Published in final edited form as:
Cancer. 2010 May 1; 116(9): 2140–2147. doi:10.1002/cncr.25075.

Increased Risk of High-Grade Prostate Cancer Among Infertile Men

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Abstract

BACKGROUND—It has been reported that fatherhood status may be a risk factor for prostate cancer. In the current study, the authors examined the subsequent occurrence of prostate cancer in a cohort of men evaluated for infertility to determine whether male infertility is a risk factor for prostate cancer.

METHODS—A total of 22,562 men who were evaluated for infertility from 1967 to 1998 were indentified from 15 California infertility centers and linked to the California Cancer Registry. The incidence of prostate cancer was compared with the incidence in an age-matched and geography-matched sample of men from the general population. The risk of prostate cancer in men with and those without male factor infertility was modeled using a Cox proportional hazards regression model.

RESULTS—A total of 168 cases of prostate cancer that developed after infertility were identified. Men evaluated for infertility but not necessarily with male factors were not found to have an increased

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CONFLICT OF INTEREST DISCLOSURES

Supported by The National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development (K12 HD053943012) (to T.J.W.); The National Institutes of Health (1 RO1 CA69619) (to M.S.C.); and The California Urology Foundation (to P.J.T.). The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract N01-PC-35,136 awarded to the Northern California Cancer Center, contract N01-PC-35,139 awarded to the University of Southern California, and contract N02-PC-15,105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

risk of cancer compared with the general population (standardized incidence ratio [SIR], 0.9; 95% confidence interval [95% CI], 0.8-1.1). This risk was found to be highest for men with male factor infertility who developed high–grade prostate cancer (SIR, 2.0; 95% CI, 1.2-3.0). On multivariate analyses, men with male factor infertility were found to be 2.6 times more likely to be diagnosed with high–grade prostate cancer (hazard ratio, 2.6; 95% CI, 1.4-4.8).

CONCLUSIONS—Men with male factor infertility were found to have an increased risk of subsequently developing high–grade prostate cancer. Male infertility may be an early and identifiable risk factor for the development of clinically significant prostate cancer.

Keywords

prostate cancer; male infertility; incidence; risk

Prostate cancer is the most common malignancy diagnosed in men; however, its etiology is poorly understood. To our knowledge to date, the most established and agreed on risk factors are age, family history, and race.[1] More recently, it has been proposed that fatherhood status may be associated with prostate cancer, although the results of several epidemiologic studies performed to date have been mixed.[2]

A Danish cohort and Swedish case-control study both reported that childless men were less likely to be diagnosed with prostate cancer compared with men with children.[2,3] The former study found that among men with children, cancer risk was highest among men with the fewest children with evidence of dose response, whereby the risk decreased with each additional child. In contrast, an Italian study reported no association with infertility.[4] This latter result was in keeping with a meta-analysis of a series of small studies that reported no association.[5]

Each of these studies relied on a surrogate marker for male fertility, namely the number of offspring sired, in the absence of a specific fertility evaluation. A man's ability to father children is intimately related to his partner's fecundability, and the number of children fathered may not accurately reflect a man's ability to cause a pregnancy. To address this issue, we evaluated the association between male infertility and prostate cancer using a multi-institutional cohort of men evaluated for infertility in the United States.

MATERIALS AND METHODS

Study Population

After Institutional Review Board approval, men were identified from a cohort of 51,461 couples who sought evaluation for infertility in the state of California. Details of the cohort assembly have been previously described.[6] This cohort was comprised of couples in whom both partners were aged >18 years and who received care from 40 different providers at 15 infertility centers between January 1, 1967 and January 1, 1998. Eleven fertility centers were located in northern California and 4 in southern California. Four of the fertility centers were part of the Kaiser Permanente Medical Care Program. All ethnic and language groups were included. However, data regarding race were available for only 27% of female cohort members, 73% of whom were white; data concerning race were not available for men. Couples were excluded if: 1) the woman was not attempting pregnancy, or 2) the woman was a non-US resident. Identifying information was obtained from the medical records of all study subjects and 42,274 male partners were identified. Couples sought care from reproductive endocrinology practices in which the primary focus of care was the female partner. As a result, complete demographic information, including date of birth, was not available for all male partners. Complete information was available for the 22,562 men who represent the final study cohort (Fig. 1).

