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Authors

Le, Jesse D Cooperberg, Matthew R Sadetsky, Natalia <u>et al.</u>

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BJUI Changes in specific domains of sexual function and sexual bother after radical prostatectomy

Jesse D. Le, Matthew R. Cooperberg, Natalia Sadetsky, Adam B. Hittelman*, Maxwell V. Meng, Janet E. Cowan, David M. Latini⁺, Peter R. Carroll and the CaPSURE Investigators

University of California San Francisco, San Francisco, CA, *Yale School of Medicine, New Haven, CT, and ⁺Baylor College of Medicine and Michael E. DeBakey VA Medical Center, Houston, TX, USA Accepted for publication 9 November 2009

Study Type – Therapy (outcomes research) Level of Evidence 2c

OBJECTIVE

To quantitatively assess the effect of radical prostatectomy (RP) on the specific domains that comprise overall sexual function (SF), focusing on the relationships among these domains and overall SF, and to identify predictors for recovery of SF over time, as a decline in SF and sexual bother (SB) are known potential complications of treatment for prostate cancer.

PATIENTS AND METHODS

Within the Cancer of the Prostate Strategic Urologic Research Endeavor database, we identified men diagnosed between 1995 and 2001 with localized prostate cancer treated with RP. SF and SB outcomes, measured using the University of California Los Angeles Prostate Cancer Index, were assessed at 6-month intervals for 4 years after RP.

RESULTS

In all, 620 men met the study criteria; at 6 months after RP, overall and all the specific domains of SF declined, with improvement in most specific domains by 2 years after RP. The greatest declines were in the ability to achieve erections, high-guality erections, and frequent erections; these domains were also most strongly correlated with overall SF. Sexual desire was relatively preserved, and there was a weak correlation between overall SF and sexual desire after RP, when there was the greatest discrepancy between sexual desire and other domains of function. SB showed continued improvement over time to 4 years but was not well correlated with any measurements of SF assessed. Younger age, college education, sexual aid and medication use, the absence of comorbid conditions, and nerve-sparing surgery were

predictive of significant recovery of function in several specific domains of SF.

CONCLUSIONS

RP affects specific domains of SF to differing degrees. Compromised erectile function is most commonly reported among these specific domains and seems to play a more dominant role in determining overall SF, but notably none of the domains of function were closely linked to SB. Because education is protective in the perception of bother, appropriate counselling and the setting of expectations for outcomes in overall and specific domains of SF might lead to improved quality of life after treatment for prostate cancer.

KEYWORDS

prostate cancer, radical prostatectomy, sexual function, sexual bother, quality of life

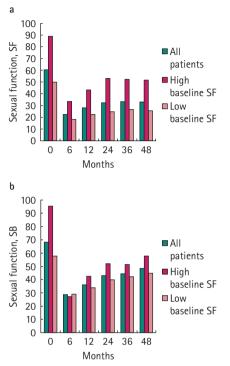
INTRODUCTION

Prostate cancer represents the second leading cause of cancer mortality and is the most common noncutaneous cancer in American men, with an estimated 192 280 new diagnoses in 2009 [1]. Whereas historically physicians have focused on recurrence and survival as the primary outcomes of interest with interventions for prostate cancer, the success of various therapeutic options and stage migration to more pathologically organ-confined cancers [2,3], and the protracted natural history of the disease [4], have led to a greater focus on other outcomes of treatment, specifically issues focused on health-related quality of life (HRQL).

Many studies have been conducted to compare HRQL outcomes [5–8]. HRQL issues clearly play a role in the decision-making process, and studies have suggested that patients might choose specific treatments to optimize HRQL over survival [9]. Among the various forms of treatment, general HRQL appears to be mostly unaffected and patient satisfaction equivalent [5]. However, diseasespecific HRQL outcomes vary among treatments in many domains. Decreased sexual function (SF) is a well-known potential complication of all active treatments for prostate cancer, including radical prostatectomy (RP) [10]. SF is multifaceted, and the effect of treatment on its specific domains has also been examined, including the effect of surgery on erections and successful intercourse [11,12], sexual desire [13], and orgasm and ejaculation [14,15]. In addition, studies evaluating the effect of RP on sexual bother (SB) have also been reported [10,16]. Although the effects of prostate cancer treatment on SF specific domains have

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FIG. 1. (a) Overall SF scores after RP; a high baselineSF was defined as a PCI SF summary score of 80–100;(b) SB scores after RP.



previously been reported, less attention has been focused on the interaction among these domains.

