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ORIGINAL ARTICLE

Prostate Cancer

The association between sexual function and prostate cancer risk in US veterans

Daniel F Zapata[1,2], Lauren E Howard[1,2], Jennifer Frank[2], Ross M Simon[1,2], Cathrine Hoyo[3], Delores J Grant[4], Stephen J Freedland[2,5], Adriana C Vidal[2,5]

Sexual dysfunction and prostate cancer are common among older men. Few studies explored the association between these two illnesses. We examined whether sexual function is associated with prostate cancer risk among older men. Among 448 men undergoing prostate biopsy at the Durham Veterans Affairs Hospital, sexual function was ascertained from the Expanded Prostate Cancer Index Composite sexual assessment. We tested the link between sexual function and prostate cancer risk adjusting for multiple demographic and clinical characteristics using logistic regression. Multinomial logistic regression was used to test the associations with risk of low-grade (Gleason ≤6) and high-grade (Gleason ≥7 or ≥4 + 3) disease versus no cancer. Of 448 men, 209 (47%) had a positive biopsy; these men were less likely to be white (43% *vs* 55%, *P* = 0.013), had higher prostate-specific antigen (PSA) (6.0 *vs* 5.4 ng ml^{-1}, *P* < 0.001), but with lower mean sexual function score (47 *vs* 54, *P* = 0.007). There was no difference in age, BMI, pack years smoked, history of heart disease and/or diabetes. After adjusting for baseline differences, sexual function was linked with a decreased risk of overall prostate cancer risk (OR: 0.91 per 10-point change in sexual function, *P* = 0.004) and high-grade disease whether defined as Gleason ≥7 (OR: 0.86, *P* = 0.001) or ≥4 + 3 (OR: 0.85, *P* = 0.009). Sexual function was unrelated to low-grade prostate cancer (OR: 0.94, *P* = 0.13). Thus, among men undergoing prostate biopsy, higher sexual function was associated with a decreased risk of overall and high-grade prostate cancer. Confirmatory studies are needed.
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INTRODUCTION

Despite prostate cancer being the second most commonly diagnosed noncutaneous malignancy in men,[1] its etiology is still unclear. There are well-established risk factors for prostate cancer including age, race, and family history.[2] Beyond prostate cancer, another very common condition among older men is erectile dysfunction (ED). ED is the most frequently diagnosed sexual dysfunction in older men affecting up to 52% of men between 40 and 70 years, and it is associated with a decreased quality of life.[3] ED and prostate cancer are very prevalent conditions among older men. To our knowledge, no study to date has examined the association between these two common conditions.

While no study has examined ED or even global sexual function and prostate cancer risk, a few studies have examined sexual activity, estimated by the number of partners or number of ejaculations, and the subsequent risk to develop prostate cancer.[4–6] However, such indicators do not account for abstinence. Likewise, a frequent sexual activity could be accompanied by poor function.

Recent data have suggested that ED may be a harbinger of heart disease.[7,8] Importantly, heart disease is associated with high cholesterol levels, obesity, metabolic syndrome, inflammation, and other processes that are thought to possibly also be important in prostate cancer etiology.[9] Indeed, we have previously shown that coronary artery disease is a significant predictor of prostate cancer risk on repeat biopsy.[10] Based on this, we hypothesized that ED and worse global sexual function would be associated with increased prostate cancer risk.

To test this hypothesis, we used the Expanded Prostate Cancer Index Composite[11] to measure sexual function among men undergoing prostate biopsy at the Durham Veterans Affairs Medical Center (DVAMC) in Durham, NC, USA, and tested the association between sexual function and biopsy outcome.

MATERIALS AND METHODS

Study population

Data collection methods have been described previously.[12,13] Briefly, men with no prior history of prostate cancer who were undergoing a prostate needle biopsy because of abnormal PSA and/or suspicious digital rectal exam were recruited to participate in an ongoing case–control study at the DVAMC. Participants were recruited between January 2007 and July 2013 from the urology clinic. Of the 1221 eligible cases, 847 consented to participate (response rate of 69%). We excluded men who had missing information on sexual function (n = 361), age (n = 1), body mass index (BMI) (n = 1), smoking status (n = 21), cardiovascular disease (n = 4) or diabetes type 2 (n = 1), and those with a PSA >50 ng dl^{-1} (n = 10), as most men with a PSA >50 ng ml^{-1} have

[1]Duke University Medical Center, Division of Urology, Department of Surgery, Durham, NC 27710, USA; [2]Durham Veterans Affairs Medical Center, Urology Division, Durham, NC 27710, USA; [3]North Carolina State University, Department of Biology, Raleigh, NC 27695, USA; [4]North Carolina Central University, Department of Biology, Durham, NC 27707, USA; [5]Department of Surgery, Division of Urology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA.
Correspondence: Dr. AC Vidal (adriana.vidal@cshs.org)
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prostate cancer and to limit the influence of outliers, resulting in a study population of 448 men. This study was approved by the Institutional Review Board at the DVAMC and written informed consent was obtained from all participants before enrollment on the study.

