ORIGINAL ARTICLE

Obese men have more advanced and more aggressive prostate cancer at time of surgery than non-obese men after adjusting for screening PSA level and age: results from two independent nested case–control studies

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BACKGROUND: It remains unclear whether the hemodilution effect of body mass index (BMI) on PSA levels translates to inappropriate prostate cancer (PCa) screening in obese men. To address this, we conducted two nested case–control studies within prospective cohorts of men undergoing radical prostatectomy for newly diagnosed PCa.
METHODS: We identified 1817 men with BMI $\geqslant 30 \, \text{kg m}^{-2}$ (cases) and 1244 men with BMI $< 25 \, \text{kg m}^{-2}$ (controls) who underwent surgery to treat PCa at Mayo Clinic in Rochester between 2000 and 2009. Cases and controls were frequency matched on age and PSA level. In a similar manner, we identified 206 cases and 133 controls treated at Mayo Clinic in Florida between 2006 and 2011. We employed logistic regression models to evaluate the association of pathologic features of aggressiveness with obesity status.
RESULTS: After adjusting for age and PSA level, we noted that obese men in the Rochester population are more likely to present with Gleason grade 8–10 tumors (OR = 1.50; 95% CI 1.14–1.96; $P = 0.003$) and pT3, pT4, pTxN+ stage disease (OR = 1.30; 95% CI 1.05–1.62). We noted a similar association seminal vesicle involvement (OR = 1.41; 95% CI 1.03–1.92; $P = 0.03$). Results from the smaller Florida population supported these same associations but did not achieve conventional statistical significance.
CONCLUSIONS: Obese men present with more aggressive PCa tumors compared with non-obese men of similar age and PSA screening values. If confirmed, this would support the need to explore PSA-based screening in obese men to possibly account for a hemodilution effect.

INTRODUCTION

The use of PSA as a screening tool for prostate cancer detection remains a controversial issue.[1–2] Related to this, the reported inverse association between blood levels of PSA and body mass index (BMI) suggests that there is a hemodilution effect on PSA in obese men secondary to increased circulating blood volume.[3–14] On the basis of this proposed hemodilution effect, some investigators have suggested new PSA cut points for prostate cancer (PCa) screening in obese men, whereas others have developed specific equations to standardize PSA test results for differences in body size.[3,8,14]

Although lower PSA levels in obese men are well reported, what remains in question is whether this results in a need to adjust PSA screening levels among obese men. That is, a key clinical question centers on whether obese men present with more aggressive PCa when compared with non-obese men of similar age and with similar PSA screenings levels. Although data from prospective, randomized screening studies would be ideal, a rationale and cost-effective first step would be to assess the association between BMI and PCa aggressiveness after adjusting for age and PSA level in large, well-annotated cohorts of men treated surgically for newly diagnosed PCa. Specifically, we hypothesize that obese men are more likely to present with more advanced

(that is, later stage) and more aggressive PCa tumors (that is, higher grade) at time of surgery compared with non-obese men after controlling for age and screening PSA level. To test this hypothesis, we conducted independent, retrospective nested case–control studies within two cohorts of men undergoing radical prostatectomy for newly diagnosed, clinically localized PCa.

MATERIALS AND METHODS

Patient selection

After obtaining approval from our institutional review board, we used the Prostatectomy Registry maintained at Mayo Clinic in Rochester, Minnesota to identify 1817 men treated with radical prostatectomy for newly diagnosed, clinically localized prostate cancer between 2000 and 2009 who had a BMI $\geqslant 30 \, \text{kg m}^{-2}$ at the time of prostatectomy (that is, 'cases'). We excluded from our study sample any men who received neo-adjuvant therapy. We then selected 1244 similar men from the Registry who had a BMI $< 25 \, \text{kg m}^{-2}$ at the time of prostatectomy (that is, 'controls'). When selecting our controls, we performed frequency-matching to the cases on age at the time of surgery and PSA level to ensure that our cases and controls had similar distributions with regard to these two covariates. In a similar manner to that described above, we harnessed the Prostatectomy Registry effort at Mayo Clinic in Jacksonville, Florida, USA to select a second, independent validation set of 206 cases and 133 controls from

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men undergoing prostatectomy for newly diagnosed, clinically localized PCa between 2006 and 2011.