The goal of this study was to assess the effect of RP on specific domains of SF, focusing on the relationships among these domains and overall SF and SB. This knowledge will assist physicians and patients in anticipating outcomes, educating and managing expectations, and facilitating preoperative decision-making.

PATIENTS AND METHODS

Participants were men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study, a longitudinal, observational disease registry for men with biopsy confirmed prostate cancer. The CaPSURE database contains demographic, clinical, treatment and outcomes data for >13 000 men with prostate cancer treated at 40 clinical sites nationwide. Men are recruited by urologists at each site, and they complete a self-administered questionnaire upon enrolment into the study and every 6 months thereafter. CaPSURE questionnaires include the University of California Los Angeles (UCLA) Prostate Cancer Index (PCI) survey to assess HRQL [17].

Clinical variables collected include PSA level at diagnosis. Gleason score, clinical T stage, body mass index, presence of specific pretreatment comorbidities related to SF (such as hypertension, heart disease, stroke, diabetes, kidney disease, and urinary conditions including dysuria, haematuria and LUTS), and use of phosphodiesterase-5 inhibitors or sexual aids. Clinical risk categories were based on a modification of the risk groups of D'Amico et al. [18]. Patients were considered as: low-risk if they had a PSA level of <10 ng/ mL, Gleason sum of <7 with no primary or secondary Gleason of 4 or 5, and clinical stage T1-T2a; intermediate-risk if they had a PSA level of 10.1-20 ng/mL, Gleason sum 7 or Gleason secondary 4 or 5, or T stage cT2b-2c; and high-risk if they had a PSA level of >20 ng/mL, Gleason sum >7 or Gleason primary 4 or 5, or T stage cT3a. More detailed descriptions of the CaPSURE project methods are described elsewhere [19].

Patients with ≥4 years of follow-up data who were newly diagnosed at enrollment and who had RP as the primary treatment from 1995 to 2001 were included in this study. Patients who received neoadjuvant and/or adjuvant therapy were excluded; 620 patients thus constituted the analytic dataset.

The UCLA PCI is a self-reported questionnaire that measures sexual, urinary, and bowel function and bother for men with prostate cancer. The measure has been used extensively in research on prostate cancer HRQL, and has been shown to be both reliable and valid when used as a summary measure [17]. In terms of SF, this analysis focuses on eight subscale questions (sexual desire, ability to achieve erections, ability to achieve orgasm, guality of erections, frequency of erections, awakening with an erection, frequency of intercourse, and SF in the last 4 weeks). Responses to these questions contribute to the SF summary score. The PCI assesses the amount of associated bother measured with one question on patients' SB in the last 4 weeks. In the present study we used responses to the PCI SF subscale questions as a measure of specific domains of SF. and we used the SF summary score as a measure of overall SF.

Specific domains are scored on 3-, 4- and 5point scales, and are scaled relative to a maximum of 100 points. Higher scores indicate better HRQL. We created binary outcome variables for specific domains of SF based on thresholds for high and low functioning in each of these areas. Six outcomes were defined according to previous work by Krupski *et al.* [20], and the remaining four were adapted to the PCI from the Prostate Cancer Outcomes Study items and standards proposed by Penson *et al.* [11]. Throughout this report a high SF was defined as an overall SF score of \geq 80, as defined by Krupski *et al.* [20].

The demographic and clinical characteristics at baseline were evaluated by chi-square analysis for categorical and ANOVA for continuous variables. Cronbach's α was calculated to assess internal consistency. The Pearson correlation coefficient (r) was used to test the strength of correlation among specific domains and overall SF. The association between binary outcome variables for specific domains and various clinical and demographic variables over time was evaluated with a generalized linear regression model. These repeated measures models used generalized estimating equations to account for multiple comparisons of discrete, correlated outcomes. Analyses modelled the probability of achieving high function in each SF domain.

