ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

ORIGINAL ARTICLE

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Keywords:
contraception, prostate-specific antigen, prostatic neoplasm, vasectomy

Received: 19-Apr-2018
Revised: 13-Jul-2018
Accepted: 3-Nov-2018

doi: 10.1111/andr.12570

Vasectomy and the risk of prostate cancer in a prospective US Cohort: Data from the NIH-AARP Diet and Health Study

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ABSTRACT

Background: Several studies have linked vasectomy with the risk of prostate cancer; however, this association has been attributed to selection bias. Since vasectomy is a common and effective form of contraception, these implications are significant. Therefore, we sought to test this association in a large observational cohort.

Objective: To evaluate the potential association between prior vasectomy and the risk of developing prostate cancer.

Materials and Methods: We evaluated the relationship between vasectomy and prostate cancer in the NIH-AARP Diet and Health Study. Of the 111,914 men, prostate cancer was identified in 13,885 men and vasectomies were performed in 48,657. We used multivariate analysis to examine the relationship between prostate cancer and vasectomy. We also performed propensity score-adjusted and propensity score-matched analysis.

Results: Men utilizing vasectomy were more likely to be ever married, fathers, educated, white, and screened for prostate cancer. During 4,251,863 person-years of follow-up, there was a small association between vasectomy and incident prostate cancer with a hazard ratio of 1.05 (95% CI, 1.01–1.11). However, no significant association was found when looking separately at prostate cancer by grade or stage. Conclusions were similar when using propensity adjustment and matching. Importantly, a significant interaction between vasectomy and PSA screening was identified.

Discussion: Estimates of the association between vasectomy and prostate cancer are sensitive to analytic method underscoring the tenuous nature of the connection. Given the differences between men who do and do not utilize vasectomy, selection bias appears likely to explain any identified association between vasectomy and prostate cancer.

Conclusions: With over 20 years of follow-up, no convincing relationship between vasectomy and prostate cancer of any grade was identified.

INTRODUCTION

Vasectomy is the fourth most commonly utilized means of contraception in the United States with around 500,000 performed annually across the United States (Eisenberg & Lipshultz, 2010; Mosher & Jones, 2010). While there is little morbidity associated with the procedure (Awsare *et al.*, 2005), there has been significant debate regarding the association of increased risk of prostate cancer in men with prior vasectomy. In 1993, a population-based analysis of data from the Health Professionals Follow-up Study found a slight increase in the risk of incident prostate cancer after vasectomy (Giovannucci *et al.*, 1993a,b; Dennis *et al.*, 2002);. Later studies, however, found no association between prior vasectomy and the risk of prostate cancer (Lynge, 2002; Cox *et al.*, 2002; Schwingl *et al.*, 2009; Holt *et al.*, 2008; Sidney *et al.*, 1993). In 2014, an updated analysis of the data from the Health Professionals Follow-up Study again demonstrated a slight increased risk of high-grade (grade group 4 and 5) and lethal prostate cancer in men with prior vasectomy, but no association with lower grade localized of prostate cancer (Siddiqui *et al.*, 2014).

Since 2014, other groups from both the United States and internationally have re-evaluated this question. Invariably, they have found no association between prior vasectomy and prostate cancer. Yet, the studies did not contain granular data on patient characteristics, such as prostate cancer screening practices, that could confound the association between vasectomy and prostate cancer.

In this study, we use data from men enrolled in the NIH-AARP Diet and Health Study to evaluate the association between vasectomy and the risk of prostate cancer while accounting for prostate cancer screening.

METHODS

The NIH-AARP Diet and Health Study was initiated in 1995, using questionnaires regarding medical history and lifestyle characteristics, which were mailed to 3.5 million members of the AARP who were between the ages of 50–71 and living in one of six states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) or in one of two metropolitan areas (Atlanta, GA and Detroit, MI). Of these members, 334,908 returned the completed survey, and in 2004, the living AARP members received a follow-up survey.

Identification of vasectomy status

In the 2004 follow-up questionnaire, male participants were asked 'Have you ever had any of the following procedures performed?' These procedures included coronary artery bypass or angioplasty, gallbladder removal, cataract extraction and vasectomy. Those responding in the affirmative were then asked to identify a time frame of the procedure including 'Before 1985', '1985-1994', '1995-1999' and '2000 to present'. Timing of vasectomy was then set at 31 December 1985, 15 June 1989, 15 June 1997, or the date of the follow-up survey completion.

