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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Vasectomy and Risk of Prostate Cancer in a Screening Trial

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Abstract

Background: Vasectomy has been implicated as a risk factor for prostate cancer in multiple epidemiologic studies over the past 25 years. Whether this relationship is causal remains unclear. This study examines the association between vasectomy and prostate cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, which randomized men to usual care or annual prostate cancer screening.

Methods: We performed a retrospective analysis of 13-year screening and outcomes data from the PLCO trial. Multivariable Cox proportional hazards regression stratified by study arm and age at vasectomy was performed.

Results: There was an increased risk of prostate cancer in men who had undergone a vasectomy and were randomized to the usual care arm of the study (adjusted HR, 1.11; 95% confidence interval, 1.03–1.20; $P = 0.008$). There was no association between vasectomy and diagnosis of prostate cancer in men randomized to the prostate cancer screening arm. Only men undergoing vasectomy at an older age in the usual care arm of the study, but not the prostate cancer screening arm, were at increased risk of being diagnosed with prostate cancer.

Conclusions: Vasectomy was not associated with prostate cancer risk among men who were screened for prostate cancer as part of a clinical trial, but was associated with prostate cancer detection in men receiving usual care.

Impact: The positive association between vasectomy and prostate cancer is likely related to increased detection of prostate cancer based on patterns of care rather than a biological effect of vasectomy on prostate cancer development. *Cancer Epidemiol Biomarkers Prev; 26(11); 1653–9. ©2017 AACR.*

Introduction

Vasectomy is the safest and most cost effective form of permanent sterilization (1, 2). It has been estimated that more than 500,000 vasectomies are performed annually in the United States, with 11.4% of men ages 30–45 years reporting having had a vasectomy (3–5). Concerns about an increased risk of prostate cancer associated with vasectomy initially arose from case–control studies in the late 1980s and early 1990s (6–8). This association was reinforced by two large cohort studies that found an approximately 1.6-fold increase in the relative risk of prostate cancer in men who had undergone a vasectomy (9, 10). These studies led many urologists to screen vasectomized men for prostate cancer or to discourage a vasectomy in men with known risk factors or a strong family history (11). An update to previously published work using the Health Professionals Follow-up Study again identified a relationship between vasectomy and prostate cancer detection, particularly with high-grade and lethal disease (12). Conversely, recently published studies evaluating the Cancer Prevention Study (CPS)-II cohort and healthcare databases from Ontario, Canada, demonstrated no association between vasectomy and either overall prostate cancer incidence or mortality (13, 14). In addition, while it would be anticipated that having a vasectomy at a younger age would result in a longer exposure, and therefore increase the risk of prostate cancer, this has not been demonstrated (15).

The association between vasectomy and prostate cancer is inconsistent among different cohorts, and multiple meta-analyses of the data have raised concerns about methodologic issues and potential confounders (16–26). Notably, this association may be due, all or in part, to detection bias, as men who choose to have vasectomies likely have unique patterns of healthcare utilization that include being more likely to seek or undergo prostate cancer screening, and are generally under the care of a urologist (24–27).

With the widespread use of vasectomy and the high prevalence of prostate cancer, any association could be of clinical importance. Controlling for possible detection bias is of preeminent concern given that prostate cancer detection and vasectomy are two of the most common reasons for urologic consultation and men who elect to undergo a vasectomy may preferentially seek out and use healthcare resources (28, 29). To truly mitigate this bias would

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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require either randomizing men to vasectomy, which is not feasible, or standardizing prostate cancer detection protocols between men who have, and have not had, a vasectomy. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial provided a unique opportunity to assess the relationship between vasectomy and prostate cancer in a modern cohort of men who were uniformly screened for prostate cancer (30, 31). While we previously reported on the very high rate of PSA screening in both arms of the trial, we hypothesized that men in the screening arm would have undergone standardized detection protocols, while men in the control arm would have had more variable detection based on vasectomy status (32). Furthermore, if vasectomy altered the underlying predisposition to developing prostate cancer, we hypothesized that men who had a vasectomy at a younger age would have the longest exposure, and therefore the greatest increase in prostate cancer risk.