Men were considered to have male factor infertility based on a clinical presentation with abnormal semen parameters as defined by World Health Organization (WHO) criteria.[7] The presence or absence of male factor infertility was determined by the treating clinician and coded as a dichotomous variable (yes/no). The presence or absence of male factor infertility was known for 19,106 (84%) men, 4548 (24%) of whom had male factor infertility and 14,557 (76%) of whom did not.

Linkage Procedures

The cohort was linked to the California Cancer Registry (CCR) to determine cancer rates. The CCR combines all registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) for the State of California, and contains information regarding all cases of histologically confirmed cancer since January 1, 1988. The CCR collects data regarding the date of diagnosis, age at diagnosis, vital status, tumor behavior (according to International Classification of Diseases for Oncology-2nd edition [ICD–O-2] coding), and histologic type (also according to ICD–O-2 coding). All prostate cancers were identified by ICD–O site codes (prostate: C619) and categorized by grade according the SEER program (grade 1: Gleason score of 2-4; grade 2: Gleason score of 5-7; grade 3: Gleason score of 8-10; and grade 4: “aggressive variants”).

We performed automated, probabilistic matching using the patient’s social security number, first name, middle name, last name, date of birth, and address. A match was considered definite if there was complete agreement on social security number, first name, last name, and date of birth. All cases of prostate cancer were definite matches. All matches were reviewed by hand and consensus was obtained by 3 investigators (T.W., M.S., and M.C.).

Data Analysis

Cancer cases occurring before 1988 could not be identified by the CCR; therefore, our analysis was left truncated beginning on December 31, 1987. Using this methodology, men evaluated for infertility before cancer registry availability do not accumulate “at risk time” until 1987, but remain as members of the cohort in whom cancer cases can be identified. Each cohort member contributed person-years at risk for prostate cancer from the date of infertility evaluation or January 1, 1988 (whichever came last) until the date of cancer diagnosis, death, or final cancer registry accrual (December 31, 2004). Men diagnosed with cancer before the date of infertility evaluation or within 1 year after infertility evaluation were excluded from analysis given our inability to determine whether the treatment of cancer or the presence of an occult cancer led to infertility. The rate of prostate cancer among men in the current study cohort was compared with the rate among white men in California using standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs). Although racial data were not available for men, we assumed that the male race distribution was similar to that of their female partners, who were predominantly white. The expected number of prostate cancer cases in the cohort was calculated by multiplying the number of years at risk by the 5-year age strata and year-specific primary prostate cancer rates from all SEER registries in California. The SIR was calculated by dividing the number of observed cancer cases in the cohort by the number of expected cases. Analyses were performed for the entire cohort of men seeking infertility care and for subgroups of men with and without male factor infertility.

The risk for prostate cancer was analyzed in men with male factor infertility compared with those without male factor infertility using Cox proportional hazards regression modeling, controlling for age, duration of treatment, and site of treatment. Follow-up time in these analyses was initiated at the time of entry into the infertility network and used age as the time scale. The proportional hazards assumptions were checked by evaluating the Wald test for the interaction of male infertility with log-time in the model. The *P* value for this interaction was

not significant ($P = .73$), which supported the proportional hazards assumptions. We performed stratified analyses by histologic grade. Hazard ratios (HRs) and their 95% CIs were used to estimate the association between infertility and prostate cancer, examining men within the infertility cohort only. Men with unknown male factor infertility status were excluded from multivariate regression analyses. A P value of .05 was considered statistically significant, and all tests were 2-sided. All statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

Table 1 presents the characteristics of men with and without male factor infertility. Although men with and without male factor infertility were generally similar with regard to the majority of factors, those with male factor infertility were slightly older at the time of infertility evaluation (mean age, 38.1 years vs 36.4 years) and had a longer duration of infertility care (mean duration, 1.7 years vs 1.5 years) than men without male infertility factors. Both groups had the same duration of follow-up (mean duration, 11.4 years). A larger proportion of men with male factor infertility developed prostate cancer compared with those without male factor infertility (1.2% vs 0.4%). Four cancers (2%) were diagnosed before the widespread introduction of prostate-specific antigen screening in 1995. The exclusion of these cancers did not appreciably alter the results of any analyses (data not shown); therefore, they were included in all presented analyses.