RESULTS

The characteristics of the 620 patients analysed are summarized in Table 1; the mean (SD) age was 61.4 (6.8) years. Most patients had low- to intermediate-risk characteristics, including a PSA level of <10 ng/mL (86%), stage T1 or T2 (98%) and a Gleason score of <6 (76%). Reliability analysis of the sample showed that responses to the PCI questionnaire had high internal consistency at baseline (Cronbach's α , 0.92), 1 year (0.90) and 2 years after RP (0.90).

We compared trends in overall SF over time in all patients with trends for subpopulations stratified by low (0–79) and high (80–100) baseline overall SF [20] (Fig. 1a). Only 28% of men met the criteria for a high baseline overall SF. This subset of patients had a nadir in function at 6 months after RP, with partial recovery of function to a mean (SD) overall SF score of 53 (25) at 2 years after RP. Patients

TABLE 1 The demographic and clinical characteristics of patients undergoing RP

Variable	n (%)
Demographic	
Age at diagnosis, years	
<60	241 (39)
60–64	155 (25)
≥65	224 (36)
Race	FF ((00)
White Other	554 (89)
Education	66 (11)
High school graduate or less	205 (33)
Some college	119 (19)
College graduate	292 (47)
Income level	. ,
Low	289 (49)
Intermediate	216 (37)
High	81 (14)
Relationship	
In a relationship	580 (94)
Single	35 (6)
Insurance Mediates and supplement	124 (20)
Medicare and supplement Medicare	124 (20) 57 (9)
Private	393 (63)
Other/None	46 (7)
Clinical	
PSA level, ng/mL	
≤4	88 (15)
4.1-10	423 (71)
10.1–20	69 (12)
>20	18 (3)
Clinical T stage	
T1 T2	324 (54)
T2 T3	261 (44) 12 (2)
Biopsy Gleason total	12 (2)
2-4	15 (2)
5-6	447 (74)
7	127 (21)
8–10	19 (3)
Clinical risk category	
Low	289 (49)
Intermediate	216 (37)
High	81 (14)
Nerve-sparing RP	407 (00)
No	127 (20)
Yes Unknown	413 (67) 80 (13)
Body mass index (kg/m ²)	60 (13)
Normal (<25.0)	155 (25)
Overweight (25.0–29.9)	348 (57)
Obese (≥30.0)	110 (18)
SF-related comorbidities	. ,
None	282 (46)
1	227 (37)
≥2	107 (17)
ED medication at 6 months after RP	127 (20)
Use of sexual device	121 (20)

Categories might not total to N due to missing values. Percentages might not total 100 due to rounding.

FIG. 2. The percentage of men reporting high function in specific domains of SF after RP. High function in specific domains is defined in Table 2.

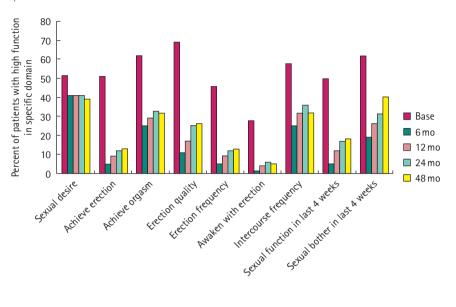
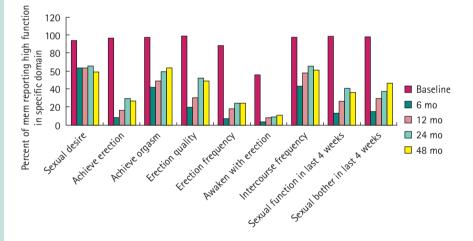


FIG. 3. The percentage of men with a high baseline SF reporting high function in specific domains of SF after RP. High baseline SF was defined as a PCI SF summary score of 80–100. High function in specific domains is defined in Table 2.



with a low overall SF score at baseline also recovered function over the same period, with a mean score of 25 (22) at 2 years. There was no additional improvement in mean overall SF score in either group at 4 years after RP. However, patients in both groups continued to have less bother over time (Fig. 1b). At 4 years, the SB score for the high-baseline SF group was 58 (36) and for the low-baseline SF group was 45 (39).