Materials and Methods

Subjects and study design

The PLCO trial randomized 76,693 men ages 55–74 years to usual care or to annual PSA screening for 6 years and annual digital rectal examination for 4 years between 1993 and 2001. The overall design and outcomes of the trial have been described in detail previously (30, 33, 34). We obtained 13-year screening and outcomes data from the PLCO prostate cancer screening trial. Details of patients included in our analyses are shown in the Supplementary Fig. S1. Of the 76,693 originally randomized, 10 withdrew consents and 679 had no follow-up (i.e., the time interval between date of randomization and date of trial exit was 0 days). In addition, $n = 2{,}824$ subjects were missing vasectomy status, which was our primary predictor of interest. As such, vasectomy status and follow-up information was available for 73,180 participants. As detailed in Supplementary Fig. S1, this number was further limited on adjusted analysis due to missing covariate information or information on age at vasectomy, with the most limited models including 60,564 subjects. We also performed multiple imputation of missing data in addition to models using only subjects for whom complete information was available.

Variables and outcomes

At study entry, subjects completed a baseline questionnaire in which they were asked about vasectomy status as assessed by the question "Have you had a vasectomy, that is, a sterilization procedure for men?" and the age range at the time of their vasectomy, which was documented as <25, 25–34, 35–44, or 45+ years. History of rectal exam and PSA screening in the preceding three years was also assessed. Data on prostate cancer including detection, staging, and survival were collected as described previously (30, 33, 35).

Relevant baseline characteristics were selected on the basis of those used in the literature previously or thought to have an association with prostate cancer (12, 36). Specifically, covariates used in previous studies examining the relationship between vasectomy and prostate cancer including race, body mass index (BMI), smoking, type II diabetes mellitus, family history of prostate cancer, and history of PSA testing and digital rectal exam prior to entry into the PLCO trial (12) as well as aspirin use, and history of hypertension (37, 38), were incorporated into the model. The primary outcome of our study was any prostate cancer diagnosis. Secondary outcomes included prostate cancer severity as classified by Gleason grade, clinical stage, and death from prostate cancer. Secondary outcomes were selected and defined to resemble those used in previous reports, namely risk of Gleason 7 or 8–10 prostate cancer, lethal prostate cancer, or advanced prostate cancer (defined as lethal or pathological stage III or IV at diagnosis; refs. 9, 12).

Age category at vasectomy was assessed at study entry. We categorized subjects into those who underwent vasectomy before age 35 and those who underwent vasectomy at age 35 or above. A waiver was obtained from the institutional review board at Weill Cornell Medical College, as data was deidentified.

Statistical analysis and reporting

All analyses were stratified by study arm given the discrepancies between groups in prostate cancer screening protocols and our hypothesis at study outset that there may be a different association between vasectomy and prostate cancer between arms. For comparison of baseline characteristics between subjects with and without vasectomy (Table 1) age-adjusted linear models, generalized linear models, and quantile regressions were used for comparing means or medians of baseline covariates and associated *P* values. For the association between a history of vasectomy and prior screening logistic regression was performed adjusting for the indicated variables.

Cox proportional hazards regression was performed to evaluate the independent association between vasectomy and prostate cancer incidence. We adjusted for age, and then additionally adjusted for factors thought to be associated with prostate cancer risk. Covariates were included in the model *a priori*, independent of univariate *P* values for the association between vasectomy and prostate cancer. Prostate cancer–free survival time was measured from the date of randomization to the date of prostate cancer diagnosis (i.e., primary outcome of interest), date of death from a cause other than prostate cancer, or date of trial exit otherwise (whichever came first; ref. 30). Subjects who died of causes other than prostate cancer or who exited the trial for other reasons were censored at their respective death/exit dates. In addition to death from a cause other than prostate cancer, censored events included last annual study update, participant withdrawal or lost contact, cutoff for data collection from the screening center, or arrival at the thirteen-year cutoff of the trial. For secondary outcomes of Gleason score, aggressiveness, and death from prostate cancer, all cancers not of the outcome of interest were censored at the time of diagnosis.