Prostate cancer occurred at least 1 year after the initiation of infertility evaluation among 168 cohort members. Of the prostate cancers, 163 (97%) were adenocarcinomas, with the remainder classified as being of unknown histologies. Greater than two-thirds of men had a Gleason score ≤ 7, with the majority being classified as having a Gleason score of 5 through 7 (68%) (Table 2). The remaining prostate cancers were high-grade adenocarcinomas (Gleason score of 8-10). The median time from infertility evaluation to cancer diagnosis was 11 years (range, 1-22 years) for all men who developed cancer, 9 years (range, 1-22 years) for those with no male factor infertility, 10 years (range, 1-17 years) for those with male factor infertility, and 16 years (range, 7-22 years) for those with unknown male factor infertility status.

Risk of Prostate Cancer

After exclusions, 168 men were identified with prostate cancer in the study cohort compared with an expected number of 185 (SIR, 0.9; 95% CI, 0.8-1.1), suggesting that overall, men in the infertility cohort were not at a higher risk of being diagnosed with any prostate cancer compared with the general population (Table 3). In the stratum of patients with a Gleason score of 5 to 7, 115 cancers were identified compared with an expected 133 (SIR, 0.9; 95% CI, 0.7-1.0), and in the stratum of patients with a Gleason score of 8 to 10, 45 cancers were identified compared with an expected 42 (SIR, 1.1; 95% CI, 0.8-1.5). When we considered male factor infertility and prostate cancer risk, men with male factor infertility only demonstrated a significantly elevated risk of high–grade prostate cancer: SIRs were 1.3 (95% CI, 1.0-1.7), 1.2 (95% CI, 0.8-1.6), and 2.0 (95% CI, 1.2-3.0), respectively, for all, low-grade, and high-grade cancers. Conversely, men without male factor infertility were found to have lower risks of developing all, low-grade, and high-grade prostate cancer, and in some cases there was a statistically significant protective effect, with SIRs of 0.7 (95% CI, 0.6-0.9), 0.7 (95% CI, 0.6-1.0), and 0.8 (95% CI, 0.5-1.3), respectively.

We examined the risk of prostate cancer in men with and without male factor infertility in the infertility cohort, using multivariate Cox proportional hazards regression analysis (Table 4). In the unadjusted model, men with male factor infertility were found to be 2.8 times more likely

to develop any prostate cancer compared with those without male factor infertility (HR, 2.8; 95% CI, 2.0-4.0). When controlling for age, duration of infertility treatment, and infertility treatment facility, men with male factor infertility were found to have 1.8 times the hazard of any prostate cancer compared with those without male factor infertility (95% CI, 1.2-2.5). For each additional year of receiving infertility treatment, men had 1.2 times the hazard of developing prostate cancer (HR, 1.2; 95% CI, 1.1-1.4). Similar modeling was performed after stratifying cancers by histologic grade. Men with male factor infertility were 1.6 (95% CI, 1.0-2.4) times more likely to be diagnosed with a Gleason score 5 to 7 tumor compared with men without male factor infertility, after controlling for age, infertility treatment duration, and infertility treatment facility. Men with male factor infertility were 2.6 times (95% CI, 1.4-4.8) more likely to be diagnosed with a Gleason score 8 to 10 cancer. For each of these models, age was found to be the strongest independent predictor of prostate cancer, whereby with each additional year of life, a man's risk of cancer increased by approximately 10% (HR, 1.1; 95% CI, 1.10-1.15).

