RESEARCH

The inverse relationship between prostate specific antigen (PSA) and obesity

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Abstract

Obese men have lower serum prostate-specific antigen (PSA) than comparably aged lean men, but the underlying mechanism remains unclear. The aim of this study was to determine the effect of obesity on PSA and the potential contributing mechanisms. A cohort of 1195 men aged 35 years and over at recruitment, with demographic, anthropometric (BMI, waist circumference (WC)) and serum hormone (serum testosterone, estradiol (E2)) PSA and hematology assessments obtained over two waves was assessed. Men with a history of prostate cancer or missing PSA were excluded, leaving 970 men for the final analysis. Mixed-effects regressions and mediation analyses adjusting for hormonal and volumetric factors explore the potential mechanisms relating obesity to PSA. After adjusting for age, PSA levels were lower in men with greater WC ($P=0.001$). In a multivariable model including WC, age, E2/testosterone and PlasV as predictors, no statistically significant associations were observed between with PSA and either WC ($P=0.36$) or PlasV ($P=0.49$), while strong associations were observed with both E2/testosterone ($P<0.001$) and age ($P<0.001$). In the mediation analyses with PlasV as the mediator, the average causal mediation effect (ACME) explained roughly 20% of the total effect of WC on PSA ($P=0.31$), while when E2/testosterone is a mediator, the ACME explained roughly 50% of the effect ($P<0.001$). Our findings indicate that lower PSA levels in obese men, as compared to normal weight men, can be explained both by hormonal changes (elevated E2/testosterone ratio) and hemodilution. Hormonal factors therefore represent a substantial but underappreciated mediating pathway.

Key Words

- prostate cancer
- obesity
- estradiol
- testosterone
- hemodilution
- PSA
- prostate cancer screening

Introduction

Prostate cancer is the most common cancer affecting men in developed countries (Torre et al. 2015). Although the advent of prostate specific antigen (PSA) testing has resulted in earlier detection of prostate cancer, its role in decreasing prostate cancer-specific mortality is far less certain (Pron 2015). Contradictory findings of screening...
studies undertaken to date may reflect the impact of potential modifiers of PSA levels, with considerable attention focused on obesity. Men who are obese have consistently lower PSA concentrations in serum samples than non-obese men (Zhang et al. 2015, 2016, Bonn et al. 2016). The predictive power of the PSA test was not altered by BMI (kg/m^2), a relatively crude measure of obesity, in two independent studies (Banez et al. 2014, Vidal et al. 2015). Other studies have shown that the sensitivity of PSA detection is decreased by approximately 16% in obese men (Negron et al. 2010), leading to the proposal that an obesity-specific PSA model is required to improve the sensitivity of the PSA blood test (Hekal & Ibrahiem 2010, Liang et al. 2010). However, the development and implementation of such a model will be most optimally achieved with an understanding of the mechanisms underlying the relationship between obesity and serum PSA concentrations.

Currently, there are two major hypotheses to explain the reduced PSA levels in obese men (Fig. 1): the effect of hemodilution (Li et al. 2015, Klaassen et al. 2017) and low serum testosterone (Gates et al. 2013, Parikesit et al. 2016). The former is the generally accepted explanation. Men with obesity have a larger plasma volume, which dilutes the serum concentrations of tumor markers such as PSA. Obesity is associated with lower serum testosterone levels (Gates et al. 2013, Parikesit et al. 2016) and, as the prostate gland is an androgen-dependent organ, lower levels of testosterone would be expected to associate with reduced prostate gland volume and PSA secretion. As significant weight loss has been associated with increased serum testosterone and PSA, as well as decreased plasma volume (Woodard et al. 2012), both hormonal and hemodilution mechanisms are credible modifiers of PSA levels in a clinical setting of obesity.

A major shortcoming in the study of obesity-related changes in serum PSA, highlighted by several groups previously, is that some of the studies to date have been undertaken in cohorts of men diagnosed with prostate cancer, rather than cancer-free individuals (Banez et al. 2007, Bonn et al. 2016). The aim of this study is to assess the influence of obesity on serum PSA concentrations and to explore the underlying mechanism for these changes in a longitudinal population-based cohort of men.

