Pleiotropy between Genetic Markers of Obesity and Risk of Prostate Cancer

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Abstract

Background: To address inconsistent findings of obesity and prostate cancer risk, we analyzed the association between prostate cancer and genetic markers of obesity and metabolism.

Methods: Analyses included 176,520 single-nucleotide polymorphisms (SNP) associated with 23 metabolic traits. We examined the association between SNPs and prostate cancer in 871 cases and 906 controls, including 427 high-grade cases with Gleason ≥ 7. Genetic risk scores (GRS) for body mass index (BMI) and waist-to-hip ratio (WHR) were also created by summing alleles associated with increasing BMI or WHR.

Results: Prostate cancer was associated with five loci, including cyclin M2, with P values less than 1 x 10^-4. In addition, the WHR GRS was associated with high-grade prostate cancer versus controls [OR, 1.05; 95% confidence interval (CI), 1.00–1.11; P = 0.048] and high-grade prostate cancer versus low-grade prostate cancer (OR, 1.07; 95% CI, 1.01–1.13; P = 0.03). None of these findings exceeds the threshold for significance after correction for multiple testing.

Conclusions: Variants in genes known to be associated with metabolism and obesity may be associated with prostate cancer. We show evidence for pleiotropy between WHR GRS and prostate cancer grade. This finding is consistent with the function of several WHR genes and previously described relationships with cancer traits.

Impact: Limitations in standard obesity measures suggest alternative characterizations of obesity may be needed to understand the role of metabolic dysregulation in prostate cancer. The underlying genetics of WHR or other Metabochip SNPs, while not statistically significant beyond multiple testing thresholds within our sample size, support the metabolic hypothesis of prostate carcinogenesis and warrant further investigation in independent samples. Cancer Epidemiol Biomarkers Prev; 22(9); 1538–46. ©2013 AACR.
prostate cancer risk, although the separate roles of obesity from T2D treatments such as metformin to control insulin activity remain unclear (16, 17).

Further elucidation of the pathway(s) connecting obesity to prostate cancer is needed to understand whether total and visceral obesity could advance and perhaps also inhibit prostate cancer progression, or whether stage/grade-specific associations are an artifact of differential detection associated with obesity (18). Studies of blood biomarkers of prostate cancer have had varying levels of success, perhaps most notably the association with blood insulin-like growth factor 1 (IGF1) and associated IGF-binding protein levels in advancing prostate cancer (19–27). Further clues toward mechanism have been gained from genome-wide association studies (GWAS), in which a pleiotropic effect was identified for loci in JAZF1 and HNFIB (formerly TCF2) across T2D and prostate cancer (28, 29). These genes encode transcription factors involved in cell-cycle regulation, whereas JAZF1 also downregulates fatty acid synthase (30) previously associated with BMI and advanced prostate cancer (31).

The purpose of this investigation is to use a genetic approach and extend the analysis of mechanisms linking obesity to prostate cancer to consider the role of genetic loci previously associated with 23 metabolic traits inducing BMI and estimates of visceral adiposity. Results may identify novel genetic metabolic loci associated with prostate cancer, provide insight into candidate biologic mechanisms linking obesity to prostate cancer, and define obesity subgroups at greater risk for prostate cancer.

Methods

The Nashville Men’s Health Study (NMHS) is a multi-centered, rapid-recruitment protocol to investigate the clinical, genetic, and behavioral determinants of prostate cancer detection, progression, and treatment outcomes. All recruitment and data collection protocols were approved by International Review Boards (IRB) at Vanderbilt University and the Tennessee Valley Veteran’s Administration (Nashville, TN). Men referred for prostate biopsy to Vanderbilt University Medical Center, a large community urology practice in Nashville, and the Tennessee Valley Veterans Administration Medical Center were targeted for recruitment. Exclusion criteria included age less than 40 years, a prior prostate cancer diagnosis, prior prostate surgery, current androgen supplementation use, or English insufficiency for informed consent. These urology clinics receive referrals from physicians throughout metro Nashville, TN, and are the primary providers of diagnostic services for urologic disease in the region. Thus, all NMHS participants have healthcare access sufficient to be diagnosed with prostate cancer. Recruitment occurred before the prostate biopsy procedure such that biases associated with treatment or knowledge of their disease status are prevented. Approximately 90% of eligible men approached for recruitment consented to participate.

