aspects. *J Gerontol A Biol Sci Med Sci.* 1999;54:M237-M241.
8. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin.* 2003;53:5-26.
9. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. *Epidemiology.* 2002;13:72-79.
10. Giles GG, Severi G, English DR, et al. Sexual factors and prostate cancer. *BJU Int.* 2003;92:211-216.
11. Jakobsson L, Loven L, Hallberg IR. Sexual problems in men with prostate cancer in comparison with men with benign prostatic hyperplasia and men from the general population. *J Clin Nurs.* 2001;10:573-582.
12. Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer.* 1989;64:598-604.
13. Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res.* 1989;49:1857-1860.
14. Cox DR. Regression models and lifetables. *J R Stat Soc Ser B.* 1972;34:187-220.
15. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med.* 2000;30:328-338.
16. Mirone V, Imbimbo C, Bortolotti A, et al. Cigarette smoking as risk factor for erectile dysfunction: results from an Italian epidemiological study. *Eur Urol.* 2002;41:294-297.
17. White JR, Case DA, McWhirter D, Mattison AM. Enhanced sexual behavior in exercising men. *Arch Sex Behav.* 1990;19:193-209.

18. Matthias RE, Lubben JE, Atchison KA, Schweitzer SO. Sexual activity and satisfaction among very old adults: results from a community-dwelling Medicare population survey. *Gerontologist.* 1997;37:6-14.
19. Leigh BC, Temple MT, Trocki KF. The sexual behavior of US adults: results from a national survey. *Am J Public Health.* 1993;83:1400-1408.
20. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol.* 1991; 133:810-817.
21. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology.* 1996;7:81-86.
22. Aumuller G. Postnatal development of the prostate. *Bull Assoc Anat (Nancy).* 1991;75:39-42.
23. Chaklin AV, Plotnikov SV. Importance of various factors in the occurrence of prostatic cancer [in Russian]. *Urol Nefrol.* 1984;4:46-51.
24. Oishi K, Okada K, Yoshida O, et al. A case-control study of prostatic cancer in Kyoto, Japan: sexual risk factors. *Prostate.* 1990;17:269-279.
25. Ilic M, Vlajinac H, Marinkovic J. Case-control study of risk factors for prostate cancer. *Br J Cancer.* 1996; 74:1682-1686.
26. Du SF, Shi LY, He SP. A case-control study of prostate cancer [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi.* 1996;17:343-345.
27. Ross RK, Shimizu H, Paganini-Hill A, Honda G, Henderson BE. Case-control studies of prostate cancer in blacks and whites in southern California. *J Natl Cancer Inst.* 1987;78:869-874.
28. Jackson MA, Kovi J, Heshmat MY, Jones GW, Rao MS, Ahluwalia BS. Factors involved in the high incidence of prostatic cancer among American blacks. *Prog Clin Biol Res.* 1981;53:111-132.
29. Ross RK, Paganini-Hill A, Henderson BE. The etiology of prostate cancer: what does the epidemiology suggest? *Prostate.* 1983;4:333-344.
30. Hayes RB, de Jong FH, Raatgever J, et al. Physical characteristics and factors related to sexual development and behaviour and the risk for prostatic cancer. *Eur J Cancer Prev.* 1992;1:239-245.
31. La Vecchia C, Franceschi S, Talamini R, Negri E, Boyle P, B Da. Marital status: indicators of sexual activity and prostatic cancer. *J Epidemiol Community Health.* 1993;47:450-453.
32. Rosenblatt KA, Wicklund KG, Stanford JL. Sexual factors and the risk of prostate cancer. *Am J Epidemiol.* 2001;153:1152-1158.
33. Banerjee AK. Carcinoma of prostate and sexual activity [letter]. *Urology.* 1986;28:159.
34. Baker LH, Mebust WK, Chin TD, Chapman AL, Hinthorn D, Towle D. The relationship of herpesvirus to carcinoma of the prostate. *J Urol.* 1981;125:370-374.