For analyses by age at vasectomy, the proportion of vasectomized men falling into the age categories at vasectomy of <25, 25–34, 35–44, or 45+, was 1.5%, 32.3%, 51.1%, and 15.2%, respectively. To yield sufficient numbers in each age grouping, grouping was simplified into <35 and 35 or above. Adjusted HRs were calculated from from a single multivariable model incorporating levels of age category at the time of vasectomy and reflect the increased (or decreased) risk of prostate cancer incidence.

We have presented all models with the maximum number of subjects with covariate information available, rather than excluding those with missing data from all analyses or using a missing-value indicator. Subjects with missing covariate data were therefore excluded from the multivariable adjusted analyses as indicated in the Supplementary Fig. S1. This method was performed because the use of a complete case analysis would

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Table 1. Age-adjusted baseline characteristics of subjects by vasectomy status and trial arm

	Control arm		Screening arm	
	No vasectomy	**Vasectomy**	**No vasectomy**	**Vasectomy**
N (%)	26,249 (72.4%)	9,987 (27.6%)	27,276 (73.0%)	10,083 (27.0%)
Age, mean (SD)[a,b]	63.3 (5.4)	61.5 (4.8)	63.1 (5.4)	61.5 (4.8)
Age at vasectomy, *n* (%)				
<25	—	155 (1.6%)	—	136 (1.4%)
25–34	—	3,201 (32.2%)	—	3,244 (32.3%)
35–44	—	5,084 (51.1%)	—	5,124 (51.1%)
45+	—	1,501 (15.1%)	—	1,527 (15.2%)
Body mass index (kg/m^2), mean (SD)	27.6 (2.6)	27.5 (4.2)	27.6 (2.5)	27.6 (4.2)
Smoking pack years, median (IQR)[a,b]	13.9 (0.0–41.6)	14.6 (0.0–43.3)	13.1 (0.0–40.6)	16.7 (0.0–42.6)
Prostate cancer family history, *n* (%)				
No	24,306 (92.6%)	9,278 (92.9%)	25,230 (92.5%)	9,337 (92.6%)
Yes	1,943 (7.4%)	709 (7.1%)	2,046 (7.5%)	746 (7.4%)
Black, *n* (%)[a,b]	1,549 (5.9%)	110 (1.1%)	1,609 (5.9%)	91 (0.9%)
Hispanic, *n* (%)[b]	656 (2.5%)	220 (2.2%)	682 (2.5%)	192 (1.9%)
Aspirin use, *n* (%)[a,b]	13,387 (51%)	5,433 (54.4%)	14,129 (51.8%)	5,263 (52.2%)
Hypertension, *n* (%)[a,b]	9,292 (35.4%)	3,246 (32.5%)	9,356 (34.3%)	3,317 (32.9%)
Diabetes, *n* (%)[a,b]	2,441 (9.3%)	767 (7.7%)	2,564 (9.4%)	766 (7.6%)
PSA test in last 3 years prior to study entry, *n* (%)[a,b]				
No	13,361 (50.9%)	4,484 (44.9%)	14,184 (52%)	4,729 (46.9%)
Yes	12,888 (49.1%)	5,503 (55.1%)	13,092 (48.0%)	5,354 (53.1%)
Digital rectal exam in 3 years prior to study entry, *n* (%)[a,b]				
No	15,014 (42.8%)	3,745 (37.5%)	11,756 (43.1%)	3,922 (38.9%)
Yes	11,235 (57.2%)	6,242 (62.5%)	15,520 (56.9%)	6,161 (61.1%)

NOTE: *P* values generated using age-adjusted linear models, generalized linear models, and quantile regressions to compare means or medians of baseline covariates.

[a]$P < 0.05$ between no vasectomy and vasectomy groups in the control arm of the trial.