To assess changes in specific domains of SF, we assessed the percentage of men reporting high function in each domain after RP (Fig. 2); high function thresholds are defined in Table 2. Most men reported at least some compromise at baseline, with the most baseline dysfunction reported in frequency of erection and awakening with erections. The largest declines in function from before treatment to 4 years after RP were in the ability to achieve erections, quality of erections, and awakening with erections. The least change was in sexual desire, but it was less likely to improve over time. Performance in all other specific domains improved between 6 months and 2 years after RP. The pattern of effect on specific domains of SF was similar when considering men with a high baseline SF (Fig. 3). Patients reported

TABLE 2 Specific domain definitions for high and low SF

PCI component (in last			
4 weeks)	High function	Low function	Source
Level of sexual desire	Very good	Fair	[11]
	Good	Poor	
		Very Poor	
Ability to have an erection	Very good	Fair	[11]
	Good	Poor	
		Very Poor	
Ability to reach orgasm	Very good	Fair	[11]
	Good	Poor	
		Very poor	
Usual quality of erections	Firm enough for intercourse	Firm enough for masturbation and foreplay only	[20]
		Not firm enough for any sexual activity	
		None at all	
Frequency of erections	Whenever I wanted	More than half the time	[20]
		About half the time	
		Less than the time	
		Never	
Awakening with an erection	Very often	Not often	[20]
	Often	Seldom	
		Never	
Frequency of intercourse	Yes, more than once Yes, once	None	[20]
SF	Very good	Fair	[20]
	Good	Poor	
		Very poor	
SB	No problem	Small problem	[11]
	Very small problem	Moderate problem	
	, , , , , , , , , , , , , , , , , , , ,	Big problem	
Overall SF score	80-100	<80	[20]

reduced SB over the entire study period, with 40% of all men and 47% of men with high SF scores at baseline reporting 'no problem' or a 'very small problem' with their given level of function at 4 years after RP.

The strength of correlations among overall SF and its specific domains varied greatly. Table 3 shows Pearson's correlation coefficients at 6 months after RP: overall SF was most strongly correlated with the ability to achieve erections, erection quality, and erection frequency, and SF in the last 4 weeks. There were also relatively strong correlations between overall SF and the ability to achieve orgasm and frequency of intercourse. However, overall SF was only weakly correlated with sexual desire and awakening with erections. In terms of sexual desire, the correlation between overall SF and sexual desire decreased markedly from a baseline r = 0.75 (not shown in Table 3) to 0.52 at 6 months after RP. When considering the correlation between the subscale question specifically assessing SF over the last 4 weeks with the other subscale questions, the trends were similar. None of the specific domains of SF had a strong correlation with SB.

Repeated-measures regression models were used to identify predictors of improvement for each specific domain of SF, controlling for multiple variables over time. Significant improvements in function were associated with younger age, erectile device and medication use, RP nerve-sparing surgery, more education, and the absence of comorbid conditions. The odds of having high function in each specific domain for various

TABLE 3 Pearson's correlation coefficient among overall SF, SB and specific domain scores at 6 months after RP

	Sexual	Achieve	Achieve	Erection	Erection	Awaken with	Intercourse	SF last
Domain	desire	erection	orgasm	quality	frequency	erection	frequency	4 weeks
Sexual desire	1.00							
Achieve erection	0.23	1.00						
Achieve orgasm	0.47	0.47	1.00					
Erection quality	0.26	0.71	0.49	1.00				
Erection frequency	0.19	0.73	0.40	0.67	1.00			
Awaken with erection	0.09	0.54	0.18	0.48	0.51	1.00		
Intercourse frequency	0.23	0.45	0.40	0.50	0.40	0.25	1.00	
SF last 4 week	0.29	0.76	0.55	0.67	0.70	0.45	0.64	1.00
SB last 4 week	*	0.38	0.21	0.27	0.41	0.22	0.14	0.44
Overall SF	0.52	0.81	0.72	0.83	0.77	0.53	0.71	0.86

All P < 0.01, except * not significant. Comparisons omitted where redundant.