35. Hsieh CC, Thanos A, Mitropoulos D, Deliveliotis C, Mantzoros CS, Trichopoulos D. Risk factors for prostate cancer: a case-control study in Greece. *Int J Cancer.* 1999;80:699-703.
36. Mandel JS, Schuman LM. Sexual factors and prostatic cancer: results from a case-control study. *J Gerontol.* 1987;42:259-264.
37. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer.* 1988;57:326-331.
38. Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. *Prostate.* 1985;6:423-436.
39. Hayes RB, Pottern LM, Strickler H, et al. Sexual behaviour, STDs and risks for prostate cancer. *Br J Cancer.* 2000;82:718-725.
40. Shaneyfelt T, Husein R, Bubley G, Mantzoros CS. Hormonal predictors of prostate cancer: a meta-analysis. *J Clin Oncol.* 2000;18:847-853.
41. Schiavi RC, Schreiner-Engel P, Mandeli J, Schanzer H, Cohen E. Healthy aging and male sexual function. *Am J Psychiatry.* 1990;147:766-771.
42. Ahn HS, Park CM, Lee SW. The clinical relevance of sex hormone levels and sexual activity in the ageing male. *BJU Int.* 2002;89:526-530.
43. Mantzoros CS, Georgiadis EI, Trichopoulos D. Contribution of dihydrotestosterone to male sexual behaviour. *BMJ.* 1995;310:1289-1291.
44. Pichini S, Zuccaro P, Pacifici R. Drugs in semen. *Clin Pharmacokinet.* 1994;26:356-373.
45. Smith ER, Hagopian M. Uptake and secretion of carcinogenic chemicals by the dog and rat prostate. *Prog Clin Biol Res.* 1981;75B:131-163.
46. Del Rosario AD, Bui HX, Abdulla M, Ross JS. Sulfur-rich prostatic intraluminal crystalloids: a surgical pathologic and electron probe x-ray microanalytic study. *Hum Pathol.* 1993;24:1159-1167.
47. Holmes EJ. Crystalloids of prostatic carcinoma: relationship to Bence-Jones crystals. *Cancer.* 1977;39: 2073-2080.
48. Ro JY, Ayala AG, Ordonez NG, Cartwright J Jr, Mackay B. Intraluminal crystalloids in prostatic adenocarcinoma: immunohistochemical, electron microscopic, and x-ray microanalytic studies. *Cancer.* 1986; 57:2397-2407.
49. Anton RC, Chakraborty S, Wheeler TM. The significance of intraluminal prostatic crystalloids in benign needle biopsies. *Am J Surg Pathol.* 1998;22:446-449.
50. Kelly RW, Critchley HO. Immunomodulation by human seminal plasma: a benefit for spermatozoon and pathogen? *Hum Reprod.* 1997;12:2200-2207.
51. Binks S, Pockley AG. Modulation of leukocyte phagocytic and oxidative burst responses by human seminal plasma. *Immunol Invest.* 1999;28:353-364.
52. Tarter TH, Ablin RJ. Immunoregulatory properties of seminal plasma: perspective and prospective considerations. *J Investig Allergol Clin Immunol.* 1992; 2:106-112.
53. Okamoto M, Byrn R, Eyre RC, Mullen T, Church P, Kiessling AA. Seminal plasma induces programmed cell death in cultured peripheral blood mononuclear cells. *AIDS Res Hum Retroviruses.* 2002;18: 797-803.
54. Newman HF, Reiss H, Northup JD. Physical basis of emission, ejaculation, and orgasm in the male. *Urology.* 1982;19:341-350.
55. Djakiew D. Role of nerve growth factor-like protein in the paracrine regulation of prostate growth. *J Androl.* 1992;13:476-487.
56. McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, McKenna KE. Growth of the rat prostate gland is facilitated by the autonomic nervous system. *Biol Reprod.* 1994;51:99-107.