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Does obesity modify prostate cancer detection in a European cohort?

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Introduction To investigate prostate-specific antigen (PSA) accuracy and digital rectal examination (DRE) accuracy in detecting prostate cancer according to body mass index (BMI) in Spanish men with an indication of the first prostate biopsy.

Material and methods We reviewed the clinical and histopathological data of 1,319 patients who underwent transrectal ultrasound-guided prostate needle biopsy. The patients were categorised according to the BMI as follows: <25 kg/m^2 (normal weight); 25–29.9 kg/m^2 (overweight); and ≥30 kg/m^2 (obese). Receiver operator characteristic curves were used to assess PSA accuracy and DRE accuracy by calculating the area under the curve.

Results The obesity rate of the cohort was 14%. PSA accuracy for predicting prostate cancer in each BMI category was 0.52, 0.58 and 0.62, respectively (p = 0.01). After stratification by DRE findings, there was no difference in the performance accuracy of PSA in predicting the presence of cancer across BMI groups in abnormal DRE (p = 0.90). Serum PSA, DRE and BMI were strong predictors of prostate cancer diagnosis (odds ratio 1.07, 2.02 and 1.4, respectively; p <0.001). When the DRE was abnormal, a BMI ≥30 increased the risk of prostate cancer twice. With the addition of BMI to the model, the area under the curve of the combined PSA and DRE for diagnosing prostate cancer improved from 0.60 to 0.63.

Conclusions The predictive value of PSA in predicting prostate cancer is not poorer in the obese population and the predictive value of an abnormal DRE in cancer detection is significantly modified by the patient's BMI.

Key Words: prostate-specific antigen ‹› obesity ‹› digital rectal examination ‹› biopsy ‹› prostatic neoplasms

INTRODUCTION

Prostate cancer is the most commonly diagnosed solid cancer in men, with 220,800 estimated new cases and 27,540 estimated deaths in the United States recorded in 2015 [1]. GLOBOCAN 2012 sources estimate prostate cancer incidence in the European Union at 345,195 new cases, with a crude rate of 139, making it the most commonly diagnosed cancer in European men, with 71,789 estimated cancer deaths (the third cause of cancer death behind lung and colorectal cancer) [2]. Patient factors associated with the development of prostate cancer include age [3, 4], race [5] and family history, all of which are nonmodifiable factors, with age as the most important nonmodifiable factor. The most important environmental risk factors of prostate cancer are lifestyle-associated, with nutrition and dietary habits being among the most important.

Obesity is an excess of accumulation of adipose tissue in the body; genetics and lifestyle-related factors are thought to be the primary obesity determinants. Many researchers have studied the impact of obesity on prostate cancer. A recent meta-analysis has demonstrated that a high body mass index (BMI) correlated positively with prostate cancer detection

– particularly high-grade prostate cancer detection [6]; another recent meta-analysis provides preliminary evidence to demonstrate that obesity is a significant risk factor for aggressive prostate cancer and prostate cancer-specific mortality [7].
Prostate-specific antigen (PSA), despite its controversies, remains the mainstay of early prostate cancer detection [8], and several population- and nonpopulation-based studies have shown a negative association between BMI and PSA. These results could lead to a delayed diagnosis of prostate cancer with an unfavourable prognosis in the obese population [9, 10, 11]. One of the mechanisms proposed to lower PSA in the obese population is the increased plasma volume in obese men and the resulting haemodilution [12].
To address this concern, we have investigated whether the predictive accuracy of PSA and the digital rectal examination (DRE) is modified by obesity in a cohort of 1,319 patients undergoing the first prostate biopsy.