Age - - - - - - - - 1.61 1.56 - - - 1.61 1.56 - - - 1.61 1.56 - - - - 1.61 1.56 - - - 1.61 1.56 - - - 1.61 1.56 - - - - 1.61 1.56 - - - - 1.61 1.56 - - - - 1.61 1.56 - - - - 1.61 1.56 - - - - 1.61 1.56 - - - - 1.56 1.55 2.11 2.22 2.16 1.92 1.83 1.86 1.92 1.31-2.83'' (1.18-2.86)'' (1.31-2.63)'' (1.34-2.84)''' - ED 0.02 0.03 - - 0.132 0.66 - 0.66 - 0.661 - 0.61 - 0.143 2.04 1.43-2.81''' 1.43-2.81'''' 1.43-2.81''''''''' - 1.61	Comparison	Sexual desire	Achieve erection	Achieve orgasm	Erection quality	Erection frequency	Awaken with erection	Intercourse last 4 weeks	SF last last 4 weeks	SB last 4 weeks
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- $(0.41-0.83)^*$ $(0.47-0.87)^*$ - $(0.43-0.87)^*$ - (0.46-0.91) $(0.55-0.91)^*$ ≥2 vs none - 0.42 0.64 - 0.43 0.46 0.57 0.57 0.68	SF-related comorbid	ities								
≥2 vs none – 0.42 0.64 – 0.43 0.46 0.57 0.57 0.68	1 vs none	-			-		-	-		
		-	· · · · · ·		-		-	-	· · · · ·	(0.55–0.97)
	≥2 vs none	-			-					

Odds ratio of achieving high function in each specific domain given with 95% Cl when significant (P < 0.05, except where *P < 0.01).

comparison groups are given in Table 4. There were no significant trends with race, relationship status, or clinical risk group.

DISCUSSION

The management of localized prostate cancer remains controversial, and most patients with early-stage disease have several treatment options available. Downward stage migration at diagnosis and improved cancer-specific survival have lead to a greater focus on treatment-related morbidity and HRQL. Although much information has been collected on SF after RP, less focus has been placed on the specific domains of function that comprise SF and the interaction between these specific domains and the assessment of overall SF. In the present analysis we evaluated SF outcomes, focusing on the effect of RP on specific domains of SF as measured by the PCI survey [17] in the CaPSURE population. We hypothesized that while an overall assessment of SF offers a general summary, surgery affects specific domains of function differently, and that further, these specific domains of SF vary in their relative contributions to overall SF. This type of analysis might provide new information for patients and physicians about how SF changes after RP, and offers an opportunity for education and intervention.

Our study outlines the baseline and longitudinal outcomes of both overall and specific domains of SF in a group of men undergoing RP. Many patients have compromised SF at baseline. The largest declines were in the four erection domains (ability to achieve erections, erection frequency, erection guality, awakening with erections), and the least decline was in sexual desire. There were declines in all specific domains at 6 months, with improvement of most domains at 2 years. This finding was similar to that in a study by Penson et al. [11], that evaluated sexual outcomes after RP, confirming a nadir of SF at 6 months, and noting improvement at 2 years, with a small minority steadily improving through to 5 years. The findings were similar when we examined the subset of patients with higher baseline SF. There was a large variation in our study population, but the degree of SB that men experienced seemed to improve over the 4-year study interval, despite a less robust improvement in function from 2 to 4 years after RP.

Analysis of the correlation between overall SF and specific domains showed the strongest correlations with three of four erection domains assessed by the PCI (ability to achieve, frequency, and quality). Overall SF scores reflect an averaged scaled score of each specific domain [17], and because four of the eight PCI domains assess erections, a strong correlation between erections and overall SF might be expected. To overcome this possible bias, we examined correlations between patient-reported SF in the past 4 weeks and other domains of function; we also saw a similar pattern here.

