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Associations of sexual dysfunction symptoms with PSA-detected localised and advanced prostate cancer: A case-control study nested within the UK population-based ProtecT (Prostate testing for cancer and Treatment) study

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ABSTRACT

Background: Sexual dysfunction might be symptomatic of cancer spreading beyond the prostate by local invasion, a mechanism of tumour progression associated with prognosis. Conversely, among men with raised prostate-specific antigen (PSA) levels, a negative association might be expected if sexual dysfunction was symptomatic of benign, rather than malignant, prostatic disease.

Patients and methods: Cases and controls were selected from among men recruited to the UK population-based ProtecT (Prostate testing for cancer and Treatment) study. Men aged 50–69 years were invited for PSA testing and those with a PSA level $\geqslant$3.0 ng/ml were invited for biopsy. We investigated whether symptoms of sexual dysfunction, determined by self-completed questionnaire prior to biopsy, were associated with prostate cancer.

Results: Of the 8924 men who had a PSA level $\geqslant$3.0 ng/ml (11% of the men who had a PSA test), 6585 underwent biopsy of whom 2813 and 421, respectively, were subsequently diagnosed with localised and advanced prostate cancer and 3351 had a negative biopsy result. No individual symptom of sexual dysfunction was associated with risk of prostate cancer. The symptom score was associated with advanced (odds ratio (OR) per one unit increase in score = 1.06; 1.00–1.12; $P = 0.07$) but not with localised (OR = 1.00; 0.97–1.02; $P = 0.9$) prostate cancer ($P = 0.05$ for heterogeneity).

Conclusions: Our study provides weak evidence that sexual dysfunction may be associated with PSA-detected advanced, but not localised, prostate cancer among men with raised PSA levels.

1. Introduction

A positive association of sexual dysfunction with prostate cancer might be expected if sexual dysfunction were symptomatic of cancer spreading beyond the prostate by local invasion,[1] a mechanism of tumour progression associated with prognosis.[2] Conversely, among men with raised prostate-specific antigen levels, a negative association might be

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expected if sexual dysfunction were symptomatic of benign, rather than malignant, prostatic disease.[3,4]

A recent case-control study based on general practitioner records reported a positive association between impotence and clinically detected prostate cancer,[5] but this finding was likely to have been biased because sexual problems may make it more likely that a man would present, undergo investigation and have prostate cancer detected. An observational study comparing men diagnosed with prostate cancer with a random sample of men from the general population found a higher risk of impotence and ejaculate volume among untreated prostate cancer patients,[6] although it could be argued that a diagnosis of cancer would have a psychological effect on sexual function or perception of symptoms.[7] In contrast, an observational study reported no differences in (pre-treatment) intercourse frequency or satisfaction comparing men diagnosed with prostate cancer with a sample from the general population.[8] Without consistent, robust evidence of any association between sexual dysfunction and prostate cancer, PSA testing in men with sexual dysfunction equates to screening, a practice which remains highly controversial.[9]

Our purpose was to establish, within the large population-based, multi-centre cohort of men with a raised ($\geqslant$3.0 ng/ml) PSA level provided by the ProtecT (Prostate testing for cancer and Treatment) study, whether symptoms of sexual dysfunction were associated with a subsequent diagnosis of prostate cancer, including the stage and grade (localised or advanced).

Table 1 – Associations of symptoms of sexual dysfunction with a subsequent diagnosis of prostate cancer among men who had a raised PSA level ($\geqslant$3 ng/ml) – earlier version of sexual matters questionnaire.