A blood sample collected at recruitment was refrigerated immediately after collection and hand-delivered cold on that day to our DNA core lab at Vanderbilt University for DNA extraction and processing. All body size measures were obtained at the time of recruitment by trained research staff. Weight (in kg; no shoes, hospital gown) was measured on a calibrated scale, and height (within 0.1 cm) was measured by stadiometer. Body circumferences were measured using an anthropometric tape measure with built-in tension meter (Gullick II) to ensure an even tension was administered to the tape across participants. Waist circumference was measured at the plane across the iliac crest and usually represents the narrowest part of the torso. Hip circumference was measured at the maximum posterior extension of the buttocks. Two measurements at each site are made in rotational order, with a third measurement if the first 2 differed by more than 1 cm. WHR was calculated from the average waist and hip circumference for each participant. Participants also provided the time of their last food and beverage intakes.

Diagnostic status was abstracted from medical charts. A single pathologist reviewed more than 90% of biopsies. Biopsy Gleason score was recorded for participants diagnosed with cancer to define tumor aggressiveness, with a total Gleason score of 7 or more defined as high-grade prostate cancer.

We targeted 1,920 NMHS participants for DNA plating and genetic analysis. All participants were recruited between January 1, 2006 and March 30, 2011. At that time, there were 941 eligible prostate cancer cases eligible for DNA plating and analysis. Controls were selected among those men without prostate cancer, high-grade prostatic intraepithelial neoplasia, or atypia suspicious for prostate cancer. From more than 3,000 eligible controls at the time, we randomly selected 979 for DNA plating.

Genotyping was conducted using the Illumina Metabochip (ref. 32; Illumina Inc.), and genotypes were called using GenomeStudio. The Metabochip is a genotyping array designed by several consortia to thoroughly investigate candidate genes for metabolic phenomena. A total of 257 genomic regions are assayed using 217,695 single-nucleotide polymorphisms (SNP) in gene regions implicated by previous studies of 23 traits, including obesity, T2D, blood lipids, cardiovascular traits, fasting glucose, and blood cell counts.

Quality control

Quality control (QC) procedures were conducted on called genotypes using the PLINK software package (33). Of the 941 prostate cancer cases and 979 randomly selected controls, genotyping was successfully completed on 899 prostate cancer cases and 941 controls. Samples were removed for genotyping efficiency less than 95% (18 cases, 36 controls), and then SNPs were removed for genotyping efficiency less than 98% (15,716 SNPs). The plink–sex check option was used on common SNPs on the X chromosome with minor allele frequencies (MAF) greater than
0.2, and no participants were found not to be genetically male. Cryptic relatedness was also assessed with identity-by-descent analysis of genotypes using linkage disequilibrium (LD)-pruned SNPs, and one member of any pair of participants who were related at the level of first cousins or more was removed, with preference for retaining cases over controls. We removed 10 participants (1 case, 9 controls) for cryptic relatedness. If a pair of participants was found to be monozygotic twins or inadvertent duplicates, both were removed because the identity of the individuals could not be confirmed (9 cases, 10 controls).

Once participants and SNPs had been through QC, we also ran tests of Hardy–Weinberg equilibrium (HWE) at each SNP and dropped all SNPs with HWE $P < 1 \times 10^{-6}$ (4,712 SNPs). We had QC samples on each genotyping plate, and we compared these sample genotypes with duplicate genotypes across plates to assess genotyping fidelity. On average, genotypes among QC samples were 99.4% concordant. We evaluated population substructure using principle components analysis with the EIGENSOFT software package (34). We selected 38,980 LD-pruned common SNPs with MAF $> 0.05$ from the data and extracted prostate cancer s for plotting our participants against International HapMap Project participants to assess population stratification in our sample (Supplementary Fig. S1). We also present quantile–quantile (QQ) plots of observed $P$ values against $P$ values from the uniform distribution for analyses with and without adjustment for ancestry, where the unadjusted analyses had a $\lambda_{GC}$ of 1.04, and the adjusted analyses had a $\lambda_{GC}$ of 1.01 (Supplementary Figs. S2 and S3).