Figure 1
Hypothesized mechanistic pathways. Adiposity is associated with increases in both plasma volume and conversion of testosterone to E2. Each of these factors negatively influences serum PSA. DHT, dihydrotestosterone; E2, estradiol; PlasV, plasma volume; PSA, prostate specific antigen; SHBG, sex hormone-binding globulin
Materials and methods

Study population and design

To study the effect of obesity on PSA as well as the underlying mechanisms, we used data from the Florey Adelaide Male Ageing Study (FAMAS) cohort. A full description of this cohort has been previously published (Martin et al. 2007). Briefly, 1195 urban community-dwelling men aged 35 years and over were enrolled and underwent baseline clinical assessments between 2002 and 2005. A second wave of clinical assessments was undertaken between 2007 and 2010, and 950 men returned.

There was a mean of 4.9 years between the two assessment waves. Men with prostate cancer (n=109 (9%)) and men with at least one PSA assessment of more than 4 ng/mL (n=116 (10%)), to ensure the exclusion of any undiagnosed prostate cancer cases, were excluded. For 710 men, PSA and other demographic factors were available at both assessment waves, while 260 men had only one assessment (Fig. 2). Supplementary Table 1 (see section on supplementary data given at the end of this article) presents the number of men assessed at each assessment wave and the number of non-missing data per variable and thereby the data included in the analysis cohort.

Measures

Anthropometry measures (including weight, height and waist measurements as per Norton & Olds (2001)) and a fasting blood sample were taken twice, at the first baseline clinic visit and during the second wave of assessment. We included the following parameters from both assessment time points for our analysis: age at assessment (years), weight (kg), height (m), BMI (kg/m²) and waist circumference (WC) (cm). In addition, we included the following blood investigation, which was taken after 8- to 12-h fasting (Martin et al. 2007): PSA (ng/mL), total testosterone (nmol/L), estradiol (E2) (pmol/L), dihydrotestosterone (DHT) (nmol/L) and sex hormone-binding globulin (SHBG) (nmol/L). Testosterone was measured using a validated stable-isotope dilution liquid chromatography–tandem mass spectrometry; E2 was measured using Immunolite I; PSA was measured using Abbott ARCHITECT. Plasma volume (PlasV) was calculated using Nadler’s formula (Nadler et al. 1962): 

\[ \text{PlasV} = ((0.3669 \times (\text{height in meters})^3 + 0.03219 \times \text{weight in kg} + 0.6041) \times (1 - \text{hematocrit})). \]

PSA-mass (µg) was calculated as the product of PSA and PlasV.

Statistical methods

Demographic summary statistics are reported as mean (s.d.) for continuous and frequency (%) for discrete variables unless otherwise stated, and compared between obesity groups (categorized by WC) using non-parametric Mann–Whitney tests for continuous variables and Fisher’s exact test for discrete. Data from both assessment waves were included in the analyses of PSA. As the majority of individuals contributed two observations for both the outcome and the predictors, mixed-effect models were employed with a random intercept per individual. Non-linearity was included via restricted cubic splines with 3 degrees of freedom. After visual inspection of residual distributions, we log-transformed PSA and PSA-mass. PlasV was also log-transformed due to the assumed relation: \( \log(\text{PSA}) = \log(\text{PSA-mass}) - \log(\text{PlasV}) \). Being concentrations, we also log transformed the hormonal factors. To estimate obesity and hormonal associations with PSA, we constructed age-adjusted linear models.

Initially to explore the mechanistic action of obesity on PSA, we compared the magnitudes of associations of WC with adjustment for PlasV and the hormonal variables separately. Full multivariable mixed-effects linear models were constructed with age, WC, E2, testosterone and PlasV as predictors. Of note, the magnitude of effect of...
E2 and testosterone were equal but opposite, motivating the inclusion of the E2/testosterone ratio variable in all analyses. We used WC throughout due to it being more representative of abdominal fat as practically relevant methods to assess obesity. In the multivariable models missing data were imputed using multivariate imputation with chained equations (100 imputations). Sensitivity analyses for the multivariable models were performed by (i) a complete-case analysis, (ii) excluding WC, (iii) using BMI instead of WC, (iv) using the entire cohort without excluding those with PSA more than 4 ng/mL and (v) repeating the analyses using linear regressions of the cohort for each assessment wave separately. Mixed-effects coefficient of determination (R2) was calculated as per Jaeger et al. (2017). Finally, we considered a mechanistic model where adiposity affects PSA via either the plasma volume pathway or hormonal pathway (Fig. 1). Being controlled through a feedback regulatory axis, there was no concern that PlasV has any causal effect on hormonal levels (E2, testosterone, DHT); equally, there was no reason to believe that hormonal factors would have any causal effect on the plasma volume, nor that obesity in our cohort is a result of primary hormonal dysfunction. As such, we employed mediation analyses (Tingley et al. 2014) to estimate the direct effects of WC on PSA and the proportion associated with either plasma volume or the E2/testosterone ratio. These were complete case analyses adjusting for age. Linear associations are presented as estimated coefficient = β (95% CI). All statistical analyses were performed using R software (version 3.3.0, The R foundation for statistical computing, 2016).