Data collection

All the demographic, clinical and pathological features studied in this investigation were abstracted from the ongoing Prostatectomy Registries at both institutions. At each site, these data are routinely abstracted from the medical record by experienced and certified coordinators with expertise in chart review and data abstraction for PCa patients. The demographic and clinical data evaluated as part of this study included self-reported year of surgery, type of surgery (open vs laparoscopic), age at surgery, BMI (calculated from height and weight recorded in anesthesia record at the time of surgery), clinical Gleason grade and pre-operative PSA level. For this investigation, we included the following variables abstracted related to PCa aggressiveness: pT stage, Gleason score, tumor volume, seminal vesicle involvement, margin status and extracapsular extension. The tumor stage was assigned using the 1997 International Union Against Cancer-American Joint Committee on Cancer TNM system. For estimating tumor volume (and prostate volume), we used data collected on three dimensions during pathology review and then applied the prolate ellipsoid formula (L*W*D*0.52). For those patients with multiple foci, we added together the estimated volumes from each individual foci.

Statistical methods

Our primary analysis focused on estimating the association of standard measures of PCa aggressiveness (that is, Gleason grade, pT stage, extracapsular involvement) with case vs control status (that is, obese vs non-obese). We analyzed pathologic stage as a dichotomized variable (pT2 vs pT3, pT4, pTxN+). For pathologic Gleason grade, we used a three level categorical variable of $\leqslant 6$ (reference), 7 and 8–10. For extra-capsular extension, seminal vesicle involvement and surgical margins, we used dichotomized categories of no (reference) and yes. Finally, tumor volume and prostatic volume were treated as continuous, modeled using a log2 transformation and reported as the association with a doubling in those variables.

We employed logistic regression models to estimate the magnitude of the association of obesity status with our pathologic measures of PCa aggressiveness in a univariate setting and after adjusting for residual confounding by screening PSA level and age (that is, we already matched on these two variables) as well as potential confounding by year of surgery and prostate volume. For reporting purposes, we summarized estimates of association from our logistic models with odds ratios (OR) and 95% confidence intervals (CIs). Finally, we repeated our analysis using a more stringent definition of obesity that required a BMI $> 35\,\mathrm{kg\,m}^{-2}$. For this analysis using a higher BMI to designate obesity, those men with a BMI of 30–35 $\mathrm{kg\,m}^{-2}$ were excluded altogether (rather than including them with the controls). All statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA). All tests were two-sided, and P-values $\leqslant 0.05$ were considered statistically significant.

RESULTS

In Table 1 we provide comparisons of demographic and clinical features between our cases and controls at both sites. As a result of our frequency matching efforts, cases and controls are of similar age at the time of surgery and have comparable pre-operative PSA levels. Specifically, the median pre-operative PSA level for cases from Mayo Clinic in Rochester is 5.6 ng ml^{-1} compared with 5.7 ng ml^{-1} for controls, whereas the median pre-operative PSA level for cases from Mayo Clinic in Florida is 5.2 ng ml^{-1} compared with 5.4 ng ml^{-1} for controls. Similarly, the median age for cases from Mayo Clinic in Rochester is 62.0 compared with 62.0 for controls, whereas the median age for cases from Mayo Clinic in Florida is 64.2 compared with 62.7 for controls. In Table 1 we also provide distributions for surgery year to show that cases and controls have similar distributions within each institution with respect to when the surgeries were performed. We also provide in Table 1 the distribution of BMI within our cases and controls from each site. Finally, we include information on surgery type to underscore that, although a higher percentage of the surgeries are

performed laparoscopically at Mayo Clinic in Florida compared with Mayo Clinic in Rochester, within each institution the cases and controls had similar distributions with respect to type of surgery.