[b]$P < 0.05$ between no vasectomy and vasectomy groups in the screening arm of the trial.

have been problematic due to the exclusion of prostate cancer events, and the use of a missing-value indicator was avoided as it would likely reflect a mix of actual levels of the variable, which could result in biased estimates of the overall effect of the study exposure (i.e., vasectomy status; ref. 39). Multiple imputation for missing data was also performed (Supplementary Table S2) using the Gibbs sampling procedure to impute missing values. This allowed us to run the same model as in the complete cases analysis but without loss of information. We created 5 "complete" data frames (with no missing data) with the same size as the original data frame using the mice package in R statistical software. Use of a missing indicator yielded results nearly identical to those when using multiple imputation; thus, results from that analysis are not shown.

All *P* values are two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (CI) for adjusted HRs and sub-HRs were calculated to assess the precision of the obtained estimates. All analyses were performed in Stata Version 13.1 or 14.0 (StataCorp).

Results

Participant characteristics

Data regarding vasectomy status were available for 73,180 participants of whom 9,933 (27.6%) in the control arm, and 10,032 (27.0%) in the intervention arm reported a history of vasectomy. Baseline demographic and clinical characteristics in the PLCO trial have been previously reported (30). Age-adjusted baseline characteristics between subjects who underwent a vasectomy and those that did not are shown in Table 1 according to vasectomy status and trial arm. Men who had a vasectomy differed in many of these characteristics compared with those who did not. Men with a history of vasectomy were more likely to have been screened for prostate cancer prior to study entry with PSA and digital rectal exam (Table 1). This relationship persisted even adjusting for age and other baseline characteristics ($P < 0.001$; Supplementary Table S1).

Risk of prostate cancer

In the control arm of the study, controlling for age only, men with a history of vasectomy had a HR of 1.06 [95% confidence interval (CI), 0.98–1.13; $P = 0.129$] for being diagnosed with prostate cancer. Following adjustment for other covariates including a history of screening with PSA and digital rectal exam, vasectomy was associated with an increased risk of prostate cancer in the control arm of the study (HR, 1.11; 95% CI, 1.03–1.20; $P = 0.008$; Table 2). In contrast, no such relationship was seen in the screening arm of the study in either the age or multivariable adjusted models (Table 2). This result remained the same even when applying a different technique (multiple imputation) to address missing data (Supplementary Table S2).

We then examined the relationship between vasectomy and the severity of prostate cancer. Men who underwent vasectomy were found to have an increased risk of low grade (Gleason 2–6) prostate cancer in the control arm in both the age-adjusted and multivariable models (HR, 1.12; 95% CI, 1.01–1.23; $P = 0.028$ for age-adjusted; and HR, 1.15; 95% CI, 1.03–1.27; $P = 0.012$, for multivariable model, respectively). There was no association between vasectomy and the risk of Gleason 7 or 8–10 prostate

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Table 2. Risk of prostate cancer according to vasectomy status and trial arm

	Control arm			Screening arm		
	No vasectomy	Vasectomy		No vasectomy	Vasectomy	
	HR	HR (95% CI)	*P*	HR	HR (95% CI)	*P*
Age adjusted (total $N = 73{,}180$)	1.0	1.06 (0.98–1.13)	0.129	1.0	1.00 (0.93–1.07)	0.970
(*n*)	2,785/26,075	1,082/9,933		3,206/27,140	1,138/10,032	
Time at risk, y	268,637	104,981		278,412	105,424	
Adjusted[a] (total $N = 60{,}644$)	1.0	1.11 (1.03–1.20)	0.008[b]	1.0	1.03 (0.95–1.11)	0.469
(*n*)	2,311/21,300	947/8,343		2,698/22,500	991/8,501	
Time at risk, y	219,604	88,112		231,132	89,243	

NOTE: (*n*) denotes number of subjects with prostate cancer in each category over total number in that category.