Data collection

Trained interviewers collected the questionnaire data which included past medical and social history, obtained anthropometric measurements (weight and height), and abstracted other data from electronic medical records. Weight was measured using a digital scale, and a stadiometer was used to measure height. These measurements were used to calculate BMI, defined as weight (in kilograms) divided by height (in meters) squared. All questionnaires were self-administered and typically filled out on the day of the biopsy or returned shortly thereafter by mail prior to the patient knowing the outcome of his biopsy. Transrectal ultrasound-guided prostate needle biopsy (TRUS) was performed in men with an abnormal DRE and/or an elevated PSA (>4.0 ng ml^{-1}). TRUS-guided biopsies were double lateral sextant prostate biopsies that obtained 12 cores per patient.

Sexual function data were obtained using the Expanded Prostate Cancer Index Composite (EPIC) sexual assessment, prior to biopsy.[11] This survey includes questions pertaining to the ability to have erections overall, ability to have an orgasm, quality and frequency of erections, overall sexual function, as well as a rating of how big a problem that participants thought their erections were. Most of these questions had a score from 1 to 5 (1 = very poor, 5 = very good). Quality of erections was measured from 1 to 4 (1 = none at all, 4 = firm enough for intercourse). To transform these scores into a continuous variable, each number was mapped to a score from 0 to 100 (1 = 0, 2 = 25, 3 = 50, 4 = 75, 5 = 100 and 1 = 0, 2 = 33, 3 = 66, 4 = 100, respectively) and then, all scores were averaged to create an overall sexual function score that ranged from 0 to 100. The variables were transformed differently if they were listed from 1 to 4 (1 = 0, 2 = 33, 3 = 66, 4 = 100) or 1 to 5 (1 = 0, 2 = 25, 3 = 50, 4 = 75, 5 = 100).

Statistical analysis

In primary analysis, we tested the hypothesis that higher sexual function scores predict a lower risk of overall prostate cancer. We compared demographic and clinical characteristics which included age, race (African American *vs* Caucasian), PSA, year of consent, BMI, pack years smoked, history of diabetes and heart disease, and sexual function score between biopsy-positive and biopsy-negative patients. Associations were tested using *t*-test for continuous, normally distributed variables, Wilcoxon rank sum test for continuous, nonnormally distributed variables, and Chi-squared test for categorical variables.

We used crude and adjusted logistic regression to test the association between sexual function per 10-point change and overall prostate cancer risk as our primary outcome. As a secondary outcome, we used multinomial logistic regression to test the association between sexual function and the risk of low-grade prostate cancer (Gleason ≤6) versus no cancer and the risk of high-grade (separate analyses were conducted defining high-grade as either Gleason ≥7 or Gleason ≥4 + 3) versus no cancer. We had insufficient men with Gleason 8–10 to examine this group separately. Of note, Gleason sum ≥7 was considered high-grade as defined by the FDA for the prostate cancer prevention trial (PCPT) and the REDUCE study.[14] All multivariable models were adjusted for possible confounders based on the previous studies, including age (continuous), PSA (log-transformed), year of consent (continuous), BMI, race (Caucasian/African American), pack years of cigarettes smoked (log-transformed + 1 to account for never smokers), heart disease (yes/no), and diabetes (yes/no). Odds ratios were only presented for our main predictor (sexual function) as interpretation of the associations with confounders of prostate cancer risk would detract from our primary outcome and lead to an increased multiple testing. Given race is a known predictor of prostate cancer, we tested whether the association between sexual function and prostate cancer risk varied by race by testing the interaction between race and sexual function in the multivariable models.

Locally weighted regression analysis (LOWESS) was used to visualize the association between sexual function and the outcomes of prostate cancer, low-grade prostate cancer, and high-grade prostate cancer.

All tests were performed using Stata 11.2 (Stata, Corp., College Station, TX, USA). Statistical significance was two-sided with $P < 0.05$.