Sexual function during month before biopsy (earlier version of questionnaire)		Score[a]	Biopsy negative	Biopsy positive	Age-adjusted odds ratio (95% CI)
Do you get erections?			*n* = 1276	*n* = 1146	
	Yes, with normal stiffness	0	59.4%	56.5%	1.00
	Yes, with reduced stiffness	1	28.7%	31.4%	1.13 (0.94, 1.35)
	Yes, with severely reduced stiffness	2	8.0%	7.9%	1.00 (0.74, 1.36)
	No, erection not possible	3	3.9%	4.2%	1.08 (0.71, 1.64)
			Test for trend		*P* = 0.5
Do you ejaculate?			*n* = 1257	*n* = 1131	
	Yes, normal quantity of semen	0	59.0%	59.1%	1.00
	Yes, but reduced quantity of semen	1	27.5%	29.2%	1.03 (0.85, 1.24)
	Yes, but significantly reduced quantity of semen	2	7.6%	6.7%	0.83 (0.60, 1.16)
	Yes, but no semen	3	1.5%	1.1%	0.66 (0.31, 1.37)
	No ejaculation	4	4.5%	4.0%	0.84 (0.55, 1.26)
			Test for trend		*P* = 0.2
Do you have pain or discomfort during ejaculation?			*n* = 1251	*n* = 1127	
	No pain or discomfort	0	95.4%	94.5%	1.00
	Yes, slight pain or discomfort	1	4.4%	4.8%	1.10 (0.75, 1.61)
	Yes, moderate pain or discomfort	2	0.2%	0.6%	2.64 (0.68, 10.22)
	Yes, severe pain or discomfort	3	0.0%	0.1%	-
			Test for trend		*P* = 0.2
Do you experience the sensation of orgasm?			*n* = 1241	*n* = 913	
	Yes, normally	0	73.7%	72.7%	1.00
	Yes, but slightly reduced	1	19.4%	19.4%	1.00 (0.80, 1.24)
	Yes, but severely reduced	2	4.2%	4.5%	1.06 (0.69, 1.62)
	No sensation of orgasm	3	2.7%	3.4%	1.22 (0.74, 2.02)
			Test for trend		*P* = 0.5
Has your sex life changed compared with one year ago?			*n* = 1155	*n* = 1097	
	It is better	–	2.1%	2.8%	1.00
	It has stayed the same	–	83.7%	83.8%	0.75 (0.44, 1.27)
	It is worse	–	14.2%	13.4%	0.70 (0.40, 1.23)
			Test for trend		*P* = 0.3
If you do not have sex now, how long ago did this stop?			*n* = 445	*n* = 412	
	Less than 3 months ago	–	13.7%	16.3%	1.00
	3–5 Months ago	–	9.4%	8.5%	0.75 (0.42, 1.32)
	6–11 Months ago	–	14.4%	11.4%	0.66 (0.40, 1.10)
	1–2 Years ago	–	22.9%	17.7%	0.64 (0.41, 1.02)
	3–5 Years ago	–	18.7%	16.5%	0.73 (0.46, 1.18)
	More than 5 years ago	–	20.9%	29.6%	1.16 (0.75, 1.82)
			Test for trend		*P* = 0.4

a Contribution to sexual dysfunction symptom score.

2. Methods

2.1. ProtecT study

The ProtecT study is a randomised controlled trial of the effectiveness, cost-effectiveness and acceptability of active monitoring, radical prostatectomy and radical conformal radiotherapy for men with localised prostate cancer (ISRCTN #20141217). Recruitment to the study occurred between 2001 and 2008. Men aged 50–69 years in general practices located around nine UK cities were invited to attend a nurse-led prostate check clinic, and if they consented, to have a PSA test. Participants with a single raised PSA test result between 3.0 and 19.9 ng/ml were invited to attend the centre's urology department for digital rectal examination (DRE), repeat PSA test and transrectal ultrasound (TRUS)-guided biopsy (10 cores). Men with clinically localised disease were eligible to participate in the treatment trial. Men with a PSA level $\geqslant$20 ng/ml were referred as a matter of urgency to a urologist, and were eligible to participate in the treatment trial only if localised cancer was confirmed. A diagnosis of localised prostate cancer was defined as a positive biopsy, clinical stage T1–T2, NX, M0; advanced prostate cancer was defined as a positive biopsy, clinical stage T3–T4 or N1 or M1. All men provided written informed consent. Trent Multicentre Research Ethics Committee approved the study.