MATERIAL AND METHODS

Study population

A total of 1,319 men who underwent the first transrectal ultrasound-guided prostate needle biopsy from 2007–2011 at a University Hospital in Spain were included in this study, and data concerning these patients were retrospectively collected. There was no age limit in the study; however, the range in the age of patients ran from 48 to 84 years-old. Patients with inhibitors of 5-alpha reductase (5 ARI) intake were included (118 patients). Indications for prostate biopsy were a PSA higher than 4.0 ng/ml, an abnormal DRE or both. All the patients had between 10–12 cores taken during the biopsy, and the prostate was biopsied bilaterally near the base, mid-gland and apex regions. No patients showed missing PSA or BMI data; thus, all 1,319 patients were included in the analysis.

Study variables

Patient BMI was categorised as follows: <25 kg/m^2 (normal weight); 25–29.9 kg/m^2 (overweight); and ≥30 kg/m^2 (obese), as defined by the World Health Organisation. When the DRE suggested prostate cancer, the case was classified as abnormal. Prostate volume in cm3 was measured by planimetry during the biopsy procedure.

Statistical analysis

Baseline variables were compared across BMI categories using the chi-squared test (categorical) and the Kruskal-Wallis test (continuous). A linear regression model controlling for age, digital rectal findings and transrectal ultrasound (TRUS) volume was used to calculate mean-adjusted PSA concentrations with 95% confidence intervals (CI) for each BMI category. Receiver operator characteristic (ROC) curves plotted as false-positive rate (1 minus specificity) versus sensitivity, were used to assess PSA accuracy for predicting prostate cancer overall, then stratified according to the DRE findings using the area under the ROC curve (AUC) to measure the accuracy of PSA

Table 1. *Baseline characteristics of the study population (overall and stratified by BMI groups)*

	Overall	BMI <25	BMI 25-29.9	BMI ≥30	p value
Number (%)	1319 (100)	661 (50)	476 (36)	182 (14)	
Age (years); median (interquartile range)	66 (61-71)	67 (61-72)	66 (61-70)	67 (61-71)	0.17*
PSA (ng/ml); median (interquartile range)	6.5 (5.16-8.75)	6.6 (5.1-6.6)	6.4 (5.1-9)	6.5 (5.3-8.6)	0.7*
DRE; n (%)					
Normal	1063 (80)	536 (81)	388 (81)	139 (76)	0.2‡
Abnormal	256 (20)	125 (19)	88 (19)	43 (24)	
TRUS volume (cc); median (interquartile range)	49 (38-65)	49 (38-65)	48 (37-65)	47 (36-66)	0.6*
Biopsy results; n (%)					
Benign	802 (60)	446 (67)	262 (55)	94 (52)	< 0.001‡
Cancer	517 (40)	215 (32)	214 (45)	88 (48)	
Biopsy Gleason sum; n (%)					
<7	374	160 (80)	156 (79)	58 (71)	0.2‡
≥7	107	41 (20)	42 (21)	24 (29)	

PSA – prostate-specific antigen; DRE – digital rectal examination; TRUS – transrectal ultrasound; p* – Kruskal-Wallis test; p‡ – chi-square test

as a predictor of prostate biopsy results. AUCs were compared across the BMI groups overall and stratified according to DRE findings using the chi-squared test. ROC curves were also used to assess the PSA accuracy in predicting a biopsy Gleason score ≥7 and in calculating the predictive value of DRE according to BMI. Multivariate logistic regression analysis was used to examine the association between BMI and prostate cancer and between BMI and Gleason score as determined by the TRUS biopsy, after adjusting for age, prostate volume, PSA level and DRE findings. A two-tailed p <0.05 was considered to indicate statistical significance in all the analyses.

RESULTS

Demographic and clinical features of the study cohort

Overall characteristics of the study cohort at baseline and stratified by BMI are listed in Table 1. Fourteen percent of the patients (n = 182) in the study were in the obese group. The median prebiopsy PSA was 6.5 ng/ml and no differences were observed in the PSA levels across the groups (p = 0.7). The number of patients with an abnormal DRE (24%) was higher in the obese group. A diagnosis of cancer was more common among the overweight (45%) and the obese group (48%) (p <0.001). A total of 32 patients, who were taking 5 ARI, were diagnosed of prostate cancer. The percentage of patients with a biopsy Gleason score ≥7 was higher in the obese group (29%); however, the difference was not statistically significant (p = 0.2).