[a]Adjusted for age, BMI, smoking (pack years), family history of prostate cancer (no, or yes + maybe), black race, Hispanic identification, aspirin use, diabetes, hypertension, reported history of PSA testing in previous 3 years (none, once, and more than once) and digital rectal exam in the past three years (none, once, and more than once).

[b]$P < 0.05$ comparing vasectomy to no vasectomy within each study arm.

cancer, lethal prostate cancer, or advanced prostate cancer (12) in either study arm (Table 3).

Age at time of vasectomy

We found that there was no association between vasectomy and prostate cancer in men who had a vasectomy prior to age 35 in any of our models. However, we did see an increased risk in men who had a vasectomy at an older age in both our age-adjusted (HR, 1.11; 95% CI, 1.02–1.20; $P = 0.014$) and adjusted models (HR, 1.14; 95% CI, 1.05–1.24; $P = 0.002$), in the control arm of the study (Table 3). In contrast, there was no increased risk of prostate cancer diagnosis among men who had a vasectomy at an older age in the screening arm of the study (Table 4).

Discussion

The potential relationship between vasectomy and prostate cancer has been an ongoing area of investigation for decades, creating a challenge in properly counseling men about the risks of the procedure (9, 11). The PLCO trial randomized subjects to usual care or standardized prostate cancer screening. We recently demonstrated very high levels of PSA testing in the control arm of the PLCO trial (32). However, men who have undergone a vasectomy likely have multiple factors that alter detection of prostate cancer, other than the number of PSA tests or digital rectal exams, such as having screens performed by a urologist rather than a primary care physician. If vasectomy was associated with an increased risk of prostate cancer due to differing patterns of healthcare utilization in vasectomized men, we therefore hypothesized that we would see an association between vasectomy and prostate cancer in the control arm, but not the screening arm (where men underwent standardized screening as a part of the trial). In line with this hypothesis, we found that men who had undergone a vasectomy in the control arm of PLCO were 11% more likely to have prostate cancer detected after adjustment for a variety of factors including prostate cancer screening in the three years prior to study entry. This 11% risk in the vasectomized control arm is similar to the 10% risk of prostate cancer reported by Siddiqui and colleagues, in which they similarly attempted to control for a history of prostate cancer screening (12).

In our study, there was no increased risk of prostate cancer diagnosis in men with a history of vasectomy in the screening arm of PLCO. These were men who were highly compliant (>85%) with annual PSA and digital rectal exam and thus were rigorously screened for prostate cancer regardless of an established relationship with a urologist or predisposition to health care utilization. This finding suggests that the positive associations previously reported in the literature between vasectomy and prostate cancer detection may be the result of bias inherent to practice patterns rather than causal. The presence of this relationship in the control arm even when controlling for PSA and digital rectal exam suggests that other confounders may contribute to the alteration in risk of prostate cancer detection in vasectomized men. These may be related to being under the care of a urologist or differing attitudes toward obtaining and utilizing healthcare among vasectomized men. Our conclusions are in line with recently published data from the CPS-II cohort in which there was no association between prior vasectomy and either overall prostate cancer incidence, high-grade prostate cancer incidence, or prostate cancer mortality (13). They similarly noted that there was a slightly increased risk of diagnosis of low-grade, nonaggressive prostate cancer in those with prior vasectomy, detected during the final years of the cohorts' follow-up.

In our study, men in the control arm with a history of vasectomy were 15% more likely to be diagnosed with Gleason 2–6 prostate cancer, and we did not see any association between vasectomy and higher grade or lethal prostate cancers. In addition, in the screening arm, we found no association between vasectomy and any grade of prostate cancer or prostate cancer mortality. This stands in contrast to prior reports that have found an association between vasectomy and lethal or aggressive prostate cancer (9, 12); however, it is in line with two recent studies that did not find this association (13, 14).

One possible explanation for this discrepancy is that the length of follow-up was also not as long as some studies, such as the Health Professionals Follow-up Study (13 vs. 24 years; ref. 12). The predominance of low-grade disease seen this study likely more accurately reflects the current epidemiology of prostate cancer in the United States than prior studies utilizing cohorts established in the pre-PSA era.