RESULTS

Baseline demographics and clinical characteristics

Clinical and demographic characteristics of the study participants are described in **Table 1**. Our total population was 448 men, of which 209 (47%) had a positive biopsy and 239 (53%) had a negative biopsy. Overall, men with a positive biopsy were less likely to be white (43% *vs* 55%, $P = 0.013$), more recently accrued (2010 *vs* 2009, $P < 0.001$), had a higher median PSA (6.0 *vs* 5.4 ng ml^{-1}, $P < 0.001$), and had a lower average sexual function score (47 *vs* 54, $P = 0.007$), compared to men with a negative biopsy. There was no difference in age, BMI, pack years smoked, history of heart disease and/or diabetes (all $P > 0.3$) between the two groups.

Sexual function and overall prostate cancer risk

On crude analysis, higher sexual function was associated with a decreased overall risk for prostate cancer (OR: 0.93, $P = 0.015$, **Figure 1**). After adjustment for multiple clinical and demographic characteristics, higher sexual function was associated with a decreased risk of overall prostate cancer (OR: 0.91, $P = 0.004$, **Table 2**). For each

Table 1: Patient demographic and clinical characteristics

	Biopsy-negative n=239 (53%)	*Biopsy-positive n=209 (47%)*	*P*
Age (years), mean±s.d.	62.9±5.6	63.0±6.0	0.539*
Race, *n* (%)			
Caucasian	108 (55)	119 (43)	0.013$^{\delta}$
African American	131 (45)	90 (57)	
BMI (kg m^{-2}), median (Q1–Q3)	29.4 (26.1–32.8)	28.4 (26.0–32.3)	0.384†
Year of consent, median (Q1–Q3)	2009 (2008–2010)	2010 (2008–2011)	<0.001†
PSA ng ml^{-1}, median (Q1–Q3)	5.4 (4.3–6.7)	6.0 (4.7–8.1)	<0.001†
Overall sexual function score, mean±s.d.	54±30	47±32	<0.007*
Pack years smoked, mean±s.d.	7.6±6.7	8.5±7.1	0.911*
Diabetes, *n* (%)			
No	171 (72)	155 (74)	0.535$^{\delta}$
Yes	68 (28)	54 (26)	
Heart disease, *n* (%)			
No	190 (80)	164 (78)	0.790$^{\delta}$
Yes	49 (20)	45 (22)	

P values calculated by **t*-test, †Wilcoxon- rank sum test, or $^{\delta}$Chi-square test. BMI: body mass index; PSA: prostate-specific antigen; Q1: 25th percentile; Q3: 75th percentile; s.d.: standard deviation

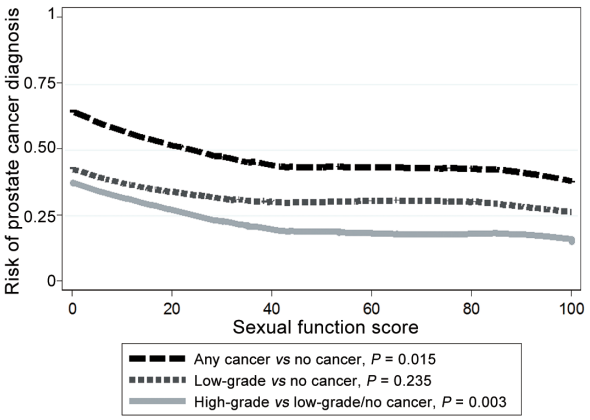

Figure 1: Sexual function and prostate cancer risk. Locally weighted regression analysis (LOWESS) was used to visualize the association between sexual function and prostate cancer. Higher sexual function was associated with a decreased overall risk for prostate cancer ($P = 0.015$) and a decreased risk of high-grade disease ($P = 0.003$), but was not associated with low-grade disease (OR: 0.96, $P = 0.235$).

10-point higher in sexual function, the risk of prostate cancer was 9% lower. Results were similar in African American and Caucasian men (P-interaction = 0.939).