2.2. Data

Information on sexual function was collected by self-completed questionnaire at the time of the biopsy appointment (before diagnosis). This questionnaire was re-designed midway through the ProtecT study (August 2004). The earlier version of the questionnaire (six items) was as devised by Frankel and colleagues,[10] plus two additional questions asking whether the man had an active sex life (Table 1). The later version of the questionnaire comprised nine items from the Expanded Prostate Cancer Index Composite (EPIC) instrument[11]: seven relating to symptoms and two relating to activity (Table 2). We derived variables for erectile dysfunction (quality of erections, in four categories) and ejaculatory dysfunction (sensation of orgasm/ability to reach orgasm, in four categories) from equivalent questions in each version of the questionnaire. We also derived an overall symptom score (range 0–10) from the number and severity of symptoms reported in either questionnaire (see Tables 1 and 2 for details). We used questionnaire data which had been entered on to the study database by the end of December 2008 (Fig. 1). These data were routinely entered for all men who attended the biopsy. Men without a diagnosis of prostate cancer were only included in our analysis if their most recent biopsy was negative.

2.3. Statistical methods

Logistic regression models were used to estimate odds ratios (ORs) for associations of individual symptoms of sexual dysfunction, measures of erectile and ejaculatory dysfunction and overall symptom score with prostate cancer, adjusted for age at time of PSA test. Age-adjusted odds ratios for associations of symptoms with localised and advanced prostate cancer were compared using the Wald tests for heterogeneity estimated in multinomial logistic regression models. The relationships of increasing severity of symptoms with the odds of prostate cancer were assessed for trend by the Wald tests. In this predominantly white (98.7%) study population, we did not adjust for race. All statistical analyses were performed using Stata Release 10 (StataCorp, 2007, *Stata Statistical Software: Release 10*, College Station, TX).

3. Results

3.1. PSA levels and prostate cancer among men recruited to the ProtecT study

By December 2008, 81,542 men had a PSA test result (Fig. 1); 8924 (11%) had PSA $\geqslant$3.0 ng/ml, and of these men 6585 (74%) had a biopsy result. Of the men with biopsy results: 3234 (49%) were diagnosed with prostate cancer, comprising 2813 localised and 421 advanced cancers; and 3351 (51%) had a negative biopsy. Sexual function data had been obtained and entered for 4842 (74%) of men with biopsy results (positive or negative), of whom 2440 and 2402 had completed the earlier and later versions of the questionnaire, respectively. Measures of erectile and ejaculatory dysfunction based on the combined data from both versions of the questionnaire were available for 2475 men with a negative biopsy, and for 2001 men with positive biopsy (including 165 advanced cancers). An overall symptom score was available for 2413 men with a negative biopsy, and for 1953 men with a positive biopsy (including 163 advanced cancers).

3.2. Factors associated with prostate cancer among men with PSA $\geqslant$3 ng/ml

Older age (OR per increase in 5-year (50–54, 55–59, 60–64, 65–69 years) age group = 1.13; 95% CI 1.08–1.19), paternal or fraternal history of prostate cancer (age-adjusted OR = 1.31; 1.08–1.60) and PSA level (age-adjusted OR per one ng/ml increase in PSA level = 1.17; 1.15–1.19) were all associated with a higher odds of a subsequent diagnosis of prostate cancer. Older age (but not PSA level or family history of prostate cancer) was strongly associated with symptoms of sexual dysfunction. After controlling for age, no individual symptom of sexual dysfunction in the earlier (Table 1) or later (Table 2) versions of the questionnaire was associated with prostate cancer. Neither the measures of erectile (test for trend, $P = 0.6$) and ejaculatory (test for trend, $P = 0.9$) dysfunction, nor the symptom score (age-adjusted OR per one unit increase in score = 1.00; 0.98–1.03), all of which were derived from both questionnaire versions, was associated with prostate cancer. There was no evidence that the association of symptoms of sexual dysfunction with prostate cancer varied by age (tests for interaction: erectile dysfunction, $P = 0.1$; ejaculatory dysfunction, $P = 0.4$; symptom score, $P = 0.5$).