Statistical analysis
We used logistic regression in PLINK to evaluate additively encoded SNP genotypes for association with prostate cancer risk, adjusting for age and 10 principal components of ancestry. Separate analyses also adjusted for prostate volume and BMI or WHR. Tests were run for all SNPs with MAFs greater than 1%. We also stratified high- and low-grade prostate cancer cases and compared each stratum with controls. Additional analyses compared high- with low-grade prostate cancer to identify genetic risk factors associated with cancer grade. Genomic risk scores (GRS) were created to assess the cumulative effect of alleles associated with increasing BMI or WHR on prostate cancer risk. SNPs that had been previously reported from large consortia GWAS studies in European populations for association with BMI (35) and WHR (36) were identified in the Metabochip data. GRSs were calculated indexing the count of trait-increasing alleles divided by the number of available genotypes in each study participant. We also created a second GRS for BMI or WHR that weighted these scores by the regression coefficient from the original reports for the BMI or WHR increase per allele for each SNP. The GRS for BMI included 24 of 32 SNPs from the original reports after QC, whereas the GRS for WHR included 14 of 14 identified SNPs from the original reports.

We fit logistic regression models in STATA (STATA Inc.) with terms for either the BMI or WHR GRS and addition for age, 10 principal components of ancestry, and BMI or WHR, respectively. We also fit models adjusted for prostate volume. These analyses were conducted in the entire study and also in cases stratified by grade, as described for the analyses of individual SNPs. In addition, we feature association results for the individual SNPs from the WHR score (Supplementary Tables S1 and S2).

Results

Single SNP associations
Our final analysis included 871 prostate cancer cases and 906 controls. Prostate cancer cases were significantly older, more likely to be African American, and had smaller prostate volumes than controls but did not significantly differ with regard to BMI, WHR, family history of prostate cancer, diabetes, or statin use (Table 1). Examination of genetic ancestry using principal components revealed a majority of the participants to be of European ancestry (Supplementary Fig. S1). Although BMI and WHR were not associated with total prostate cancer, we found marginally significant associations for WHR [OR, 1.20; 95% confidence interval (CI), 0.99–1.46] per 0.1 unit increase, $P = 0.06$ and BMI (OR, 1.15; 95% CI, 0.99–1.33) per 5 unit increase, $P = 0.07$ with high-grade prostate cancer ($n = 427$) in comparison to low-grade prostate cancer ($n = 444$).

In primary analysis using a logistic regression model adjusted for age and 10 principal components, prostate cancer was associated with 5 distinct loci at a $P < 1 \times 10^{-4}$ (Table 2). Noteworthy SNPs [chromosome (CHR): position] included CHR10:104745421 in CNNM2 (OR, 1.55; 95% CI, 1.25–1.92; $P = 3.6 \times 10^{-5}$); CHR12:109231826 in ATP2A2 and near ANAPC7 (OR, 0.40; 95% CI, 0.25–0.61; $P = 2.3 \times 10^{-3}$); rs13111540 near ELOVL6 (OR, 1.31; 95% CI, 1.14–1.50; $P = 7.8 \times 10^{-3}$); and CHR6:160836326 in LPAL2 (OR, 1.34; 95% CI, 0.32–5.60; $P = 5.8 \times 10^{-3}$).

In analyses stratified by cancer grade, we found that SNPs in the genes ZNF57, PLCE1, CADM2, and CAYBR were associated high-grade prostate cancer with $P < 10^{-4}$ compared with controls (Table 3). Compared with low-grade prostate cancer, we also found a unique set of SNPs associated with high-grade prostate cancer near the genes ZNF536, CCT6B, ASB7, HSP90AA6P, and ROBO1 & 2 had $P < 10^{-4}$ (Table 3). Tests for interaction between listed SNPs with either WHR or BMI were not statistically significant (data not shown). Furthermore, the SNPs rs9409226, rs3786418, rs7252787, and rs1355625 listed in Table 3 were no longer significant at $P < 1 \times 10^{-4}$ after controlling for WHR, prostate size, and genetic ancestry.