Sexual function and risk of high-grade and low-grade prostate cancer

On crude analyses, higher sexual function was associated with a decreased risk of high-grade disease (OR: 0.89, $P = 0.003$, **Figure 1**), but was unrelated to low-grade disease (OR: 0.96, $P = 0.235$, **Figure 1**). After adjustment for multiple clinical and demographic characteristics, results were little changed in that higher sexual function was unrelated to low-grade prostate cancer (OR: 0.94, $P = 0.129$; **Table 2**), and it remained associated with a decreased risk of high-grade prostate cancer (OR: 0.86, $P = 0.001$). When high grade was defined as Gleason ≥4 + 3, higher sexual function remained associated with lower risk of high-grade disease (OR: 0.85, $P = 0.009$) (**Table 3**). Results were similar in African American and Caucasian men whether high-grade was defined as Gleason 3 + 4 or 4 + 3 (P-interaction ≥0.381).

Table 2: Odds ratios for the association between SF and the risk of overall, low-grade, and high-grade PC**

PC	*OR*	*95% CI*	*P*
Overall PC			
Crude	0.93	0.87–0.99	0.015
Adjusted*	0.91	0.85–0.97	0.004
Low-grade PC			
Crude	0.96	0.89–1.02	0.235
Adjusted*	0.94	0.87–1.02	0.122
High-grade PC			
Crude	0.89	0.83–0.96	0.003
Adjusted*	0.86	0.79–0.94	0.001

*Adjusted for PSA, BMI, race, and age, PSA (log-transformed), year of consent, pack-years smoking (log transformed), heart disease, and diabetes type 2; **Referents are biopsy-negative patients. PSA: prostate-specific antigen; PC: prostate cancer; BMI: body mass index; OR: odds ratio; CI: confidence interval; SF: sexual function

Table 3: Sensitivity analysis: Redefining high-risk as Gleason 4+3 (n=43)

PC	*OR*	*95% CI*	*P*
Total PC			
Crude	0.93	0.87–0.99	0.015
Adjusted*	0.91	0.85–0.97	0.004
Low-grade (n=165) PC			
Crude	0.94	0.88–1.00	0.053
Adjusted*	0.92	0.85–0.98	0.015
High-grade PC			
Crude	0.88	0.79–0.97	0.015
Adjusted*	0.85	0.76–0.96	0.009

*Adjusted for BMI, PSA (log-transformed), race and age. BMI: body mass index; PSA: prostate-specific antigen; PC: prostate cancer; OR: odds ratio; CI: confidence interval

DISCUSSION

Although both prostate cancer and ED are common conditions among older men, to the best of our knowledge, no study has examined the association between the sexual function and prostate cancer risk. To address this gap, we analyzed the association between sexual function and the risk of prostate cancer diagnosis among veteran men and found that men with increased sexual function were less likely to be diagnosed with prostate cancer and high-grade cancer compared to men with poor function. Although this is the first study analyzing this association and confirmatory studies are needed, if confirmed in future studies, these data suggest that better sexual function may be associated with lower prostate cancer risk, especially lower risk of high-grade prostate cancer.

While no study has examined the association between sexual function and prostate cancer risk, a few studies examined the association between sexual activity (number of partners, number of ejaculations, STIs, etc.) and prostate cancer risk, and the findings are contradictory.[4–6,15–17] Dennis and Dawson[16] showed in a meta-analysis that men with a history of sexually transmitted infections are at an increased risk of developing prostate cancer. However, recently, Spence *et al.*[6] showed no association. Moreover, in a population-based case–control study, Giles *et al.*[4] analyzed the association between the number of sexual partners and the risk of prostate cancer, and found no association between the number of female sexual partners and the risk of prostate cancer. However, Spence *et al.*[6] showed that an increased number of female sexual partners was negatively associated with the risk of prostate cancer. Moreover, studies that analyzed the association between ejaculatory frequency and the risk of prostate cancer showed that increased ejaculatory frequency, especially early in adult life, is negatively associated with the subsequent risk of prostate cancer.[4,5] As such, there is still much controversy when analyzing sexual activity factors with subsequent prostate cancer risk.

Recent studies have proposed that ED may be an indicator of heart disease.[7,8,10] For example, Inman *et al.* in a population-based longitudinal study of 2447 men followed for 10 years showed that when ED occurs in men aged 40–49 years, it is associated with an increased risk of cardiac events.[8] In addition, Thompson *et al.* found that among 18 882 men who participated in the Prostate Cancer Prevention Trial (PCPT) and were followed for 7 years, ED may be a harbinger of cardiovascular events.[7] Relevantly, it is well known that cardiovascular disease is associated with different metabolic conditions such as hypercholesterolemia, diabetes, obesity, and inflammation among others.[18,19] The importance of this is that recent data suggest that these factors may also play a role in the development of prostate cancer, particularly aggressive prostate cancer.[9,10,20] In fact, we previously showed that among 8122 men who participated in the 4-year long REDUCE trial, coronary artery disease was a substantial predictor of prostate cancer risk including high-grade disease.[10] Based on these findings, we hypothesized that poor sexual function may be a marker of poor metabolic conditions that not only predict future cardiovascular risk, but would also predispose to prostate cancer.