### Ethics

The FAMAS study protocol was approved by the Royal Adelaide Hospital Research Ethics committee and, where appropriate, the Aboriginal Health Research Ethics Committee of South Australia. Participants gave informed consent to be involved in the FAMAS study.

### Results

The analysis cohort consisted of 970 men with a median age at accrual of 52 years (range 35–80). The mean (s.d.) baseline PSA concentration for the cohort was 1.0 (0.7) ng/mL, baseline BMI was 29 (4) kg/m², and baseline WC was 101 (12) cm (Table 1).

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**Table 1** Baseline demographic summary statistics.

<table>
<thead>
<tr>
<th></th>
<th>Non obese*</th>
<th>Obese*</th>
<th>Total</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>N=577 (59%)</td>
<td>N=393 (41%)</td>
<td>N=970</td>
<td></td>
</tr>
<tr>
<td>Adiposity (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>53 (11)</td>
<td>55 (11)</td>
<td>53 (11)</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>93 (7)</td>
<td>112 (9)</td>
<td>101 (12)</td>
<td>–</td>
</tr>
<tr>
<td>PlasV (L)</td>
<td>2.8 (0.3)</td>
<td>3.2 (0.4)</td>
<td>3.0 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>1.03 (0.70)</td>
<td>0.97 (0.67)</td>
<td>1.00 (0.69)</td>
<td>0.07</td>
</tr>
<tr>
<td>PSA mass (µg)</td>
<td>2.8 (1.9)</td>
<td>3.0 (2.1)</td>
<td>2.9 (2.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hormonal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>19 (7)</td>
<td>16 (7)</td>
<td>18 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E2 (pmol/L)</td>
<td>89 (38)</td>
<td>99 (37)</td>
<td>93 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DHT (nmol/L)</td>
<td>1.9 (0.8)</td>
<td>1.5 (0.9)</td>
<td>1.8 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E2/testosterone</td>
<td>32 (5%)</td>
<td>46 (12%)</td>
<td>78 (8%)</td>
<td></td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>37 (17)</td>
<td>31 (15)</td>
<td>35 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>375 (65%)</td>
<td>254 (65%)</td>
<td>629 (65%)</td>
<td>0.005***</td>
</tr>
<tr>
<td>Other</td>
<td>13 (2%)</td>
<td>0 (0%)</td>
<td>13 (1%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>189 (33%)</td>
<td>139 (35%)</td>
<td>328 (34%)</td>
<td></td>
</tr>
</tbody>
</table>

*Obesity defined as WC ≥102 cm; **P value of Mann–Whitney tests; ***P value of Fisher exact test.

DHT, 5α-dihydrotestosterone; E2/testosterone, estradiol-testosterone ratio; E2, estradiol; PlasV, plasma volume; PSA, prostate specific antigen; SHBG, sex hormone binding globulin; WC, waist circumference.
Obesity

At baseline 307 men (32%) were obese (BMI ≥30 kg/m²) of whom 32 (10%) had a WC less than 102 cm. Based on WC, 393 men (41%) were classified as obese (≥102 cm) of whom 117 (30%) had a BMI less than 30 kg/m². Both WC and BMI increased with age until roughly 60 years, and then decreased for older individuals (Supplementary Fig. 1).

In linear age-adjusted mixed-effect models, greater WC was associated with larger PlasV (β=0.0068, 95% CI=0.0064, 0.0073), higher E2 (β=0.0043, 95% CI=0.0026, 0.0060) and E2/testosterone (β=0.014, 95% CI=0.012, 0.016) and reduced testosterone (β=−0.097, 95% CI=−0.111, −0.088) and DHT (β=−0.010, 95% CI=−0.012, −0.008) (all P<0.001). Similar associations were observed for BMI (data not shown).