Weaker correlations with frequency of intercourse and awakening with erections indicate that these domains might not play as dominant role in driving perceived overall SF. or possibly that men tend to define their SF largely in terms of their erections. The correlation between SF and sexual desire decreased markedly after RP. This result shows a more complex interaction between sexual desire and SF, given that the relative preservation of sexual desire after surgery concurrent with larger functional losses in other domains is not strongly linked to the perception of preserved SF. As previously reported by Dahn et al. [13], there might be a need to independently examine sexual desire in HRQL considerations when sexual desire and other domains of function diverge.

A recent review by Mulhall [21] found large variation in the acquisition and reporting of SF outcomes after RP. Among the variety of questionnaires available to investigators, the most commonly used validated questionnaires are the PCI (or its Expanded Prostate Index Composite, EPIC) [22] and the International Index of Erectile Function (IIEF) [23] (or its abbreviated IIEF-5 also known as the Sexual Health Inventory for Men, SHIM) [24]. In a review of the studies on SF in reports on cancer, the National Institutes of Health's Cancer Patient-Reported Outcomes Measurement Information System group reported that the PCI/EPIC was used in 34% and the IIEF/SHIM in 31% of 257 studies examined [25].

While the IIEF was developed to evaluate erectile dysfunction (ED) in general, the PCI was developed for disease-specific HRQL assessment in men with prostate cancer. Like the PCI, the IIEF also contains questions pertaining to the specific domains of erection, intercourse, orgasm, desire, and overall satisfaction with function. The SHIM includes only questions on erection as it pertains to intercourse. While the IIEF and SHIM have validated diagnostic thresholds for the severity of ED [26,27], neither the PCI nor EPIC have such validated threshold ranges.

Given the widespread use of both of these questionnaire types, it is therefore important to consider the relationship between them. particularly how the PCI-derived results from this study can be interpreted in terms of the IIEF. Schroeck et al. [28] found a high degree of correlation between the SHIM and EPIC SF summary scores in men with prostate cancer, while noting that the EPIC seemed to provide more discriminating information at the highest and lowest spectrums of SF according to the SHIM, as these men had wide-ranging EPIC scores. While no similar studies exist relating specific domains of SF between the questionnaire types, it is reasonable to believe that these too might share similar trends. While the IIEF assesses only SF, the PCI assesses both SF and SB; thus our analysis of SB is unique to the PCI.

Previous studies reported that the most consistent predictors of compromised SF were non-nerve-sparing surgery, greater age at surgery, more pretreatment comorbidities, and a lower level of education [10–12,29–31]. In the present study, we examined patient demographic and clinical characteristics as predictors of improvement in specific domains of SF and confirm these findings. Although education correlated with age and race in the present cohort, Knight *et al.* [31] identified it as an independent predictor of SF in a group of men in the Veterans Affairs Health Care System, in which access to care is even across sociodemographic groups.

Previous work showed that up to 75% of patients will not use sexual aids after RP [32], and that many patients will discontinue using sexual aids within a year after surgery, despite effectively attaining erections while using them [33]. In the present study, 20% of patients reported using some ED device after RP, and 20% reported using medications at 6 months of follow-up. There was a significant association between the use of phosphodiesterase-5 inhibitors and devices for ED, and improvements in erection quality, orgasm, and frequency of intercourse. Patients not using sexual aids were twice as likely to report improved SB, but unfortunately the question of whether SB was a cause or result of men using ED devices and medications cannot be fully addressed by this study.

Previous studies showed that SF and SB do not always correlate, as perception of the problem does not necessarily reflect the level of dysfunction [10,16]. The present study showed that SB was not closely correlated to any of the other measures of SF as measured by the PCI, a widely used survey to assess HRQL. This finding reiterates the complexity of the relationship between SF and perceived SB that patients experience. We found that those men with a high school education or less were half as likely to have reduced SB than were college graduates. Knight et al. [31] also found a correlation between low education level and poor SF outcomes after RP, indicating that patients' understanding and interpretation of surgical outcomes might make them vulnerable to adverse HRQL outcomes. Thus, if education is protective against poor SF outcomes, an increased effort to provide preoperative counselling, and provide more realistic expectations of treatment outcomes and assistance in managing treatmentrelated adverse effects, might improve sexual outcomes.