WHR and BMI GRSs
Overall associations between GRSs for BMI or WHR with total prostate cancer were not statistically significant compared with controls (Table 4). Additional adjustment for prostate volume, age, ancestry, and obesity measures did not substantially affect results.
Table 1. Distribution of characteristics by case–control status among participants from the NMHS

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Controls (n = 906)</th>
<th>Cases (n = 871)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.34 (8.61)</td>
<td>66.23 (8.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>28.98 (4.59)</td>
<td>28.73 (4.64)</td>
<td>0.255</td>
</tr>
<tr>
<td>WHR</td>
<td>1.02 (0.07)</td>
<td>1.02 (0.07)</td>
<td>0.538</td>
</tr>
<tr>
<td>Natural log prostate</td>
<td>3.83 (0.51)</td>
<td>3.61 (0.46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical</th>
<th>n (%)</th>
<th>n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancestry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>80 (8.83)</td>
<td>107 (12.28)</td>
<td>0.020</td>
</tr>
<tr>
<td>European</td>
<td>787 (86.87)</td>
<td>741 (85.07)</td>
<td>0.305</td>
</tr>
<tr>
<td>East Asian</td>
<td>3 (0.03)</td>
<td>1 (0.01)</td>
<td>0.336</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12 (1.32)</td>
<td>5 (0.57)</td>
<td>0.143</td>
</tr>
<tr>
<td>Other</td>
<td>24 (2.65)</td>
<td>17 (1.95)</td>
<td>0.347</td>
</tr>
<tr>
<td>Family history of PC</td>
<td></td>
<td></td>
<td>0.259</td>
</tr>
<tr>
<td>No</td>
<td>721 (79.58)</td>
<td>674 (77.38)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185 (20.42)</td>
<td>192 (22.62)</td>
<td></td>
</tr>
<tr>
<td>Statin use</td>
<td></td>
<td></td>
<td>0.192</td>
</tr>
<tr>
<td>No</td>
<td>559 (61.70)</td>
<td>511 (58.67)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>347 (38.30)</td>
<td>360 (41.33)</td>
<td></td>
</tr>
<tr>
<td>Diabetes status</td>
<td></td>
<td></td>
<td>0.498</td>
</tr>
<tr>
<td>No</td>
<td>784 (86.53)</td>
<td>744 (85.42)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>122 (13.47)</td>
<td>127 (14.58)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Prostate volume data were missing for 30 controls and 8 cases.
Abbreviation: PC, prostate cancer.

*\(P\) values for continuous variables were based on t test assuming unequal variance. \(P\) values for categorical variables are based on Fisher exact test. Ancestry was evaluated as yes/no for each classification.

Table 5 summarizes GRS analyses stratified by prostate cancer aggressiveness. Increasing GRS for BMI was not significantly associated with low-grade prostate cancer (OR, 1.01; 95% CI, 0.97–1.05; \(P = 0.78\)) or high-grade prostate cancer prostate cancer (OR, 0.99; 95% CI, 0.95–1.04; \(P = 0.71\)). In contrast, each unit increase in WHR-GRS was associated with a statistically significant increase in high-grade prostate cancer odds (OR, 1.05; 95% CI, 1.00–1.11; \(P = 0.048\)) compared with controls. Results for WHR-GRS were similar when we compared high-grade prostate cancer with low-grade prostate cancer (OR, 1.07; 95% CI, 1.01–1.13; \(P = 0.03\)). Further adjustment for prostate volume did not affect results. Weighting GRS WHR scores for the reported association between each allele and WHR generated somewhat stronger ORs but were no longer statistically significant. None of these findings exceed the threshold for significance after correction for multiple testing.