DISCUSSION

The current cohort study, based on more than 22,000 men undergoing evaluation for infertility, observed a strong association between infertility and the subsequent diagnosis of a high-grade prostate cancer. Although men with male factor infertility did not appear to have a statistically significant increased risk of low-grade prostate cancer compared with all at-risk men in California (SIR, 1.2; 95% CI, 0.8-1.6), they were found to be twice as likely to be diagnosed with high-grade prostate cancer (SIR, 2.0; 95% CI, 1.2-3.0). On multivariate analyses, men with male factor infertility were found to be >2.5 times (HR, 2.6; 95% CI, 1.4-4.8) more likely to develop a high-grade prostate cancer than those in the cohort without male factor infertility, after adjusting for age, duration of infertility treatment, and infertility treatment facility.

These results suggest that male factor infertility may be a risk factor for the subsequent development of clinically significant prostate cancer; however, several factors may contribute to our findings. Of concern when evaluating risk factors for prostate cancer is the possibility of bias being introduced through cancer screening. Men who are seeking evaluation for infertility may have a higher likelihood of prostate cancer diagnosis given their generally higher socioeconomic status, possibly improved access to healthcare, and their greater propensity to seek medical attention, all of which are known risk factors for prostate cancer screening.[8] The analysis using SIRs would be particularly subject to biases because of these issues. Based on comparison with age-matched men in the general California population, overall, men in our cohort had a similar rate of prostate cancer diagnoses. In particular, we observed no positive association among men who were evaluated and found not to be infertile. Men with male factor infertility may have a higher likelihood of urological evaluation and thus prostate cancer screening. The lack of a significant excess of low-grade prostate cancer cases suggests that prostate cancer screening biases alone may not account for the increased risk of high-grade prostate cancer among those with male factor infertility.

Data from large observational cohorts of men diagnosed with prostate cancer have described a subset of men at very low risk of prostate cancer-specific mortality during their lifetime.[9, 10] Autopsy studies have described the unique prevalence of clinically indolent prostate cancer in men dying of other causes.[11-13] In the current study, cohort members as a whole were not found to be more likely to be diagnosed with prostate cancer, regardless of grade. However, when using grade stratification, although men with male factor infertility demonstrated no clear evidence of an increased risk of low-grade prostate cancer (SIR, 1.2; 95% CI, 0.8-1.6), their risk was 2-fold higher for the development of high-grade prostate cancer (SIR, 2.0; 95% CI, 1.2-3.0). On multivariate analyses of men from the cohort only, men with male factor infertility

were found to be 2.6 times more likely to be diagnosed with high-grade cancer (HR, 2.6; P =. 003) compared with men without male factor infertility.

The results of the current study are consistent with the findings of Jorgensen et al demonstrating a decreased prostate cancer risk with increased paternity.2 The interpretation of the study by Jorgensen et al2 is limited by its inability to account for a man's intention to cause a pregnancy and serves as the striking difference between their study and the current one. In the current analysis, all men were attempting to conceive a child, and underwent specific evaluation for infertility. The current study results are not consistent with the findings of studies indicating that childless men have a lower risk of prostate cancer compared with men who have fathered at least 1 child.3[-5] Similarly, these studies are difficult to interpret because the underlying reason that a human is childless can be because of a lack of opportunity, choice, or low reproductive potential (ie, infertility).

The Jerusalem Perinatal Study cohort provides additional insight into the association between male infertility and prostate cancer. Men who had sired stillborn offspring and had decreased paternity were found to have an increased risk of developing prostate cancer compared with those without this history.[14] Citing the recent implication of the Y chromosome as an etiologic factor in male infertility and prostate cancer, the authors hypothesized that gene defects on the Y chromosome may be a common link between prostate cancer and the decreased ability of the carrier to conceive males.[15] The authors found that men with few male offspring had an increased odds of developing prostate cancer, and that this risk appeared to follow a dose-response correlation. In addition, among all cohort members who developed prostate cancer, those with the fewest sons appeared to have the highest risk of disease-specific mortality, suggesting that these men may have more aggressive cancers.