Identification of history of prostate cancer

Cohort members were followed through 31 December 2011, with incident prostate cancer cases (International Classification of Diseases 9th version, rubric 185 or 10th version, rubric C61) identified by questionnaire and at the date of diagnosis as identified in the cancer registry database from the original eight states as well as Arizona, Nevada and Texas. Subjects were matched across databases based on names, date of birth, social security number and residency. Follow-up coverage was expanded to capture participants who moved from their original locations. Our case ascertainment method has been previously described which demonstrated approximately 90% identification of incident cancers (Michaud *et al.*, 2005). All men with a primary prostate cancer were included in the total number of prostate cancer cases. These were then stratified based on the extent of disease as classified in state cancer registries with localized prostate cancer defined as those with tumours that had not penetrated the prostate capsule or any metastatic or lymph node involvement. Furthermore, advanced prostate cancer had evidence of penetration through the prostate capsule, involvement of the lymph nodes or metastases. Fatal prostate cancer cases included those men who had a primary diagnosis of prostate cancer and died during the follow-up course of the survey from a cause of death attributed to prostate cancer as described on the death certificate. Low-grade prostate cancer was defined as SEER grade 1 (well differentiated; Gleason grade 2–4) or grade 2 (moderately well differentiated; Gleason grade 5–7). High-grade prostate cancer was defined as grade 3 (poorly differentiated; Gleason grade 8–10) or grade 4 (undifferentiated or anaplastic). Deaths from prostate cancer as the underlying cause of death were assessed through linkage with the Social Security Administration Death Master File, the National Death Index Plus, cancer registry linkage, questionnaire responses, and responses to other mailings with a final evaluation 31 December 2005.

Survey respondents were also asked questions about a prior history of prostate cancer on the baseline questionnaire. Additional questions queried whether the patients had undergone screening tests for prostate cancer including digital rectal examination and PSA testing. All responses regarding these prior screening tests were considered as positive with the exception of 'Never had one' and 'Not sure if had one'. Finally, both the 1996 supplemental survey and the 2004 follow-up study posed questions regarding a family history of prostate cancer amongst first degree relatives.

Statistical analysis

Each participant in the study contributed follow-up data from baseline data collection until the end of the current study period in the year of 2011, or until their death. Given the nature of the cohort assembly, additional sensitivity analyses were also performed to evaluate for men with a history of prostate cancer versus incident cases at the time of each survey data collection (1985, 1995 and 2003). The earliest time point that retrospective data were collected was 1985. The initial cohort assembly occurred in 1995. The final questionnaires were collected in 2003.

The study population for Table 1 comprised men who had history of prostate cancer after enrolment in the Diet and Health Study Questionnaire of National Institutes of Health and AARP. Baseline characteristics were expressed in mean ± STD for continuous, and percentages for categorical/ordinal variables. Continuous variables were examined for normality with the Kolmogorov–Smirnov univariate normality test. Anthropometric parameters were compared between people who had vasectomy and people who didn't using Student's *t*-test, Wilcoxon test and chi-square test as appropriate. Criterion values were adjusted for unequal variance when appropriate.

Follow-up began at the earliest point respondents had identified as the time frame for vasectomy status based on the 2004 questionnaire. Prostate cancer status could then be established from the corresponding questionnaire and registry data. Given that the average age of the men at cohort entry in 1995-1996 was 51 and the average of vasectomy in the United States is 30 (Eisenberg *et al.*, 2009), most men (>95%) had a vasectomy prior to cohort entry. In addition, the average age of prostate cancer diagnosis is 66. Thus, most men were not diagnosed with prostate cancer prior to cohort entry. We were able to identify the order of events for prostate cancer and vasectomy using a combination of cancer registry and questionnaire data. When the order of events could not be determined, the men were excluded from the analysis. Incident prostate cancer was defined as cases diagnosed during follow-up time. We used Cox proportional hazards regression to estimate hazard ratios with 95% confidence intervals for all prostate cancers. Sensitivity analyses were performed to change enrolment to baseline questionnaire or follow-up questionnaire completion without a change in conclusions.