In Table 2 we provide the results of our logistic regression analysis examining the association of various pathologic features of aggressiveness and case/control status. In the Mayo Clinic in Rochester patient population, we noted consistent evidence of increased risk of more aggressive pathologic features in cases vs controls. That is, after controlling for age and PSA level, the odds of an obese patient (a case) having more aggressive pathologic features were elevated compared with a non-obese patient (control). For example, compared with non-obese patients, obese patients are 36% more likely to present with Gleason 7 tumors (OR = 1.36; 95% CI: 1.17–1.60; $P < 0.001$) and 50% more likely to present with Gleason 8–10 tumors (OR = 1.50; 95% CI: 1.14–1.96; $P = 0.003$). Similarly, we noted that cases also had elevated odds of having pT3, pT4, pTxN+ disease (OR = 1.30; 95% CI: 1.05–1.62; $P < 0.02$), seminal vesicle involvement (OR = 1.41; 95% CI: 1.03–1.92; $P = 0.03$) and extra-capsular extension (OR = 1.26; 95% CI: 1.01–1.57; $P < 0.04$) compared with controls. Interestingly, obese men were more likely to present with both a larger prostate (OR = 1.49; 95% CI: 1.33–1.68; $P < 0.0001$) as well as a larger tumor volume (OR = 1.06; 95% CI: 1.03–1.09; $P < 0.0001$) compared with non-obese men. Given that we model each variable as a log2 transformation, both of the previous ORs are interpreted as the impact of a doubling in prostate and tumor volume, respectively, on the odds of being obese vs non-obese. As independent validation, our analysis of the patients from Mayo Clinic in Florida generated ORs that are consistent with the results obtained for the Mayo Clinic in Rochester patients, albeit with less power to detect these associations as statistically significant because of the smaller sample size (Table 2). For example, we observed similar ORs in the Mayo Clinic in Rochester and Mayo Clinic in Florida populations for pathologic stage pT3, pT4, pTxN+ (OR = 1.30 vs 1.45, respectively), Gleason grade 8–10 (OR = 1.50 vs 1.42, respectively), seminal vesicle involvement (OR = 1.41 vs 3.72, respectively) and extra-capsular extension (OR = 1.26 vs 1.37, respectively). Although the results from the Mayo Florida population did not achieve conventional statistical significance for most of these variables, the magnitude and direction of the ORs are strikingly similar to that of the Mayo Rochester population. Finally, further adjustment in our models for year of surgery and prostate volume did not alter our findings.

In Table 3 we provide the results of our exploratory logistic regression analysis using the more stringent definition of obesity as a BMI $> 35\,\mathrm{kg\,m}^{-2}$. For these analyses, we only report the data from the Mayo Clinic in Rochester population given that this more conservative definition of obesity resulted in a smaller case group and therefore more limited power in the validation set from Mayo Clinic in Florida. Interestingly, we noted continued evidence of increased risk of more aggressive pathologic features in cases vs controls. Most notably, the OR from these new analysis for Gleason grade 8–10 increased from 1.50 (95% CI: 1.14–1.96; $P = 0.003$, Tables 2) to 2.32 (95% CI: 1.54–3.48; $P < 0.001$, Table 3). We noted continued evidence of an association with extracapsular involve-ment (OR = 1.28; Table 3 vs OR = 1.26; Table 2) and doubling in tumor volume (OR = 1.06; Table 2 vs OR = 1.09; Table 3). By contrast, the associations with pathologic stage pT3, pT4, pTxN+ and with seminal vesicle involvement that we observed in Table 2 were attenuated slightly in Table 3 (OR = 1.30 vs 1.15 and OR = 1.41 vs 1.24, respectively).

DISCUSSION

An elevation in PSA blood level (typically > 3–4 ng ml^{-1}) is widely accepted as an indication that a man should undergo a prostate biopsy for suspicion of PCa. Of interest, several investigators have

Table 1. Comparison of demographic and clinical characteristics between cases (men with a BMI $\geqslant$ 30 kg m^{-2}) and controls (men with a BMI < 25 kg m^{-2}) at Mayo Rochester and Mayo Florida