Finally, we evaluated age at time of vasectomy as a predictor of being diagnosed with prostate cancer. If undergoing a vasectomy has a carcinogenic effect, one would expect that patients undergoing vasectomy at an earlier age would have a higher incidence of prostate cancer due to prolonged exposure. Contrary to this, our data show no association between vasectomy and prostate cancer in men who had a vasectomy at a younger age. We found men in the control arm older than age 34 at the time of vasectomy were 14% more likely to develop prostate cancer; however, this effect was not seen in the screening arm, again consistent with an

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Table 3. Risk of indicated outcomes by vasectomy status and trial arm

	Control arm			Screening arm		
	No vasectomy	Vasectomy		No vasectomy	Vasectomy	
	HR	HR (95% CI)	*P*	HR	HR (95% CI)	*P*
Gleason 8–10						
Age adjusted	1.0	0.93 (0.76–1.14)	0.49	1.0	1.05 (0.85–1.30)	0.64
(*n*)	387/26,049	123/9,924		333/27,093	117/10,021	
Time at risk, y	268,492	104,935		278,234	105,386	
Adjusted[a]	1.0	1.06 (0.84–1.33)	0.61	1.0	1.09 (0.86–1.38)	0.46
(*n*)	299/21,278	105/8.337		286/22,458	100/8,491	
Time at risk, y	219,476	88,086		230,962	89,209	
Gleason 7						
Age adjusted	1.0	1.01 (0.89–1.15)	0.85	1.0	1.01 (0.89–1.14)	0.91
(*n*)	933/26,049	358/9,924		996/27,093	360/10,021	
Time at risk, y	268,492	104,935		278,234	105,386	
Adjusted[a]	1.0	1.07 (0.94–1.23)	0.29	1.0	1.06 (0.93–1.21)	0.42
(*n*)	785/21,278	315/8,337		831/22,458	314/8,491	
Time at risk, y	219,476	88,086		230,962	89,209	
Gleason 2–6						
Age adjusted	1.0	1.12 (1.01–1.23)	0.03[b]	1.0	0.99 (0.90–1.08)	0.83
(*n*)	1,434/26,049	588/9,924		1,823/27,093	647/10,021	
Time at risk, y	268,492	104,935		278,234	104,935	
Adjusted[a]	1.0	1.15 (1.03 -1.27)	0.01[b]	1.0	1.01 (0.91–1.11)	0.91
(*n*)	1,200/21,278	517/8,337		1,532/22,458	564/8,491	
Time at risk, y	219,476	88,086		230,962	89,209	
Advanced prostate cancer						
Age adjusted	1.0	0.98 (0.79–1.21)	0.84	1.0	1.10 (0.91–1.34)	0.32
n	329/26,075	121/9,933		367/27,140	146/10,032	
Time at risk, y	268,637	104,981		278,412	10,542	
Adjusted[b]	1.0	1.00 (0.79–1.26)	0.993	1.0	1.15 (0.93–1.42)	0.19
(*n*)	272/21,300	101/8,343		312/22,500	128/8,501	
Time at risk, y	219,604	88,112		231,132	89,243	
Lethal prostate cancer						
Age adjusted	1.0	1.18 (0.80–1.73)	0.41	1.0	0.73 (0.47–1.12)	0.14
(*n*)	103/26,075	36/9,933		116/27,140	26/10,032	
Time at risk, y	268,637	104,981		278,412	10,542	
Adjusted[b]	1.0	1.18 (0.76–1.83)	0.46	1.0	0.76 (0.47–1.22)	0.26
(*n*)	85/21,300	28/8,343		98/22,500	22/8,501	
Time at risk, y	219,604	88,112		231,132	89,243	

NOTE: (*n*) Denotes number of subjects with prostate cancer in each category over total number in that category.