As prior studies suggested an association between prior vasectomy and aggressive and fatal prostate cancers, we performed separate stratified analyses examining low- and high-grade, fatal, localized and advanced prostate cancers. Person-

Table 1 Vasectomy status of study participants by demographic characteristic

	Entire cohort (n = 160, 571)		Propensity matched (n = 51,292)	
Characteristics	Vasectomy status		Vasectomy status	
	Yes (=48,657)	No (n = 111,914)	Yes (n = 25,646)	No (n = 25,646)
Mean age (Years)	61.8	60.8	61.1	61.1
Race				
White	30.9%	69.1%	49.9%	50.1%
Black	11.6%	88.4%	51.2%	48.8%
Others	24.3%	75.7%	52.5%	47.5%
Marital status				
Married	31.60%	68.40%	50.1%	49.9%
Widowed	22.10%	77.90%	43.4%	56.6%
Divorced	32.17%	67.83%	51.1%	48.9%
Separated	28.70%	71.30%	51.4%	48.6%
Never married	1.56%	98.44%	49.4%	50.6%
Children				
0	9.4%	90.6%	1.3%	1.4%
1	24.5%	75.5%	49.2%	50.8%
2	34.7%	65.3%	37.6%	62.4%
3	36.5%	63.5%	50.2%	49.8%
4	35.5%	64.5%	53.6%	46.4%
5+	26.6%	73.4%	51.1%	48.9%
Education				
<12 years	21.5%	78.5%	53.2%	46.8%
HS/Some College	31.1%	68.9%	50.3%	49.7%
≥College	30.4%	69.6%	49.6%	50.4%
Smoking status				
Never	29.6%	70.4%	49.9%	50.1%
Former	31.1%	68.9%	50.1%	49.9%
Current	28.9%	71.1%	50.1%	49.9%
Diabetes mellitus				
No	30.7%	69.3%	49.9%	50.1%
Yes	25.5%	74.5%	51.4%	48.6%
State				
CA	41.9%	58.1%	50.5%	49.5%
FL	30.5%	69.5%	49.2%	50.8%
GA	31.6%	68.4%	51.2%	48.8%
LA	22.0%	78.0%	49.6%	50.4%
MI	28.4%	71.6%	50.4%	49.6%
NC	28.2%	71.8%	49.6%	50.4%
NJ	17.8%	82.2%	49.7%	50.3%
PA	20.9%	79.1%	49.8%	50.2%
BMI, mean	27.1 (4.0)	27.2 (4.2)		
PSA				
No	27.6%	72.4%		
Yes	31.1%	68.9%		
DRE				
No	23.8%	76.2%		
Yes	31.4%	68.6%		
1st Deg Relative w PCa				
No	30.3%	69.7%		
Yes	30.8%	69.2%		
Prevalent PCa				
No	30.3%	69.7%		
Yes	30.2%	69.8%		
Incident PCa				
No	30.3%	69.7%		
Yes	30.7%	69.3%		

years of follow-up were calculated from the begin dates of each analyses until censoring (i.e. diagnosis of prostate cancer, death, or the end of follow-up (31 December 2011)). The proportional hazard assumption was tested and confirmed by modelling interaction terms of time and other covariates. Analyses were adjusted for age, marital status, education, race, state of residence, diabetes, prostate cancer screening history (PSA or DRE), family history of prostate cancer, smoking history, paternity and BMI. All hazard ratios were presented with 95% confidence interval. Propensity score matching was incorporated to adjust for selection bias and account for exposure-related covariates, specifically marital status, education status, race, state of residence, number of children, BMI categories, age in quartiles, median annual household income in quartiles and alcohol consumption in quartiles with a c statistic of 0.70. Nearest neighbour matching (<0.1) was completed, and we compared the means of covariates across participants in pairs. All analyses were performing using SAS 9.3 (Cary, NC). Two-sided tests were performed with $p < 0.05$ considered significant.

RESULTS

Among the participants in the study, data were available from 160, 571 men with known vasectomy status. In this cohort, 48,657 men (43.4%) had undergone prior vasectomy. Men utilizing vasectomy were more likely to be ever married, fathers, more educated and white consistent with prior reports. Additionally, men who utilized vasectomy reported a higher prevalence of PSA and DRE prostate cancer screening. Propensity matching produced 25,646 matched pairs with high degree of similarities in most characteristics (Table 1).