	Mayo Rochester			Mayo Florida		
	Control BMI < 25 (N = 1244)	Case BMI $\geqslant$ 30 (N = 1817)	Total (N = 3061)	Control BMI < 25 (N = 133)	Case BMI $\geqslant$ 30 (N = 206)	Total (N = 339)
Surgery Year						
2000–2002	247 (19.8%)	498 (27.4%)	745 (24.3%)	N/A	N/A	N/A
2003–2005	363 (29.1%)	486 (26.7%)	849 (27.7%)	N/A	N/A	N/A
2006–2009	634 (51.1%)	833 (45.9%)	1467 (47.9%)	104 (78.1%)	148 (71.8%)	252 (74.3%)
2010–2011	N/A	N/A	N/A	29 (21.9%)	58 (28.2%)	87 (25.7%)
Surgery Type						
RRP	991 (79.7%)	1419 (78.1%)	2410 (78.7%)	47 (35.3%)	93 (45.1%)	140 (41.3%)
Laparoscopic	253 (20.3%)	398 (21.9%)	651 (21.3%)	86 (64.7%)	113 (54.9%)	199 (58.7%)
Age at Surgery						
Mean (SD)	61.9 (6.63)	61.8 (6.16)	61.8 (6.36)	63.3 (7.5)	61.9 (7.2)	62.4 (7.3)
Median	62.0	62.0	62.0	64.2	62.7	63.0
Q1, Q3	56.5, 67.0	57.0, 66.0	57.0, 66.0	57.7, 68.9	57.5, 66.9	57.6, 67.5
Range	(50.0–80.0)	(50.0–78.0)	(50.0–80.0)	(29.9–78.4)	(43.1–78.6)	(29.9–78.6)
Age group						
< 60	495 (39.8%)	685 (37.7%)	1180 (38.5%)	40 (30.1%)	71 (34.5%)	111 (32.7%)
60 $\leqslant$ X < 70	566 (45.5%)	915 (50.4%)	1481 (48.4%)	72 (54.1%)	111 (53.9%)	183 (54.0%)
70 +	183 (14.7%)	217 (11.9%)	400 (13.1%)	21 (15.8%)	24 (11.7%)	45 (13.3%)
Pre–op PSA						
Mean (SD)	7.0 (6.24)	7.7 (13.30)	7.4 (11.00)	6.8 (6.0)	6.6 (6.1)	6.7 (6.0)
Median	5.6	5.7	5.6	5.2	5.4	5.3
Q1, Q3	4.1, 7.9	4.2, 8.0	4.1, 8.0	4.0, 7.6	4.2, 7.1	4.1, 7.3
Range	(0.7–93.6)	(0.1–467.0)	(0.1–467.0)	(0.1–40.7)	(0.1–54.3)	(0.1–54.3)
PSA group						
< 2	56 (4.5%)	86 (4.7%)	142 (4.6%)	10 (7.5%)	14 (6.8%)	24 (7.1%)
2 $\leqslant$ 4	241 (19.4%)	307 (16.9%)	548 (17.9%)	22 (16.5%)	28 (13.6%)	50 (14.7%)
4 $\leqslant$ 6	399 (32.1%)	578 (31.8%)	977 (31.9%)	49 (36.8%)	76 (36.9%)	125 (36.9%)
6 $\leqslant$ 10	360 (28.9%)	559 (30.8%)	919 (30%)	34 (25.6%)	64 (31.1%)	98 (28.9%)
10 +	188 (15.1%)	287 (15.8%)	475 (15.5%)	18 (13.5%)	24 (11.7%)	42 (12.4%)
BMI at surgery						
Mean (SD)	23.4 (1.29)	33.5 (6.19)	29.4 (6.93)	23.3 (1.4)	33.4 (3.0)	29.5 (5.5)
Median	23.7	32.4	30.6	23.7	32.7	30.7
Q1, Q3	22.6, 24.4	31.0, 34.5	24.1, 33.0	22.5, 24.4	31.2, 34.9	24.1, 33.4
Range	(16.2–25.0)	(30.0–208.7)	(16.2–208.7)	(18.5–25.0)	(30.0–45.5)	(18.5–45.5)
BMI group						
< 25	1244 (100%)	0 (0%)	1244 (40.6%)	133 (100.0%)	0 (0.0%)	133 (39.2%)
30 $\leqslant$ 35	0 (0%)	1430 (78.7%)	1430 (46.7%)	0 (0.0%)	156 (75.7%)	156 (46.0%)
35 $\leqslant$ 40	0 (0%)	309 (17%)	309 (10.1%)	0 (0.0%)	42 (20.4%)	42 (12.4%)
40 +	0 (0%)	78 (4.3%)	78 (2.5%)	0 (0.0%)	8 (3.9%)	8 (2.4%)

Abbreviations: BMI, body mass index; RRP, radical retropubic prostatectomy.