[a]Adjusted for age, BMI, smoking (pack years), family history of prostate cancer (no, or yes + maybe), black race, Hispanic identification, aspirin use, diabetes, hypertension, reported history of PSA testing in previous 3 years (none, once, and more than once), and digital rectal exam in the past three years (none, once, and more than once).

[b]$P < 0.05$ for comparison between vasectomy and no vasectomy within each study arm.

association based on altered exposure to care rather than a causal biological relationship.

Our study had several limitations that revolve around the use of the PLCO cancer screening trial cohort. Of our total cohort of 76,683 men, complete data were available for only 60,564 men in our most limited analysis. In addition, follow up in PLCO also started at trial entry rather than the date of vasectomy. As such, men who had undergone a vasectomy and developed prostate cancer prior to study entry (ages 55–74) would not be included in this cohort, introducing a selection bias, favoring our not identifying an association between vasectomy and prostate cancer.

Another limitation of our study is the very high rate of vasectomy (27%) in the PLCO cohort as compared with the general population (estimated variably at 8.7% in men over forty, up to 15.9% in men 36–45) that likely affects the representativeness of this population and generalizability (29, 40). This is likely related to the demographics of men entering the PLCO trial overlapping with those who tend to undergo vasectomy. Namely, both groups tend to be white, college educated, and married as compared with the general population (29, 41).

Limited follow up in this study also presents a significant limitation. Given the time by which prostate cancer screening advances prostate cancer diagnosis, which has been estimated at 5–7 years, also called the lead-time, this shorter (13 year) follow up is likely an important limitation of our study. This is particularly true as the length of follow up may be an important factor in the progression of prostate cancer and assessment of prostate cancer mortality. As such, this follow-up period may not be of sufficient length to assess mortality as an endpoint.

Conclusions

By taking advantage of the presence of randomized screening and control arms of the PLCO Cancer Screening Trial, we provide evidence that in the PSA era, vasectomy is likely not a risk factor for prostate cancer development but rather its detection. While additional follow up is needed to rule out a link between vasectomy and lethal prostate cancer, these data support the current American Urological Association's vasectomy guidelines, which do not support a causal association between vasectomy and prostate cancer (1). Most importantly, this study should assist in confirming the safety of vasectomy for the millions of patients and

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Table 4. Age at vasectomy and risk of prostate cancer by trial arm

		Ref[a]	Vasectomy ≤34		Vasectomy >34	
		HR	HR (95% CI)	P	HR (95% CI)	P
Control arm	Age adjusted	1.0	0.95 (0.84–1.07)	0.356	1.11 (1.02–1.20)	0.014[b]
	(*n*)	2,785/26,075	307/3,333		770/6,555	
	Adjusted[c]	1.0	0.96 (0.85–1.09)	0.499	1.14 (1.05–1.24)	0.002[b]
	(*n*)	2,311/21,300	268/2,824		675/5,483	
Screening arm	Age adjusted	1.0	0.95 (0.85–1.07)	0.404	1.02 (0.94–1.10)	0.596
	(*n*)	3,206/27,140	341/3,363		793/6,618	
	Adjusted[c]	1.0	0.98 (0.87–1.10)	0.701	1.03 (0.95–1.12)	0.470
	(*n*)	2,698/22,500	299/2,850		689/5,607	

NOTE: (*n*) Denotes number of subjects with prostate cancer in each category over total number in that category.
[a]Reference includes men without a history of vasectomy.
[b]$P < 0.05$ for comparison between vasectomy and no vasectomy within each study arm.
[c]Adjusted for age, BMI, smoking (pack years), family history of prostate cancer (no, or yes + maybe), black race, Hispanic identification, aspirin use, diabetes, hypertension, history of PSA testing in previous 3 years (none, once, and more than once) and digital rectal exam in the past three years (none, once, and more than once).

caregivers considering the risks and benefits of various forms of contraception.

Disclosure of Potential Conflicts of Interest

J.C. Hu reports receiving speakers bureau honoraria from Intuitive Surgical and Genomic Health. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the NCI.

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