Prostate-specific antigen

Serum PSA levels were higher in older men and lower in obese men (Fig. 3). After age adjustment, negative associations with PSA were identified with PlasV (P=0.007) and both E2 (P=0.002) and E2/testosterone (P<0.001), and a positive association with testosterone (P=0.008), but not with DHT (P=0.18) (Table 2 and Supplementary Fig. 2). Of note, the magnitude of effect of E2 and testosterone was equal in opposite directions, suggesting that the magnitude of the ratio is related to PSA levels.

The magnitude of the association between PSA and obesity (in terms of either WC or BMI) was reduced when either PlasV or hormonal factors were adjusted for, with the greatest attenuation after adjustment for E2/testosterone. Adjustment for E2/testosterone and plasma volume led to attenuations of 48% and 18%, respectively (Supplementary Table 2). Notably, the negative association between E2/testosterone and PSA remained significant (both P<0.001) with minimal attenuation when adjusting for age and either BMI or WC. In multivariable mixed effects regressions, age and E2/testosterone provided the greatest explanatory value for PSA, with plasma volume providing minimal additional value (Model 2 Fig. 4A and Table 2). Repeating these analyses without WC (Fig. 4B), adjusting for SHBG or DHT or replacing WC with BMI did not affect the results (Supplementary Table 3). Including men with PSA more than 4 ng/mL or restricting to a complete-case analysis did not change the conclusions (data not shown). Repeating Model 2 (Table 2) for each assessment wave separately using linear regression model (Supplementary Fig. 3A and B) resulted in similar conclusions, albeit with a slightly stronger PlasV effect at the first assessment.

In a complete-case analysis of Model 2 a total of R²=12.8% of the variance of PSA was explained, with age having the greatest effect (partial R²=11.1%) followed by E2/testosterone (R²=partial 1.3%), while plasma volume explained only 0.2% of the variance.

Mechanistic pathways

Fat mass and prostate volume increase with age in an average male (Vermeulen et al. 1999, Vesely et al. 2003). Higher levels of body fat result in both increased plasma volume (Woodard et al. 2012) and an increased E2/testosterone ratio (Gates et al. 2013). Of interest is whether hormonal and/or hemodilution (plasma volume) mediate the adiposity’s effect in reducing PSA concentrations in obese men. In the mediation analyses with plasma volume as the mediator for WC on PSA (Table 3), the average causal mediation effect (ACME) was not significant (P=0.31; Fig. 4C), the point estimate suggesting roughly one-fifth of the total

Figure 3
Non-linear mixed effect estimated PSA levels by age and adiposity. BMI, body mass index; PSA, prostate specific antigen (ng/mL); Waist circumference (cm). A full colour version of this figure is available at https://doi.org/10.1530/ERC-17-0438.
Table 2  Mixed-effect model estimates of (log transformed) PSA with age, WC, plasma volume and hormones.

<table>
<thead>
<tr>
<th></th>
<th>Age-adjusted associations</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95% CI)</td>
<td>P-value</td>
<td>Coefficient (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>0.022</td>
<td>&lt;0.001</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>(0.018, 0.025)</td>
<td></td>
<td>(0.019, 0.026)</td>
</tr>
<tr>
<td>Adiposity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC</td>
<td>−0.0050</td>
<td>0.001</td>
<td>−0.0018</td>
</tr>
<tr>
<td></td>
<td>(−0.0079, −0.0020)</td>
<td></td>
<td>(−0.0056, 0.0020)</td>
</tr>
<tr>
<td>log(PlasV)</td>
<td>−0.36</td>
<td>0.007</td>
<td>−0.12</td>
</tr>
<tr>
<td></td>
<td>(−0.62, −0.10)</td>
<td></td>
<td>(−0.46, 0.21)</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log(E2)</td>
<td>−0.13</td>
<td>0.002</td>
<td>−0.18</td>
</tr>
<tr>
<td></td>
<td>(−0.20, −0.05)</td>
<td></td>
<td>(−0.27, −0.09)</td>
</tr>
<tr>
<td>log(T)</td>
<td>0.11</td>
<td>0.008</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>(0.030, 0.20)</td>
<td></td>
<td>(0.07, 0.27)</td>
</tr>
<tr>
<td>log(E2/testosterone)</td>
<td>−0.20</td>
<td>&lt;0.001</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>(−0.27, −0.12)</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>log(DHT)</td>
<td>0.05</td>
<td>0.18</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>(−0.03, 0.13)</td>
<td></td>
<td>−</td>
</tr>
</tbody>
</table>

PSA increases with age and after age-adjustment, increases with testosterone, and decreases with WC and plasma volume, E2 and E2/testosterone ratio. In the multivariable models including age, WC, E2, testosterone and PlasV (Model 1) and age, WC, E2/testosterone and PlasV (Model 2), there are no associations detected between PSA and either WC or plasma volume, while hormonal associations remain.