Infertility may be related to the subsequent development of prostate cancer as a result of the treatment for infertility increasing the risk or ≥1 factors that infertility and prostate cancer share. The former postulate is improbable given that many cases of infertility are treated with assisted reproductive technologies rather than specific medical or surgical treatment of the male partner.[16] A more plausible explanation is that a common exposure underlies both infertility and prostate cancer. In addition to the aforementioned hypotheses surrounding the Y chromosome, prior work has suggested that certain severe forms of male infertility are associated with faulty DNA repair.[17-19] Faulty DNA repair has classically been associated with tumorigenesis, both in humans and animal models, and could underlie the association between infertility and cancer.[20,21] Importantly, defects in DNA mismatch repair also have been implicated in the etiology of prostate cancer.[22] These and other genetic abnormalities may play a role the development of both infertility and prostate cancer. Although the downstream effects of these abnormalities may lead directly to disease, they also may increase susceptibility to the negative influence of environmental factors. A study by Skinner et al suggested that in utero exposure of rats to the ubiquitous fungicide vinclozine leads initially to poor fertility, and subsequently to increased cancer diagnoses and poor prostate health.[23]

The results of the current study provide novel evidence of a potential link between male factor infertility and aggressive prostate cancer risk. They warrant further confirmation and should stimulate additional research focusing on possible common biological pathways underlying infertility and prostate cancer. These results, if confirmed, also suggest that men identified with male factor infertility earlier in life may be considered for prostate cancer screening, given the elevated risk specifically for high-grade disease.

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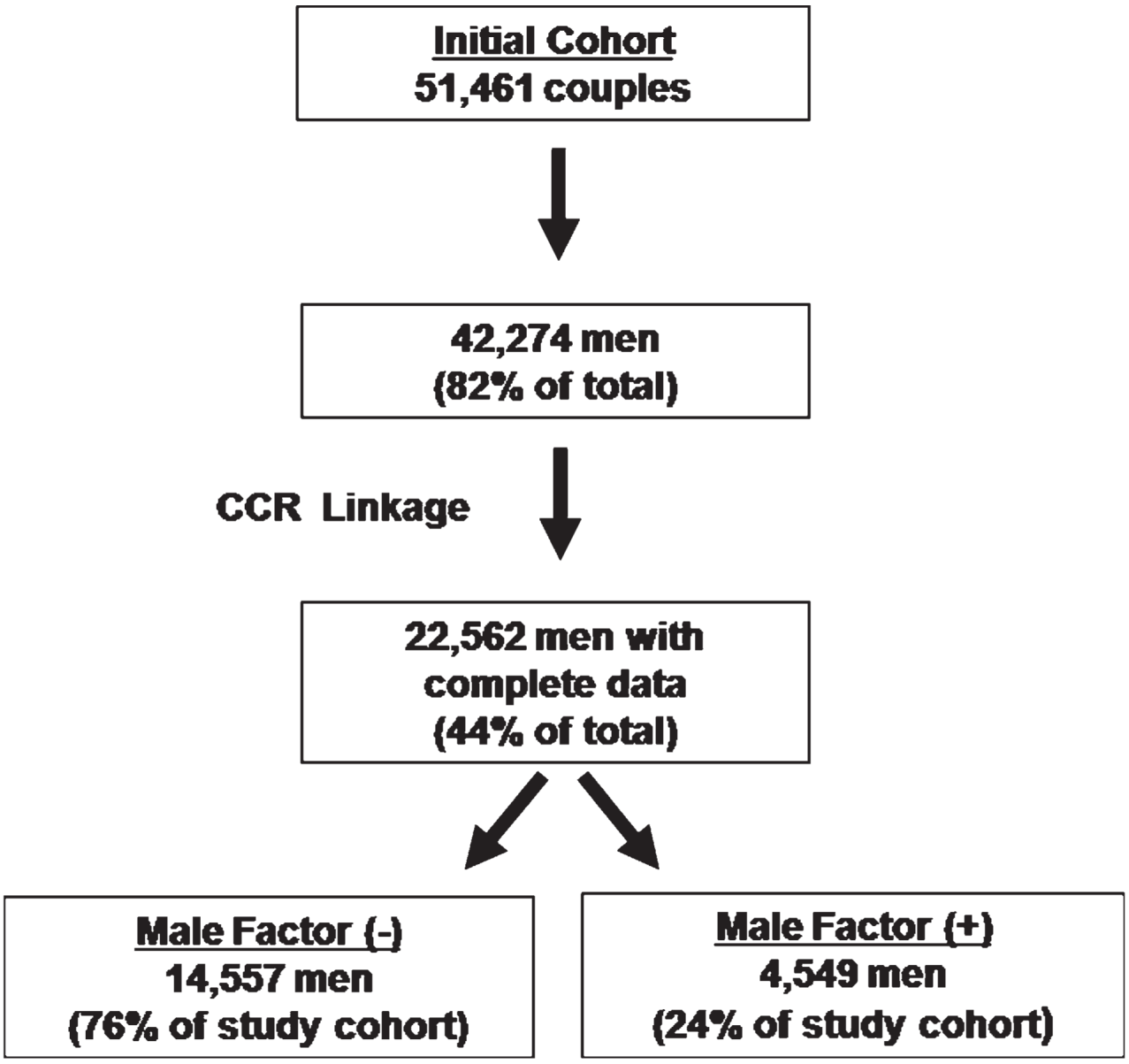