This study has several limitations. The UCLA PCI is an instrument measuring overall function, representing the composite of specific domains of SF. Although this instrument provides a useful, broad definition of overall SF, we chose to examine the individual questions of the PCI to better understand how specific domains are affected by RP, with the intention of expanding the opportunities for intervention and/or education. The UCLA PCI questionnaire has been validated only as a unitary scale [17]; the individual items have not specifically been validated. While this might limit our ability to make definitive statements about each aspect of SF, we feel that the specific domain scores provide valuable information. Krupski et al. [20] also used individual specific domain scores to assess definitions of potency. In addition, we created binary thresholds for the components of SF to distinguish between high and low SF for each SF item. While some information is lost by collapsing our data in this manner, we feel that these stratifications provide a more clinically relevant means of assessing performance. Our definition for nerve-sparing surgery did not differentiate between unilateral and bilateral nervesparing, potentially diluting the improved outcomes of patients receiving bilateral nerve-sparing RP. Nevertheless, there were still significant differences in most outcomes evaluated. This study was a retrospective

analysis, and CaPSURE collects data without regard to hypothesis at sites not chosen at random. However, CaPSURE reflects a diverse mix of locations and practice types, and is one of the few large population-based cohorts available for longitudinal analysis. As such, we were able to study a patient population with comprehensive 4-year follow-up for HRQL data.

In conclusion, treatment for prostate cancer carries the potential risk of compromised SF and increased SB. RP affects specific domains of SF (e.g. assessment of erections, desire, orgasm, and intercourse) to differing degrees. While sexual desire is relatively preserved. compromise is most commonly reported in the assessment of erectile function, which seems to play a dominant role in shaping overall SF. None of the domains of function are closely linked to SB, but a higher level of education is predictive of a reduction in perceived SB. This underscores the importance of appropriate counselling in setting patients' expectations for the outcomes in specific domains of SF, which might lead to improved HRQL outcomes.

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The current CaPSURE Investigators are: Peter R. Carroll, MD (University of California, San Francisco, San Francisco, CA); James S. Cochran, MD (Urology Clinics of North Texas, Dallas, TX); Christopher J. Kane, MD (Veterans Administration Medical Center, San Francisco, CA); Donald P. Finnerty, MD (PAPP Clinic, Newnan, GA); Eugene V. Kramolowsky, MD (The Virginia Urology Center, Richmond, VA); Robert M. Segaul, MD (Urology Associates of West Broward, Sunrise, FL); Paul Sieber, MD (Urological Associates of Lancaster, Lancaster, PA); Stanley A. Brosman, MD (Pacific Urology Institute, Santa Monica, CA); Lynn W. Conrad, MD (The Conrad Pearson Clinic, Germantown, TN); Ronald A. Chee-Awai, MD (Urologic Institute of New Orleans, Marrero, LA); Michael Flanagan, MD (Urology Specialists, PC, Waterbury, CT); Jeffrey K. Cohen, MD (Triangle Urology Group, Pittsburgh, PA); Jerrold Sharkey, MD (Urology Health Center, New Port Richey, FL); Thomas W. Coleman, MD (Bay Urology Services, Mobile, AL); Elliott C. Silbar, MD (Clinic of Urology, SC, Milwaukee, WI); Paul S. Ray, DO (John H Stroger Hospital of Cook County, Chicago, IL); David Noves, MD (Berkshire Urological Associates, PC, Pittsfield, MA); Mohammed Mostafavi, MD (Urology

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CONFLICT OF INTEREST

None declared.

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Correspondence: Peter R. Carroll, Department of Urology, University of California San Francisco/Mt. Zion Cancer Center, 1600 Divisadero St., 3rd Floor, San Francisco, CA 94115-1711, USA. e-mail: pcarroll@urol.ucsf.edu

Abbreviations: CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; ED, erectile dysfunction; EPIC, Expanded Prostate Index Composite; HRQL, health-related quality of life; IIEF, International Index of Erectile Function; UCLA PCI, University of California Los Angeles Prostate Cancer Index; RP, radical prostatectomy; SB, sexual bother; SF, sexual function; SHIM, Sexual Health Inventory for Men.