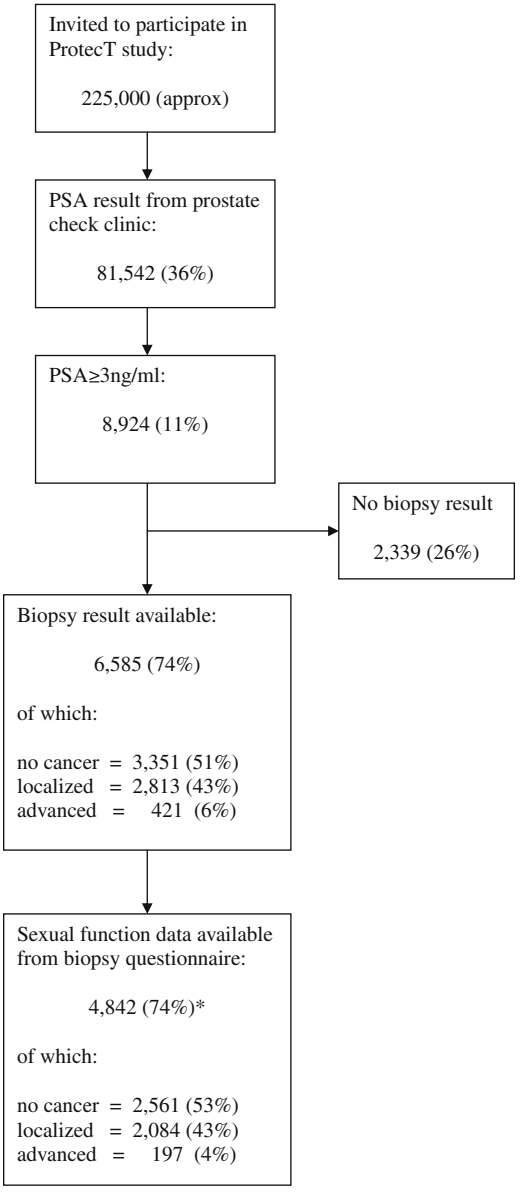
3.3. Factors associated with advanced prostate cancer among men with PSA $\geqslant$3 ng/ml

There was no evidence that associations of prostate cancer with individual symptoms from either version of the ques-

Table 2 – Associations of symptoms of sexual dysfunction with a subsequent diagnosis of prostate cancer among men who had a raised PSA level (⩾3 ng/ml) – later version of sexual matters questionnaire.