*Covariate unadjusted.

DHT, 5α-dihydrotestosterone; E2/testosterone, estradiol-testosterone ratio; E2, estradiol; PlasV, plasma volume; PSA, prostate specific antigen; WC, waist circumference.

Figure 4
(A and B) Standardized mixed-effects regression coefficients for log transformed PSA concentration with (A) WC included in the model and (B) WC excluded from the model. After adjusting for age and the E2/testosterone ratio, there were no detectable associations between PSA and either WC or plasma volume. (C and D) Causal mediation estimates (including average causal mediation effects (ACME), average direct effects (ADE) and the total effects) estimating the contribution of adiposity (WC) to reduce PSA with mediation by either (C) plasma volume, or (D) E2/testosterone. E2/testosterone, estradiol-testosterone ratio; PlasV, plasma volume; WC, waist circumference. A full colour version of this figure is available at https://doi.org/10.1530/ERC-17-0438.
Table 3  Causal mediation analyses.

<table>
<thead>
<tr>
<th></th>
<th>Estimate (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PlasV mediating WC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACME</td>
<td>−0.0011 (−0.0034, 0.0011)</td>
<td>0.31</td>
</tr>
<tr>
<td>ADE</td>
<td>0.0039 (−0.0076, −0.0001)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total effect</td>
<td>0.0050 (−0.0079, −0.0020)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E2/testosterone mediating WC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACME</td>
<td>−0.0025 (−0.0036, −0.0014)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADE</td>
<td>−0.0026 (−0.00056, 0.0007)</td>
<td>0.12</td>
</tr>
<tr>
<td>Total effect</td>
<td>−0.0050 (−0.0079, −0.0020)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The average causal mediation effect (ACME) of E2/testosterone ratio explains roughly one half of the total effect of obesity on PSA. In contrast, the ACME of the PlasV explains about one fifth of the total effect of obesity on PSA. Causal mediation analyses (including average causal mediation effects, average direct effects and the total effects) estimating the contribution of adiposity’s (WC) influence on PSA mediation by plasma volume or E2/testosterone. ACME, average causal mediation effect; ADE, average direct effect; E2/testosterone, estradiol-testosterone ratio; PlasV, plasma volume; WC, waist circumference.

Discussion

In this study, we demonstrate that in men free of prostate cancer, serum PSA concentration is inversely associated with obesity, irrespective of the modality of assessment (either WC or BMI) and provide compelling evidence for mediation of this effect by hormonal factors.

Obesity is associated with increased plasma volume, which has been proposed to have a dilution effect, thereby decreasing serum PSA concentrations (Banez et al. 2007, Grubb et al. 2009). In a study by Banez et al. (2007), the decrease of PSA associated with obesity in 14,000 men with prostate cancer from three independent cohorts was attributed to haemodilution as a result of increasing the plasma volume. In that study, the non-significant change of PSA mass (PSA multiplied by the plasma volume) with obesity was used as evidence of the haemodilution effect. In agreement with this study, we observed strong associations between PSA concentration and both WC and BMI, and no equivalent significant associations with PSA mass in age-adjusted analyses (Supplementary Table 4). However, in contrast to Banez et al. (2007), we do not conclude that the PSA concentration–obesity association is solely due to hemodilution, but rather show that hormonal factors play a major role. We note that this conclusion is in agreement with the one-compartment PSA model (Supplementary Fig. 4). The steady-state solution indicates that PSA-mass is equal to the accumulation rate (prostate excretion) divided by the body’s elimination rate multiplied by plasma volume. Hence, PSA mass, but not PSA concentration, is expected to be associated with plasma volume. In this model, the prostate excretion rate is the natural mechanism linking hormonal levels with both PSA mass and concentration. Replacing PSA with PSA mass in our multivariable regressions only changes the coefficient of PlasV, as expected, which changes from a minimal positive effect to a large negative effect as expected (Supplementary Table 4 and Fig. 5).