reported data supporting the existence of an inverse association between BMI and PSA levels in men.[3–14] These reports suggest that this phenomenon could negatively influence PSA-based screening in obese men given that PSA levels are known to positively correlate with the extent of disease and aggressiveness in PCa. That is, if obese men have lower PSA levels when compared with their normal weight counterparts, using a standard cutoff (that is, 3–4 ng ml^{-1}) to indicate a need for biopsy would result in obese men being inappropriately screened at a later point in their disease course. Citing this, some investigators have proposed regression-based equations for calculating an 'adjusted PSA level' for obese men, while others have suggested lowering the threshold for biopsy in obese men.[3,8,14] The documented evidence of lower PSA levels in obese men aside, what remains unclear is the more clinically relevant question of whether this effect is enough to warrant the proposed adjustments in

screening practices for obese men. Indeed, if the impact is clinically significant, then we would expect that obese men would present with more advanced and more aggressive PCa compared with normal-weight men after matching on age and PSA level. Herein, we provide evidence from two independent nested case-control studies that after adjusting for PSA and age, obese men present with more advanced (that is, later stage) and more aaggressive (that is, higher grade) PCa compared with non-obese men.

There is a key distinction that needs to be made between the research question we address in this investigation and one that has been previously reported by several investigators. Indeed, there are a number of reports in the literature addressing the more etiologic question of whether obesity itself is a risk factor for PCa. Although several cohort studies suggest a positive association between increasing BMI and PCa risk, there are a number of

Table 2. Association of pathologic features of aggressiveness with body mass index ⩾ 30 (vs < 25) after multivariable adjustment for patient age and pre-operative PSA

Pathologic feature	Mayo Rochester (N = 3061)		Mayo Florida (N = 339)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Prostatic volume (cm^3) doubling	1.49 (1.33–1.68)	< 0.0001	1.43 (0.94, 2.18)	0.099
Tumor volume (cm^3) doubling	1.06 (1.03–1.09)	< 0.0001	1.17 (0.95, 1.43)	0.14
Pathologic T stage[a]				
pT2	REF	—	REF	—
pT3, pT4, pTxN+	1.30 (1.05–1.62)	0.02	1.45 (0.65–3.23)	0.36
Pathologic Gleason score				
5–6	REF	—	REF	—
7	1.36 (1.17–1.60)	< 0.001	1.01 (0.62–1.64)	0.96
8–10	1.50 (1.14–1.96)	0.003	1.42 (0.55–3.66)	0.47
Positive margin				
No	REF	—	REF	—
Yes	1.56 (1.30–1.89)	< 0.001	1.61 (0.95–2.71)	0.077
Seminal vesicle involvement				
No	REF	—	REF	—
Yes	1.41 (1.03–1.92)	0.0311	3.72 (1.05–13.2)	0.042
Extra-capsular extension				
No	REF	—	REF	—
Yes	1.26 (1.01–1.57)	0.045	1.37 (0.77–2.46)	0.28

[a]1997 International Union Against Cancer-American Joint Committee on Cancer.

Table 3. Association of pathologic features of aggressiveness with body mass index (BMI) ⩾ 35 (vs BMI < 25) after multivariable adjustment for patient age and pre-operative PSA

Pathologic feature	Mayo Rochester (N = 1631)	
	OR (95% CI)	P-value
Prostatic volume (cm^3; doubling)	1.76 (1.46–2.13)	< 0.0001
Tumor volume (cm^3; doubling)	1.09 (1.04–1.14)	0.0007
Pathologic T stage[a]		
pT2	REF	—
pT3, pT4, pTxN+	1.15 (0.81–1.63)	0.45
Pathologic Gleason score		
⩽ 6	REF	—
7	1.86 (1.44–2.39)	< 0.001
8–10	2.32 (1.54–3.48)	< 0.001
Positive margin		
No	REF	—
Yes	1.68 (1.15–2.47)	0.008
Seminal vesicle involvement		
No	REF	—
Yes	1.24 (0.76–2.02)	0.38
Extra-capsular extension		
No	REF	—
Yes	1.28 (0.91–1.81)	0.16

[a]1997 International Union Against Cancer-American Joint Committee on Cancer.