Sexual symptoms at biopsy (later version of questionnaire)		Score[a]	Biopsy negative	Biopsy positive	Age-adjusted odds ratio (95% CI)
Ability to have erection			*n* = 1256	*n* = 1108	
	Very good	0	16.7%	16.7%	1.00
	Good	1	33.3%	34.1%	1.00 (0.78, 1.27)
	Fair	2	26.4%	28.2%	1.02 (0.79, 1.31)
	Poor	3	14.2%	12.9%	0.86 (0.64, 1.16)
	Very poor	4	9.5%	8.1%	0.78 (0.55, 1.11)
			Test for trend		*P* = 0.1
Quality of erections during last			*n* = 1251	*n* = 1104	
4 weeks	Firm enough for intercourse	0	64.8%	65.4%	1.00
	Firm enough for other activities	1	16.5%	17.1%	0.99 (0.79, 1.24)
	Not firm enough for any activity	2	10.2%	9.8%	0.91 (0.68, 1.20)
	None	3	8.6%	7.7%	0.83 (0.61, 1.13)
			Test for trend		*P* = 0.2
Frequency of erections			*n* = 1238	*n* = 1087	
	Whenever I want	0	46.6%	48.6%	1.00
	More than half the time	1	20.4%	19.7%	0.91 (0.73, 1.13)
	About half the time	2	11.6%	12.8%	1.03 (0.79, 1.34)
	Less than half the time	3	12.2%	10.0%	0.75 (0.57, 0.99)
	Never	4	9.2%	8.9%	0.87 (0.64, 1.17)
			Test for trend		*P* = 0.1
Erection on waking			*n* = 1256	*n* = 1108	
	Daily	0	4.7%	3.8%	1.00
	Several times per week	1	22.5%	25.0%	1.36 (0.89, 2.10)
	About once per week	2	26.0%	26.4%	1.21 (0.79, 1.86)
	Less than once per week	3	20.9%	19.3%	1.10 (0.71, 1.70)
	Never	4	25.8%	25.5%	1.16 (0.75, 1.78)
			Test for trend		*P* = 0.3
Level of sexual desire			*n* = 1259	*n* = 1115	
	Very good	0	12.5%	11.9%	1.00
	Good	1	32.9%	33.3%	1.04 (0.79, 1.36)
	Fair	2	32.8%	32.5%	1.00 (0.76, 1.31)
	Poor	3	13.3%	14.2%	1.07 (0.78, 1.47)
	Very poor	4	8.5%	8.2%	0.94 (0.65, 1.36)
			Test for trend		*P* = 0.9
Ability to reach orgasm			*n* = 1243	*n* = 1101	
	Very good	0	20.6%	18.5%	1.00
	Good	1	39.2%	40.3%	1.12 (0.89, 1.40)
	Fair	2	22.9%	24.3%	1.13 (0.88, 1.46)
	Poor	3	8.5%	10.3%	1.26 (0.91, 1.75)
	Very poor	4	8.9%	6.6%	0.77 (0.54, 1.11)
			Test for trend		*P* = 0.7
Ability to function sexually			*n* = 1242	*n* = 1099	
during past 4 weeks	Very good	0	10.8%	11.5%	1.00
	Good	1	33.7%	34.4%	0.93 (0.70, 1.24)
	Fair	2	27.8%	26.6%	0.86 (0.64, 1.15)
	Poor	3	12.9%	12.3%	0.85 (0.60, 1.19)
	Very poor	4	14.9%	15.3%	0.89 (0.64, 1.24)
			Test for trend		*P* = 0.4
Sexual activity during past			*n* = 1256	*n* = 1108	
4 weeks	Daily or several times per week	–	15.8%	14.7%	1.00
	About once per week	–	33.9%	34.5%	1.06 (0.82, 1.36)
	Less than once per week	–	24.4%	20.8%	0.88 (0.67, 1.16)
	None	–	26.0%	30.1%	1.17 (0.89, 1.53)
			Test for trend		*P* = 0.4
Sexual intercourse during past			*n* = 1254	*n* = 1114	
4 weeks	Daily or several times per week	–	10.4%	8.4%	1.00
	About once per week	–	27.3%	28.5%	1.24 (0.91, 1.69)
	Less than once per week	–	21.4%	19.3%	1.07 (0.77, 1.48)
	None	–	41.0%	43.8%	1.24 (0.92, 1.68)
			Test for trend		*P* = 0.4

a Contribution to sexual dysfunction symptom score.