After controlling for age, DRE findings and TRUS volume, the mean PSA levels were found to be lower in the obese than the overweight group, but the trend was not statistically significant (p = 0.6). The mean-adjusted PSA concentrations (95% confidence interval [CI]) for normal, overweight and obese men were 7.7 (7.3–8.0), 8.1 (7.7–8.7) and 7.9 (7.1–8.8), respectively.

Predictive accuracy of PSA by BMI category

In the overall study sample, the best AUC of serum PSA for predicting prostate cancer on biopsy corresponded to the obese group (AUC = 0.62 [0.54–0.71]) (Table 2).

When stratified according to DRE findings, the best AUC of PSA for predicting prostate cancer corresponded to the men with nonsuspicious PCa on DRE in the obese group (AUC = 0.63 [0.54–0.73]), whereas there were no significant differences among those with a DRE suspicious for prostate cancer (p = 0.90) (Table 2).

Table 2. *Accuracy of pre-biopsy PSA for predicting cancer on prostate biopsy across BMI categories*

	BMI <25	BMI 25-29.9	BMI ≥30	p
Overall				
AUC (SE)	0.52 (0.02)	0.58 (0.02)	0.62 (0.04)	0.01
95% CI	0.47-0.56	0.53-0.63	0.54-0.71	
Normal DRE				
AUC	0.48	0.57	0.63	<0.001
95% CI	0.42-0.53	0.51-0.63	0.54-0.73	
Abnormal DRE				
AUC	0.58	0.59	0.58	0.90
95% CI	0.48-0.68	0.47-0.71	0.41-0.75	

BMI – body mass index; DRE – digital rectal examination; AUC – area under the curve; SE – standard error with DeLong test; 95% CI – 95% confidence interval; p – chi-square test

Table 3. *Multivariate analysis of factors predicting prostate cancer and a biopsy Gleason sum ≥7*

Variable	Predicting prostate cancer	Predicting a biopsy Gleason sum ≥7
Age (years)		
OR	1.01	1.01
95% CI	0.95-1.07	0.98-1.05
p	0.1	0.3
PSA (ng/ml)		
OR	1.07	1.01
95% CI	1.04-1.1	0.99-1.03
p	<0.001	0.2
DRE (abnormal *vs.* normal)		
OR	2.02	1.8
95% CI	1.5-2.7	1.1-2.8
p	<0.001	0.01
BMI (kg/m^2)		
OR	1.4	1.03
95% CI	1.2-1.7	0.97-1.1
p	<0.001	0.3
Prostate volume		
OR	1.0	0.99
95% CI	0.9-1.005	0.98-1.003
p	0.9	0.1

PSA – prostate-specific antigen; DRE – digital rectal examination; BMI – body mass index; 95% CI – 95% confidence interval; OR – odds ratio; p value by multivariate logistic regression

Table 4. *Accuracy of incorporating BMI to classical predictor models of prostate cancer and a biopsy Gleason sum ≥7*

	Predicting prostate cancer	Predicting a biopsy Gleason sum ≥7
PSA plus DRE		
AUC (SE)	0.60 (0.01)	0.62 (0.02)
95% CI	0.56-0.63	0.57-0.67
p	<0.001	<0.001
PSA plus DRE plus BMI		
AUC (SE)	0.63 (0.01)	0.65 (0.02)
95% CI	0.60-0.66	0.60-0.70
p	<0.001	<0.001

BMI – body mass index; PSA – prostate-specific antigen; DRE – digital rectal examination; AUC – area under the curve; SE – standard error under the nonparametric assumption; 95% CI – 95% confidence interval; p – chi-square test

Predictive value of DRE by BMI

The impact of DRE findings on cancer detection as a function of obesity was evaluated by a multivariable analysis adjusted for BMI as a continuous variable, PSA and age at diagnosis. An abnormal DRE portended twice the odds of any prostate cancer diagnosis compared with normal DRE in each BMI group: 1.52 (1.17–1.98) in the normal weight group; 1.61 (1.14–2.20) in the overweight group; and 2.09 (1.19–3.67) in the obese group; p = 0.002, p = 0.007 and p = 0.01, respectively.