Figure 1.
Identification and classification of infertile men from 15 different treatment centers in California are shown for the years 1967 through 1998. CCR indicates the California Cancer Registry; −, negative; +, positive.

Table 1

Select Characteristics of 22,562 Men With and Without Male Factor Infertility Among a Cohort of Couples Evaluated for Infertility in California, 1967-1998

Characteristics (SD), Year	Male Factor Negative (n=14,557)	Male Factor Positive (n=4549)	Unknown Male Fertility Status (n=3456)
Mean age at infertility evaluation	36.4 (6.4)	38.1 (7.4)	35.8 (6.5)
Mean age at last follow-up or cancer diagnosis	48.4 (6.7)	50.1 (7.7)	53.7 (7.0)
Mean duration of infertility treatment	1.5 (2.1)	1.7 (2.1)	1.1 (1.6)
Mean follow-up	11.4 (2.9)	11.4 (2.9)	17.4 (3.5)

Characteristics	No. (%)	No. (%)	No. (%)
Age at infertility evaluation, y			
<25	191 (1.3)	43 (1.0)	55 (1.6)
25-29	1569 (10.8)	332 (7.3)	445 (12.9)
30-34	4101 (28.2)	1159 (25.5)	1082 (31.3)
35-39	4657 (32.0)	1335 (29.3)	1059 (30.6)
40-44	2618 (18.0)	897 (19.7)	524 (15.2)
45-49	975 (6.7)	465 (10.2)	172 (5.0)
>49	446 (3.0)	318 (7.0)	119 (3.4)
Age at last follow-up or cancer diagnosis, y			
25-29	2 (0)	2 (0)	0 (0)
30-34	133 (0.9)	28 (0.6)	9 (0.3)
35-39	925 (6.4)	199 (4.4)	57 (1.6)
40-44	3082 (21.2)	811 (17.8)	195 (5.6)
45-49	4563 (31.3)	1292 (28.4)	656 (19.0)
50-54	3421 (23.5)	1091 (24.0)	1042 (30.2)
55-59	1697 (11.7)	660 (14.5)	932 (27.0)
>59	734 (5.0)	466 (10.2)	565 (16.3)
Year of infertility evaluation			
1967-1979	3 (0)	2 (0)	69 (2.0)
1980-1984	166 (1.1)	43 (0.9)	705 (20.4)
1985-1989	1713 (11.8)	556 (12.2)	2358 (68.2)
1990-1994	8237 (56.6)	2597 (57.1)	182 (5.3)

Characteristics	No. (%)	No. (%)	No. (%)
1995-1998	4438 (30.5)	1351 (29.7)	140 (4.1)
Duration of infertility treatment, y			
<1	6099 (41.9)	1543 (33.9)	1802 (52.1)
1-3	6499 (44.6)	2262 (49.7)	1366 (39.5)
>3	1959 (13.5)	744 (16.4)	288 (8.3)
Prostate cancer			
Yes	64 (0.4)	56 (1.2)	48 (1.4)
No	14,493 (99.6)	4493 (98.8)	3408 (98.6)

SD indicates standard deviation.