* 2,440 earlier version + 2,402 later version of questionnaire

Fig. 1 – Flowchart of men invited to participate in the ProtecT study (up to December 2008) who contributed to our analyses.

tionnaire differed according to whether the cancer was localised or advanced, with the somewhat weak exception of responses to the question 'Do you ejaculate?' in the early version of the questionnaire (test for heterogeneity, $P = 0.07$). The age-adjusted odds ratios comparing 'no ejaculation' with 'ejaculation with normal quantity of semen' were 1.98 (0.91–4.30) and 0.73 (0.47–1.13) for advanced and localised cancer, respectively. There was no evidence that the measure of erectile dysfunction, derived from both versions of the questionnaire, had different associations with localised and advanced cancer, but there was weak evidence of heterogeneity ($P = 0.07$) for the measure of ejaculatory dysfunction (Table 3). The positive likelihood ratio for advanced prostate cancer comparing 'any sign of ejaculatory dysfunction' (sensation of orgasm/ability to reach orgasm = slightly reduced/fair to no sensation/very poor) with 'no sign of ejaculatory dysfunction' (sensation of orgasm/ability to reach orgasm = normal/good or very good) was 1.43 (1.06–1.92), hence minimal post-test increase in likelihood of disease. A weak association of symptom score with advanced prostate cancer (OR per one unit increase in score = 1.06 (1.00–1.12) $P = 0.07$) was not evident for localised prostate cancer (OR = 1.00 (0.97–1.02) $P = 0.9$), and these apparent differences were supported by the test for heterogeneity ($P = 0.05$).

3.4. *Representativeness*

Men with a negative biopsy were more likely to have provided partial or complete sexual function data (76% partial, 71% complete) than men diagnosed with localised (74%, 63%) or advanced (47%, 38%) prostate cancer. However, the low proportion of advanced cases who completed the biopsy questionnaire was a consequence of men in the ProtecT study who have PSA $\geqslant$20 ng/ml being referred for an urgent diagnostic appointment, at which the biopsy questionnaire was not routinely administered. Among men with localised cancer, the mean age of those who provided complete sexual function data was slightly lower than the mean age of those who did not provide data (61.6 years versus 62.2 years), but there were no differences in mean age among biopsy-negative men and advanced cases according to questionnaire completion. There were no differences in mean PSA level among any of the groups (control, localised or advanced) according to questionnaire completion, if we excluded men who had PSA $\geqslant$20 ng/ml.

4. Discussion

We found no evidence for associations between symptoms of sexual dysfunction and a subsequent diagnosis of prostate cancer among men who had a raised ($\geqslant$3 ng/ml) PSA level. Our results did suggest that the overall number and severity of symptoms were positively associated with advanced, but not with localised, prostate cancer (Table 3). This finding could be explained by the onset of sexual dysfunction as a late symptom due to invasion of the neurovascular bundle,[12,13] but evidence of this effect being restricted to men with advanced cancer was weak ($P = 0.05$).

Our study was based on a very large community sample of men invited to participate independently of symptoms, who completed a sexual function questionnaire before diagnosis. The main limitation of our study is that we were only able to investigate associations of sexual dysfunction with prostate cancer among men with a raised PSA level ($\geqslant$3 ng/ml), because only these men were invited to attend a biopsy and therefore had the presence of prostate cancer verified or refuted. Although the control group in our study comprised men with negative biopsies, this verification would still be biased due to the imperfect sensitivity of the biopsy procedure.[14] However, we would expect our results to be less biased than those from previous studies based on clinically detected incident prostate cancer cases,[5] or on patients who completed questionnaires after diagnosis.[6,8]

Table 3 – Associations of symptoms of sexual dysfunction with a subsequent diagnosis of prostate cancer (localised or advanced) among men who had a raised PSA level (⩾3 ng/ml) – combined responses and symptom score derived from both versions of the questionnaire.