Overall, 13,885 men developed prostate cancer, and of these cases, 3,440 were determined to be high grade and 460 were lethal during 4,251,863 person-years of follow-up with an average follow-up of over 18 years. Overall, there was slight increase in prostate cancer incidence among vasectomized men when examining all and localized prostate cancer (HR 1.05, 95% CI 1.01–1.11 and HR 1.06, 95% CI 0.97–1.10, respectively). However, no statistically significant association was seen when stratifying by grade of prostate cancer (i.e. low-grade (HR 1.05, 95% CI 0.99–1.10) and high-grade (HR 1.05, 95% CI 0.97–1.13) prostate cancers) but the point estimates remained similar. Similarly, advanced prostate cancer and fatal prostate cancer also showed no significant association with a man's vasectomy status (Table 2). Similar results were seen after propensity adjustment and propensity matching (Table 2).

Prior analysis of the NIH-AARP Diet and Health Study found that prostate cancer screening can powerfully influence prostate cancer diagnosis (Eisenberg *et al.*, 2011). Therefore, we also stratified the cohort based on reported PSA screening habits. We identified a significant interaction with vasectomy and PSA screening for low- and high-grade disease. For PSA unscreened men, the risk of low-grade prostate cancer after vasectomy was (HR 1.3, 95% CI 1.15–1.49) compared to that for screened men (HR 1.01, 95% CI 0.95–1.07; p for interaction = 0.0002). In contrast, vasectomized men had a higher risk of high-grade prostate cancer (HR 1.09, 95% CI 1.00–1.18) only if they had reported PSA screening (Table 3). Interactions between vasectomy status and prostate cancer screening were also seen for localized and all cases of prostate cancer (Table 3). No effect on the age of vasectomy and prostate cancer risk was identified. In addition, all conclusions were similar when other follow-up definitions were utilized (data not shown).

DISCUSSION

Using data from over 100,000 men enrolled in the NIH-AARP Diet and Health Study with up to 28 years of follow-up, no clinically significant association between vasectomy and prostate cancer was identified. While there was a slight increased risk of overall prostate cancer, there was no identified increased risk across prostate cancer grade, stage stratification, nor mortality. This disparity is likely attributed to variations in sample size amongst the respective groups and does not represent a clinically significant increased risk of prostate cancer. Importantly, the varied interactions with prostate cancer screening also affected the interpretation of the association between vasectomy and prostate cancer. Sensitivity to analytic techniques and case definitions suggest that any identified associations between vasectomy and prostate cancer are likely spurious.

The relationship between vasectomy and the risk of prostate cancer has been under significant debate for the past three decades with conflicting data published in the literature. This debate has raised significant concern for provider and patient alike, including those who had prior vasectomy and those who were considering the procedure for future contraception. The discussion was reignited in 2014 when a prospective cohort study found an association between a history of vasectomy and an increased risk of both overall prostate cancer and high-risk prostate cancer. While investigators have suggested immune or endocrine pathways to explain the association (Mo *et al.*, 1995; Flickinger *et al.*, 1999), the lack of robust data to support a plausible biological mechanism leads most to conclude that selection bias as the most likely

Table 2 Time to event analysis of incident prostate cancer based on vasectomy status (reference group is no vasectomy).

	Multivariable analysis		Propensity-adjusted analysis		Propensity-matched cohort	
	# of events	HR (95% CI)	# of events	HR (95% CI)	# of events	HR (95% CI)
All	11235	1.050 (1.007,1.095)	11228	1.043 (1.000,1.088)	6698	1.058 (1.009,1.110)
Low Grade	7153	1.048 (0.994,1.104)	7150	1.039 (0.986,1.095)	4235	1.068 (1.006,1.135)
High Grade	3461	1.047 (0.971,1.129)	3552	0.993 (0.922,1.070)	2107	1.043 (0.957,1.136)
Fatal CaP	477	0.904 (0.730,1.118)	477	0.897 (0.724,1.111)	277	0.812 (0.640,1.031)
Localized CaP	9418	1.058 (1.011,1.108)	9413	1.052 (1.005,1.101)	5608	1.065 (1.010,1.122)
Advanced CaP	1356	1.001 (0.889,1.127)	1354	0.995 (0.884,1.121)	849	1.028 (0.898,1.176)

Models adjusted for age, marital status, education, race, state of residence, diabetes, prostate cancer screening history (PSA or DRE), family history of prostate cancer, smoking history, paternity, and BMI.