BMI as a predictive factor for prostate cancer

The percentage of men in each BMI category in whom prostate cancer was detected varied, and was much higher in the obese group (p <0.001). As shown in Table 3, BMI was one of the significant factors predicting prostate cancer after adjustments for age, PSA level, prostate volume and DRE abnormality in a multivariate analysis (OR 1.4; 95% CI 1.2–1.7; p <0.001).

BMI as a predictive factor for a biopsy Gleason score ≥7

As shown in Table 3, BMI was not a significant factor predicting a biopsy Gleason score ≥7 after adjustments for age, PSA level, prostate volume and DRE abnormality in the multivariate analysis (OR 1.03; 95% CI 0.97–1.1; p = 0.3); however, an abnormal DRE was able to independently predict it.

Predictive accuracy of the incorporation of BMI in models predicting prostate cancer

The AUC of combined PSA and DRE for diagnosing prostate cancer improved from 0.60 to 0.63 with the addition of BMI to the model, as shown in Figure 1 and Table 4.

Predictive accuracy of the incorporation of BMI in models predicting a biopsy Gleason score ≥7

The AUC of combined PSA and DRE for diagnosing prostate cancer improved from 0.62 to 0.65 with the addition of BMI to the model, as shown in Figure 2 and Table 4.

DISCUSSION

In this study, we investigated whether the diagnostic accuracy of PSA is altered by obesity and DRE; thus, whether PSA is still a valid diagnostic tool in obese men. We also investigated whether DRE accuracy is modified by obesity. We have tested this concern by calculating the AUC and strengthening the model by logistic regression. A higher BMI was significant-

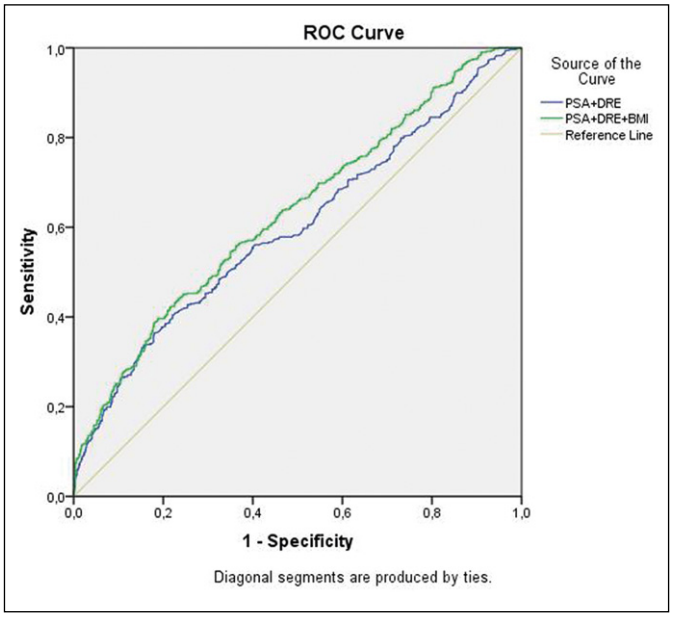

Figure 1. *ROC curves showing the accuracy of incorporating BMI to classical models in the prediction of prostate cancer detection.*
ROC – receiver operator characteristics; PSA – prostate-specific antigen; DRE – digital rectal examination; BMI – body mass index