Sexual function in month before PSA test		Biopsy negative	Biopsy positive		Localised cancer	Advanced cancer	Test for heterogeneity of trends in odds ratios[a]
			Localised	Advanced	Age-adjusted odds ratio (95% CI)	Age-adjusted odds ratio (95% CI)	
Erectile dysfunction (quality of erections)		*n* = 2,527	*n* = 2,056	*n* = 194			
	Normal	62.1%	61.2%	57.2%	1.00	1.00	
	Reduced	22.6%	24.4%	24.7%	1.07 (0.92, 1.23)	1.02 (0.71, 1.47)	
	Severely reduced	9.1%	8.7%	10.3%	0.93 (0.76, 1.15)	1.04 (0.63, 1.71)	
	None possible	6.2%	5.7%	7.7%	0.90 (0.70, 1.16)	1.07 (0.60, 1.90)	
	Test for trend				*P* = 0.5	*P* = 0.8	*P* = 0.6
Ejaculatory dysfunction (sensation of orgasm/ability to reach orgasm)		*n* = 2,484	*n* = 1,846	*n* = 168			
	Normal/good or very good	66.7%	65.9%	57.7%	1.00	1.00	
	Slightly reduced/Fair	21.2%	21.7%	25.0%	1.02 (0.88, 1.19)	1.23 (0.84, 1.80)	
	Severely reduced/Poor	6.4%	7.6%	8.3%	1.18 (0.92, 1.50)	1.29 (0.71, 2.33)	
	No sensation/Very poor	5.8%	4.8%	8.9%	0.82 (0.62, 1.08)	1.47 (0.83, 2.63)	
	Test for trend				*P* = 0.8	*P* = 0.1	*P* = 0.07
Overall symptom score	Per unit increase	*n* = 2,413	*n* = 1,790	*n* = 163	1.00 (0.97, 1.02)	1.06 (1.00, 1.12)	
		Test for trend			*P* = 0.9	*P* = 0.07	*P* = 0.05

a The Wald test in multinomial logistic regression model comparing trend in odds ratios for localised cancer with trend in odds ratios for advanced cancer.

Disproportionate missing data among men with PSA ⩾20 ng/ml may have obscured associations between symptoms and advanced prostate cancer, but the exclusion of these men by study protocol rather than by patient choice would have minimised possible selection bias. In sensitivity analyses, exclusion of men with PSA ⩾20 ng/ml made little or no difference to our findings. Sexual function and/or reporting of symptoms would not have been affected by testing and diagnosis, a bias which can occur in opposite directions among cases,[7] and controls.[15] Our 'ejaculatory dysfunction' variable was derived from responses to equivalent questions about sensation of orgasm (early version of questionnaire, Table 1) and ability to reach orgasm (later version of questionnaire, Table 2). Ideally we would have derived this variable from a question which asked specifically about ejaculation, but such a question was only asked in the earlier version of the questionnaire (Table 1). The evidence of heterogeneity between responses to this question for advanced versus localised prostate cancer ($P = 0.07$) may have been strengthened if we had been able to combine answers from both versions of the questionnaire. African-Caribbean men in the UK are at greater risk of prostate cancer,[16] but we could not adjust for race because the men in our study were predominantly (98.7%) white.

That we found no association between symptoms of sexual dysfunction and a subsequent diagnosis of prostate cancer among men who had a raised PSA level contrasts with our finding (based on a subset of the men in the present study) that lower urinary tract symptoms (LUTS) were inversely associated with prostate cancer.[3] This inverse association arose because LUTS were more likely to be caused by benign prostatic hyperplasia (BPH) than by malignant prostatic disease. There was a positive correlation between LUTS and sexual dysfunction among the men in our study (the Spearman rank correlation coefficient between urinary and sexual symptom scores = 0.15, $P < 0.001$), consistent with evidence that LUTS/BPH is an age-independent risk factor for sexual dysfunction.[17] These contrasting findings show that urinary symptoms, but not symptoms of sexual dysfunction, are of clinical utility in predicting individual risk of prostate cancer among men with raised PSA levels.

In conclusion, this study provides only weak evidence that sexual dysfunction may be associated with PSA-detected advanced, but not localised, prostate cancer among British men aged 50–69 years. The presence or absence of symptoms of sexual dysfunction in men with raised PSA levels does not contribute usefully to a clinical assessment of prostate cancer risk for individual men. Men with such symptoms can be reassured that there is no evidence of an association with risk of prostate cancer.

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Conflict of interest statement

None declared.

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