In our study, we found that men with better overall sexual function were at a decreased risk of overall and high-grade prostate cancer diagnosis, though, no association was found with low-grade disease. Importantly, after adjusting for different variables such as age, BMI, race, pack years of cigarettes smoked, history of heart disease and diabetes, sexual function was an independent predictor of overall and high-grade prostate cancer diagnosis. However, the history of heart disease is not a perfect measure of a patient's actual metabolic status. Moreover, we did not have information regarding glucose levels or metabolic syndrome, which have also shown to be involved in the development of prostate cancer and ultimately have an impact on the association between sexual function and prostate cancer risk.

Although our findings support our underlying hypothesis, alternative explanations must be entertained. For example, ED in some men may relate to other factors such as hormonal imbalances or smoking,[3] which may also play a role in prostate cancer. Although it is not clear whether there is an association between smoking and the risk of prostate cancer, the preponderance of the literature supports that smoking is a predictor for more aggressive and fatal disease.[21] In addition, while the role of hormonal activity in prostate cancer risk is hotly debated, it remains plausible that androgen activity may mediate the link between sexual function and prostate cancer risk. For example, hypogonadism is well known to be associated with sexual dysfunction. As such, it is intriguing that some studies have found that low androgen levels are correlated with more aggressive cancers,[22,23] in-line with our data that poor sexual function correlates with high-grade prostate cancer. However, a large body of contradictory literature exists on the role of androgens and prostate cancer, and poor sexual function is not solely due to low androgens.[24] In addition, studies have proposed that an increased number of ejaculations, which may correlate with better sexual function, helps eliminate toxins from the prostate and boosts immune function in the prostate.[25,26] Finally, better sexual function may be associated with other unmeasured factors (e.g., better diet, regular physical activity, etc.), which could mediate our observed association. Ultimately, future studies are needed both to confirm our findings and if confirmed to elucidate the underlying mechanism for these associations.

Our study had some limitations. As a case–control study, our study is subjected to recall bias. However, as questionnaires were returned prior to men knowing whether they had cancer or not, any recall bias which occurred would have been nondifferential, bringing associations toward the null. Likewise, our study is subjected to possible reverse causation. To minimize this, we *a priori* eliminated any men with advanced prostate cancer defined as PSA >50 ng ml^{-1}. Furthermore, our response rate was not 100% creating potential selection bias in whom participated in our study. How this may have affected our results is unknown. To assess the case–control status, we used prostate biopsy outcomes. It is well known that some men with a negative biopsy still harbor prostate cancer. However, the rate of misclassification of these men on repeat biopsy is low (~15%),[27] and misclassifications at this level are unlikely to change our results.[28] While the EPIC questionnaire was developed to measure functional outcomes after prostate cancer treatment, it has been demonstrated that it is a valid tool to use among untreated men with prostate cancer as well.[29] EPIC is, thus, a valid instrument to measure sexual function in a clinical setting.[29] In addition, we did not have information that would have been very informative for understanding the potential mechanisms linking sexual function with prostate cancer risk such as serum cholesterol, insulin, sex steroid hormone levels including testosterone, or inflammatory markers as well as medication usage, such as testosterone replacement and/or sildenafil among others. In addition, as all studies, our results are subjected to type I error rates. Finally, our study only examined veterans. As such, this could limit the generalizability of our results to the general population.

In summary, to the best of our knowledge, this is the first study to analyze the association between sexual function and the risk of prostate cancer. Among men undergoing prostate biopsy, we found an inverse association between sexual function and the risk of overall and high-grade prostate cancer. Confirmatory studies are needed to validate our results.

AUTHOR CONTRIBUTIONS

DFZ has made substantial contributions to the conception of the study; LEH ran statistical analysis; JF helped with the acquisition of data; RMS, SJF, and ACV contributed to the interpretation of data; DFZ, CH, DJG, SJF, and ACV have been involved in drafting the manuscript and revising it critically for important intellectual content; and DFZ, LEH, JF, RMS, CH, DJG, SJF, and ACV have given final approval of the version to be published.

COMPETING INTERESTS

All authors declare no competing financial interests.

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