studies reporting no association as well.[15] The conflicting data regarding an overall association notwithstanding, there is compelling evidence that obesity may increase the risk of developing more aggressive and fatal forms of PCa.[16–19] As such, this has raised interesting questions about the underlying biology of PCa development and, specifically, whether obesity may be associated with a specific carcinogenic pathway that leads to a more aggressive PCa phenotype. With the obvious strengths of these studies in mind, an alternative explanation of the link between obesity and aggressive/fatal PCa is that cancer detection in obese men is being delayed because of lower PSA levels in these men (most likely due to a hemodilution effect). Recently, Banez et al.[20] began to address this more specific question by comparing the operating characteristics (that is, area under the curve or AUC) of PSA across BMI categories among a cohort of 917 Italian men undergoing prostate biopsy. The authors report no evidence of a difference in the overall AUCs of PSA for predicting presence of PCa among normal-weight (AUC = 0.56), overweight (AUC = 0.60) and obese men (AUC = 0.60; P = 0.68) in either DRE-positive or -negative men. Although these results support the lack of a need to adjust PSA levels for obese men with regard to simply detecting the presence of PCa, they do not inform the larger question of whether PSA screening levels should be adjusted to avoid delaying diagnosis and allowing unnecessary advancement of PCa in obese men.

With our nested case-control design, we address for the first time the specific question of whether there is empirical evidence to support the need to adjust screening PSA levels in obese men to avoid a clinically significant postponing of PCa diagnosis. Although our data are supportive of the notion that lower PSA levels in obese men have PCa screening implications, it is important to note that our data are observational and more importantly, there are alternative explanations. For example, it has been reported that obesity is associated with lower PSA-driven biopsy rates. Specifically, Parekh et al.[21] reported data from the National Health Interview Survey indicating biopsy rates were lower among men with a BMI > 30 vs BMI < 25 (4.6% vs 5.8%; P = .05). This would suggest that a possible reason obese men present with more aggressive tumors is not that a hemodilution effect results in delayed screening but rather that obese men are less likely to undergo PSA-driven biopsy in the first place. Related

to this, there is some indication that it is more difficult to palpate the prostate on digital rectal exam (DRE) in obese men, and, in many cases, only the apex can be adequately assessed to detect the presence of a tumor.[22] Although the proposed challenge in performing DRE among obese men has been difficult to quantify, this would have the potential to contribute to our observation of more aggressive PCa for obese men after matching on age and PSA. That being said, we would point out that our observation that obese men present with more aggressive disease after matching on PSA holds true for the subgroup of men with higher PSA levels (that is, $> 10 \, \text{ng ml}^{-1}$) where a DRE for confirmation of tumor presence would be less likely (that is, they would be more likely to move directly to transrectal biopsy).

Issues of causality aside, we are particularly mindful of the need to interpret our observational data very carefully. It has become clear over the past decade that over-diagnosis and overtreatment of 'insignificant PCa' are real issues that have spurred concerted efforts to improve the ability to distinguish indolent from aggressive forms of PCa. Therefore, any study generating data in support of lower thresholds, even if for a specific subset of the male population, needs to be vetted with significant caution. As such, what will be needed in order to move this discussion forward in a meaningful way will be independent validation from other large, observational data sets, as well as reports from data collected as part of prospective randomized trials. Specifically, we would note that our data are from a large tertiary referral center of men undergoing surgery for PCa and, therefore, have limited generalizability to the general population seeking screening for PCa. Moreover, our study population at both sites is $> 95\%$ Caucasian and cannot be used to inform the discussion about screening practices for obese men of other racial/ethic backgrounds. Along these same lines, it should also be noted that surgery is less likely to be offered to the most obese men, and therefore they are not adequately represented in our study of surgically treated men. Finally, we are mindful that our data do not provide any evidence that lowering of PSA screening cut-points in obese men would ultimately translate to better survival for these men or simply just alter pathologic outcomes. With the need for external validation and the above mentioned limitations in mind, the specific strengths of our study include the large sample size, the use of a cost-effective, nested case–control design, the inclusion of data from two independent populations, our focus on one treatment modality (that is, surgery), the tight matching on age and PSA level, and the assessment of multiple indicators of both PCa aggressiveness and extent of disease.

CONCLUSIONS

After controlling for PSA level and age, obese men are more likely to present with pathologically advanced and more aggressive PCa compared with non-obese men. If our observations are confirmed in independent populations, this would further support the need to re-evaluate PSA-based screening practices for obese men.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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