Using the REDUCE study cohort, Klaassen et al. (2017) concluded that testosterone and DHT are responsible for only 19% of the associated reduction in the PSA with obesity with the remaining effect due to hemodilution. In our study, we compared the effect of plasma volume, estradiol, testosterone, DHT and E2/testosterone in separate models (Supplementary Table 2). In our cohort, the E2/testosterone causes the greatest attenuation in the effect of obesity on PSA. Further, the hormonal changes associated with obesity (in the form of reduced testosterone, discordant E2 and thereby elevated E2/testosterone ratio) represented a substantial proportion of the decrease in the PSA associated with obesity, a result confirmed in our mediation analyses. Our findings are consistent with previous studies that show associations between PSA and hormones (Woodard et al. 2012, Peskoe et al. 2015, Usoro et al. 2015).

Prostate cancer detection accuracy has been improved with the use of the PSA/testosterone ratio (Gurbuz et al. 2012, Xu et al. 2018). In contrast, adjusting only for obesity in addition to PSA did not improve specificity (Oh et al. 2013, Banez et al. 2014, Vidal et al. 2015, Harrison et al. 2016). This may be due to the absence of adjustment for hormonal factors in those models. Hormonal factors play a critical role in prostate cancer development, for which obesity may be a poor surrogate.

Strong evidence exists regarding the association of obesity with elevated grade and advanced stage...
prostate cancers (Bonn et al. 2016, Zhong et al. 2016), as such it is a natural question as to whether the altered hormonal milieu, characteristic of increased obesity (reflected in the E2/testosterone ratio), contributes to more aggressive disease, potentially via direct hormonal effects on the prostate gland. It is equally possible that E2/testosterone is a surrogate for other hormonal processes influencing prostate function. Metabolic effects on the hormonal environment are very complex, and potentially influenced by other factors such as sex hormone-binding globulin (SHBG) (Moran et al. 2013). Adjusting for SHBG in our models however did not qualitatively change our final conclusions regarding E2/testosterone, nor were there significant associations between PSA and SHBG. The non-significant association observed between PSA and DHT may be attributed to the fact that serum DHT does not represent the true intra-prostatic DHT concentration (Cook et al. 2017).

A major strength of our study is that we not only examined the effect of obesity on PSA, but also directly explored two hypothesized causal mechanisms. Further, we assessed two independent measures of obesity, WC and BMI, and found little difference. We explored hormonal effects using different hormonal variables, namely testosterone, E2, DHT and E2/testosterone. Finally, we calculated the plasma volume by using hematocrit, which is considered a more accurate technique than estimation using weight and height only. Our study is limited by missing clinical data; our final cohort of 970 men may have included undiagnosed prostate cancer patients. Measures of prostate volume would have further improved our analyses, however, in its absence we assume that the observed strong age effects are in part due to the growth in prostate volume with age.

**Conclusion**

Observed lower PSA levels in obese men, as compared to normal weight men, can be explained by both hormonal changes (namely elevated E2/testosterone ratio) and possible hemodilution effects. As a substantial mediating pathway between obesity and PSA, hormonal factors should be considered in the development of models of obesity-dependent PSA levels.

**Supplementary data**

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-17-0438.

**Declaration of interest**

The authors have no conflicting interests to declare, other than: P Sutherland: Advisory board for Tolmar; Investigator on clinical trials for Pfizer, Bayer, Eli Lilly; Lectures fees for Tolmar, Pfizer, Bayer, Eli Lilly. G Wittert: Received research support from Bayer Schering, Eli Lilly, Resmed Foundation, Itamar, Siemens; Investigator on clinical trials for Roche, Pfizer, Astra Zeneca, Takeda, Boehringer, BMS, Amgen, Johnson and Johnson, MSD, GSK, Lawley; Lecture fees for Bayer Schering, Sanofi, Astra Zeneca, I-Nova, Roche, Abvie, Amgen, Novo Nordisk, Merck, Besins; Paid consultant to Elsevier, Lawley Pharmaceuticals; Independent Chair of the Weight Management Council of Australia; Editor-in-Chief of Obesity Research and Clinical Practice (Elsevier).

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