Cancer. Author manuscript; available in PMC 2010 June 29.

Table 2

Tumor Characteristics Among Infertile Men Who Subsequently Developed Prostate Cancer (n=168 Cases Among 22,562 Men)

Tumor Histology	No. (%)
SEER Grade 1: Gleason score of 2-4	3 (2)
SEER Grade 2: Gleason score of 5-7	115 (68)
SEER Grade 3: Gleason score of 8-10	45 (27)
SEER Grade 4: aggressive variants	0 (0)
Unknown	5 (3)

SEER indicates Surveillance, Epidemiology, and End Results.

Table 3

Age-Aggregated SIRs and 95% CIs for Prostate Cancer in Men With and Without Male Factor Infertility From a Cohort of 22,562 Men

Fertility Status	No. of Men	Observed No. of Cases	Expected No. of Cases	SIR (95% CI)
All prostate cancers [a]				
All men	22,562	168	185	0.9 (0.8-1.1)
No male factor infertility	14,557	64	88	0.7 (0.6-0.9)[b]
Male factor infertility	4549	56	44	1.3 (1.0-1.7)
Unknown male fertility status	3456	48	53	0.9 (0.7-1.2)
Low-grade prostate cancers [c]				
All men	22,562	115	133	0.9 (0.7-1.0)
No male factor infertility	14,557	47	63	0.7 (0.6-1.0)[b]
Male factor infertility	4549	37	31	1.2 (0.8-1.6)
Unknown male fertility status	3456	31	39	0.8 (0.6-1.1)
High-grade prostate cancers [d]				
All men	22,562	45	42	1.1 (0.8-1.5)
No male factor infertility	14,557	16	20	0.8 (0.5-1.3)
Male factor infertility	4549	19	10	2.0 (1.2-3.0)[b]
Unknown male fertility status	3456	10	12	0.9 (0.4-1.6)

SIRs indicates standardized incidence ratios; 95% CI, 95% confidence intervals.

[a] Surveillance, Epidemiology, and End Results (SEER) grades 1 through 4 and unknown: grade 1: Gleason score of 2 to 4; grade 2: Gleason score of 5 to 7; grade 3: Gleason score of 8 to 10; and grade 4: aggressive variants.

[b] $P<.05$.

[c] SEER grade 2: moderately well differentiated, Gleason score of 5 to 7.

[d] SEER grade 3: poorly differentiated, Gleason score of 8 to 10.

Table 4

Adjusted HRs and 95% CIs for Prostate Cancer Among 19,106 Men With and Without Male Factor Infertility From a Cohort of Couples Evaluated for Infertility[a]

		Prostate Cancer					
	No.	**no.**	**%**	**Unadjusted HR (95% CI)**	***P***	**Adjusted HR[b] (95% CI)**	***P***
All prostate cancers							
Male factor infertility							
No	14,557	64	0.44	1.0 (referent)	–	1.0 (referent)	–
Yes	4549	56	1.23	2.8 (2.0-4.0)	<.0001	1.8 (1.2-2.5)	.0010
Low-grade prostate cancer [c]							
Male factor infertility							
No	14,557	47	0.32	1.0 (referent)	–	1.0 (referent)	–
Yes	4549	37	0.81	2.5 (1.6-3.9)	<.0001	1.6 (1.0-2.4)	.042
High-grade prostate cancer [d]							
Male factor infertility							
No	14,557	16	0.11	1.0 (referent)	–	1.0 (referent)	–
Yes	4549	19	0.42	3.8 (1.9-7.3)	<.0001	2.6 (1.4-4.8)	.0032

HRs indicates hazard ratios; 95% CIs, 95% confidence intervals.

[a] A total of 3456 men were excluded from analysis because of unknown male factor infertility status.

[b] Adjusted for age, infertility treatment duration, and infertility treatment facility.

[c] Surveillance, Epidemiology, and End Results (SEER) grade 2: moderately well-differentiated, Gleason score of 5 to 7.

[d] SEER grade 3: poorly differentiated, Gleason score of 8 to 10.