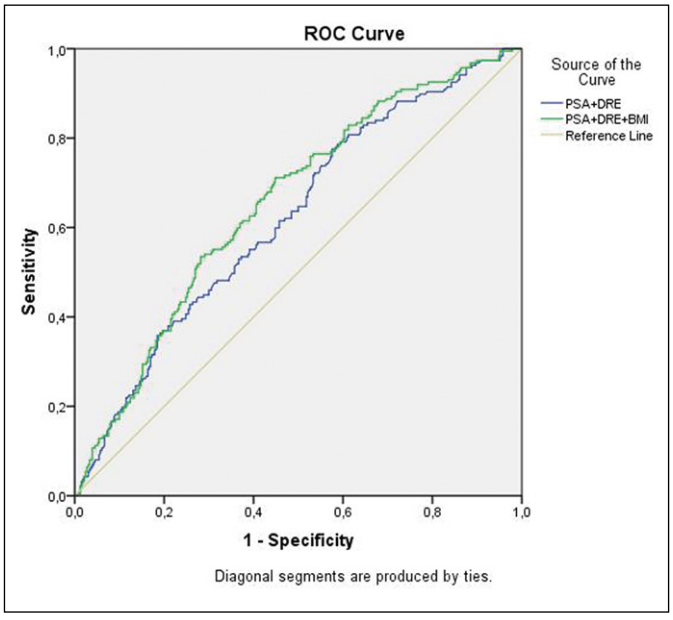

Figure 2. *ROC curves showing the accuracy of incorporating BMI to classical models in the prediction of a biopsy Gleason ≥7.*
ROC – receiver operator characteristics; PSA – prostate-specific antigen; DRE – digital rectal examination; BMI – body mass index

ly associated with an increased risk of prostate cancer detection when adjusted for age, PSA level, DRE findings and prostate volume; however, no association was found between the BMI and Gleason score ≥7 in biopsy specimens.

Although some researchers have established an inverse relationship between PSA level and BMI [9, 10, 11], we have not been able to do so; PSA levels in our study did not differ among BMI groups. Our results could reflect the fact that our study is not a population-based study; thus, our patients are at higher risk for prostate cancer because of the high PSA levels or abnormal DRE. One study which focused on European Mediterranean men, found results similar to ours with no differences in the levels of PSA across BMI groups [12]. Several explanations for this inverse relationship in the literature have been proposed. One is the anti-androgen theory; it is known that obese men have lower testosterone, leading to lower PSA production under androgen control. Another possibility is based on the haemodilution theory, which means that obese men have greater plasma volume. PSA is normally released in the seminal fluid and leaks at low levels into the serum; therefore, greater plasma volume could result in haemodilution, lowering serum PSA concentrations [13, 14]. Regardless of the reason, lower PSA concentrations mean that obese men are less likely to have an elevated PSA and are, subsequently, less likely to undergo biopsy, resulting in fewer cancers detected. To resolve this problem, a correction of the PSA value for the degree of obesity has been proposed in the United States [10]: for overweight men, the multiplication of PSA by a factor of 1.05; and for obese men, multiplication by a factor between 1.1 and 1.5. A Chinese study has demonstrated that although PSA concentration decreases with increasing BMI, PSA mass remains consistent; this study recommends a cut-off point between 3.32 and 3.68 ng/ml for PSA to screen for prostate cancer in the obese population [15].

For the purpose of the study, the operating characteristics of PSA as a function of increasing BMI were analysed and the AUC differed in obese and in nonobese men in predicting prostate cancer status; the best AUC occured in the obese population, and the difference was statistically significant. In this sense, not only does obesity not negatively affect the accuracy of PSA to detect cancer, but the accuracy is in fact better. It is not possible to explain this finding just with the haemodilution theory especially in men with a PSA ≥4, even though multiple cut-off points have been tested in the obese and nonobese populations. We do not know the role of hemodilution in patients with PSA <4 ng/ml because we have not analyzed these patients separately because only patients with an abnormal DRE and PSA which was lower than 4 ng/ml were tested.