Table 3 Association between vasectomy status and prostate cancer incidence stratified by PSA screening

Vasectomy status						
	All	Low grade	High grade	Fatal PCa	Localized PCa	Advanced PCa
No PSA Screening	1.139 (1.031,1.257)	1.310 (1.154,1.487)	0.867 (0.726,1.035)	1.181 (0.789,1.767)	1.159 (1.039,1.292)	1.034 (0.791,1.353)
Prior PSA Testing	1.034 (0.988,1.082)	1.007 (0.952,1.066)	1.089 (1.004,1.182)	0.829 (0.649,1.058)	1.040 (0.990,1.093)	0.993 (0.872,1.131)
p interaction	0.0778	0.0002	0.0200	0.1327	0.0723	0.7864

explanation (Eisenberg & Lipshultz, 2010; Mosher & Jones, 2010; Giovannucci *et al.*, 1993a).

Contemporary studies have contested any association between prior vasectomy and the risk of developing prostate cancer; however, prior cohorts were not without some limitations. A study utilizing men from the Cancer Prevent Study (CPS) evaluated over 360,000 men and demonstrated no association between vasectomy and prostate cancer (Jacobs *et al.*, 2016). Next, a Canadian group created a matched cohort utilizing claims data from Ontario and also demonstrated no association between vasectomy and prostate cancer. (Nayan *et al.*, 2016). Most recently, Smith Byrne *et al.* utilized the European Prospective Investigation into Cancer and Nutrition and overall found no association between vasectomy and prostate cancer. (Smith *et al.*, 2017). However, they did identify some heterogeneity in the analysis with a higher risk for low-grade but not high-grade disease. Lack of granular data on men's sociodemographic status, PSA screening habits and gleaning vasectomy status from a survey of wives may all impact the conclusions of the studies. (Eisenberg & Lipshultz, 2010; Mosher & Jones, 2010; Awsare *et al.*, 2005). In addition to detailed data on each man's characteristics and PSA screening, our study also used additional analytic techniques (i.e. propensity adjustment and propensity matching) to attempt to account for biases inherent to observational data. Propensity score analysis is a useful technique when large baseline differences exist between treatment groups by allowing comparison of similar patients equally likely to receive the treatment of interest. In doing so, we were able to account for the potential bias created by earlier and greater access to urologic care in men who have undergone vasectomy.

The screening for prostate cancer with PSA testing presents a potential confounding factor in this analysis. Indeed, our investigation also found that an increased rate of PSA testing results an increased detection of prostate cancer. This finding in the NIH-AARP dataset confirms prior understandings of the direct relationship between PSA testing and prostate cancer incidence. Moreover, this data further corroborate the attribution of previous association between prior vasectomy and prostate cancer to selection bias and increased access to urologic care. Interestingly, our own analysis found the interaction between vasectomy and prostate cancer was modified by PSA screening differently for low-grade and high-grade diseases. We also found a trend towards a lower risk of fatal prostate cancer in vasectomized men. These inconsistencies, which are difficult to reconcile biologically with vasectomy, suggest possible biases in the relationship between vasectomy and prostate cancer, particularly related to cancer screening and access to care. Indeed, given the differences between men utilizing and not utilizing vasectomy, any residual difference in incident prostate cancer is suspected to be the result of confounding from selection bias. Such varied interactions with prostate cancer screening may also partly explain the heterogeneity in the literature as such screening practices were not available in all studies.

Certain limitations warrant mention. Vasectomy status and timing were based on self-report and may be inaccurate. Vasectomy was not queried at study onset which could introduce bias despite our follow-up time analyses. Moreover, the intended goal of the initial study was not to address theassociation between vasectomy and prostate cancer. While we found no evidence of an effect modification by age, it is possible that the relationship between prostate cancer and vasectomy could be different for men younger than those eligible for AARP membership. In addition, the lack of exact timing of vasectomy may limit the analysis. Given prostate cancer's slow growth rate, our follow-up period was relatively short. Moreover, as only 16% of those AARP members who were invited to participate ultimately returned questionnaires, volunteer bias could affect results. Importantly, there was significant effect modification between vasectomy and PSA screening. While information regarding PSA screening around the baseline and follow-up cohort was available, screening practices at other times were not directly queried.

In conclusion, the current study of over 100,000 men from around the United States found no significant association between vasectomy and prostate cancer. This should provide reassurance to patients and that vasectomy remains a safe and effective form of contraception.

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