We do not have data concerning testosterone levels; therefore, the antiandrogen theory cannot be asserted. Other theories related to endocrine factors such as the levels of leptin – a hormonal peptide involved in the regulation of body weight – could be involved. Leptin levels are higher in patients with prostate cancer than in patients with benign prostatic hyperplasia [16]. There is *in vitro* evidence that leptin stimulates the proliferation and expression of growth factors and also the growth of androgen-independent cells [17–20].

The inverse relationship between hormones such as leptin and adiponectin has also been implicated. When levels of adiponectin have been compared in the prostate cancer population with healthy men or men with benign prostatic hyperplasia, it has been observed that levels of adiponectin are significantly lower in the men with prostate cancer, and even lower in men with aggressive prostate cancer [21, 22].

After stratification by DRE, no difference was found in the performance accuracy of PSA in predicting the presence of cancer among BMI groups in patients with an abnormal DRE, and so PSA accuracy was better in predicting prostate cancer in the obese population with normal DRE. This latter finding could also reflect the difficulty in performing DRE in obese patients, and in this sense creates a higher rate of false negatives. Although the use of DRE for screening has been criticised due to a low sensitivity [23, 24, 25], DRE is part of the screening algorithms in the guidelines of the European Association of Urology. The AUC for DRE in the present study is at least the same as for PSA (0.56).

The obese men with abnormal DRE in this study were more likely to be diagnosed with prostate cancer, but PSA diagnostic accuracy is not modified in obese patients with abnormal DRE; the accuracy is comparable with normal weight men. This fact could reflect some interaction between PSA and DRE. DRE adds a significant benefit to PSA accuracy in overweight and obese patients with normal DRE. A multicentre study that examined the predictive values of DRE for prostate cancer detection also found a higher risk of prostate cancer in the obese population with an abnormal DRE [26]. Greater BMI and DRE together with PSA were significant predictors for prostate cancer in the multivariate analysis (a higher BMI was significantly associated with an increased risk of prostate cancer when adjusted for age, PSA level, digital rectal examination findings and prostate volume), and these results are consistent with studies by Oh and Freedland [27, 28]. However,

no association has been found between BMI and the risk of a biopsy Gleason score ≥7. Many studies have found that obese men undergoing radical prostatectomy have higher-grade and larger tumors, providing further evidence that obese men undergoing radical prostatectomy have more aggressive prostate cancers [29, 30]. The reason we did not find a correlation between obesity and a higher biopsy Gleason score might lie in the low correlation between the Gleason biopsy score and that of the radical prostatectomy specimen as is described in the literature [31, 32, 33].

Another point of interest in this study is the improvement of the PSA AUC in the predictive models of prostate cancer that include BMI compared with the models that do not include it (0.63 to detect prostate cancer and 0.61 to detect a Gleason ≥7 in prostate biopsy). These results would indicate that BMI could be part of the routine items involved in prostate cancer diagnosis.

Attending to our results PSA is still a useful diagnostic tool in our obese population, however, there is some evidence in the literature that the PSA cut-off for biopsy should be lowered in the obese population; so we are taking this recommendation into account.

MRI-imaging in the obese population could be a tool to take into consideration, since DRE may be difficult in the obese patients; some nodules that are not well palpated may emerge in the MRI-image.

The present study has clear limitations that could explain the absence of the inverse association between serum total PSA level and BMI in our population. First, this is not a population study, so the men in the study represent a population with a higher risk of prostate cancer because of their PSA or their abnormal DRE. DRE was not performed by the same urologist, therefore, it could be biased. The retrospective nature of the study is another limitation because we only could collect data regarding BMI; no data was available concerning waist circumference, which might be a better indicator for obesity in adults. Our population is a white European cohort; thus, we cannot generalize our results to other populations (e.g., Asian or African-American men).

CONCLUSIONS

In conclusion, we found that the predictive value of PSA in predicting prostate cancer is something better in the obese population than in the other groups. The best AUC occurs in the obese population with a normal DRE; we might thus conclude that PSA is still a valid tool in evaluating patients for a suspicious prostate cancer. DRE findings when suspicious, are an independent predictor of prostate cancer detection in each BMI group.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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