Discussion

Prior studies report that obese men are at greater risk for advanced prostate cancer (37–39); however, standard measurements of body size cannot determine or identify novel pathways. We hypothesized that obesity genetics could deconstruct the components of obesity and help better understand those aspects of obesity relevant to prostate cancer. The Metabochip genotyping platform provides an efficient means to target in detail more than 200,000 genetic variants previously associated with metabolism and obesity. Our approach represents the first Metabochip study of prostate cancer and is based on the premise that the pathways linking obesity to prostate cancer may well extend beyond our existing framework of candidate pathways linking obesity to T2D or other chronic diseases. Our overall analysis found 5 genetic variants associated with total prostate cancer and 5 variants associated with high-grade...
Table 3. Stratified analysis representing SNPs from the Metabochip platform with $P < 10^{-4}$ comparing high-grade prostate cancer cases ($n = 427$) versus low-grade prostate cancer cases ($n = 444$) from NHMD.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr Position</th>
<th>On gene/nearby genes</th>
<th>EA/RA</th>
<th>EAF controls</th>
<th>EAF LG</th>
<th>OR</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZNF556</td>
<td>5 1,333</td>
<td>G/T</td>
<td>0.45</td>
<td>0.36</td>
<td>0.69</td>
<td>0.09</td>
<td>5.08</td>
</tr>
<tr>
<td>ZNF57</td>
<td>5 1,325</td>
<td>A/G</td>
<td>0.09</td>
<td>0.13</td>
<td>0.37</td>
<td>0.25</td>
<td>1.66</td>
</tr>
<tr>
<td>PLCE1</td>
<td>10 95918676</td>
<td>T/G</td>
<td>0.06</td>
<td>0.04</td>
<td>0.17</td>
<td>0.12</td>
<td>1.66</td>
</tr>
<tr>
<td>LIG3</td>
<td>17 30294607</td>
<td>C/A</td>
<td>0.31</td>
<td>0.31</td>
<td>0.40</td>
<td>0.40</td>
<td>1.53</td>
</tr>
<tr>
<td>ASB7</td>
<td>15 99081396</td>
<td>T/C</td>
<td>0.40</td>
<td>0.39</td>
<td>0.50</td>
<td>0.27</td>
<td>1.66</td>
</tr>
<tr>
<td>ROBO1</td>
<td>3 78439962</td>
<td>A/G</td>
<td>0.48</td>
<td>0.46</td>
<td>0.56</td>
<td>0.27</td>
<td>1.66</td>
</tr>
</tbody>
</table>

NOTE: Results adjusted for age and 10 principal components.

Prostate cancer, at $P < 10^{-4}$. In a targeted analysis investigating GRPs for BMI and WHR, we found evidence of pleiotropy between genetic markers of WHR and high-grade prostate cancer grade after adjusting for measured WHR.

The SNP most statistically associated with total prostate cancer was CHR10:104745421, an SNP on cyclin M2 (CNNM2) involved in magnesium transport and metabolism. Magnesium serves as an enzyme cofactor involved with energy metabolism, insulin activity, and glycemic control (40). Genetic variants in CNNM2 are associated with blood magnesium levels (41), and blood magnesium levels were recently associated with the development of aggressive prostate cancer independent of measured WHR.

Increasing WHR has been previously shown to increase risk of T2D (45, 46), coronary heart disease (47), and all-cause mortality (48), independent of total body adiposity estimated by BMI. Similar to a recent meta-analysis of WHR and prostate cancer reporting only a modest nonsignificant association [RR = 1.11 (0.95–1.3), for each 0.1 WHR unit], we found analysis of WHR provided little insight into the obesity–prostate cancer relationship. In contrast, we found the genetic determinants of WHR were associated with the development of aggressive prostate cancer independent of measured WHR.

The SNP that comprise the WHR GRPs from the Metabochip include the SNP rs1055144 in nuclear factor (erythroid-derived2)-like3 (NFE2L3 or Nrf3). The NFE2L3 maps near the HOXA cluster, a family of transcription factors essential to control and coordinate positional identity from anterior to posterior during development and implicated in multiple tumors (49–55). Indeed, NFE2L3 expression may be greatest during embryonic development and is also highly expressed in cancer cell lines (56). Proinflammatory cytokines such as TNF-α increase NFE2L3 expression and NFE2L3 transcripts were found in human lymphoma, breast cancer, and testicular carcinoma tissue samples (56). In this study, rs1055144 was not significant for high-grade prostate cancer, although the direction and magnitude of effect were similar.

An SNP in the WHR GRs that was also nominally associated with high-grade prostate cancer was rs4846567 on chromosome 1q41 ($P = 0.038$) in a gene desert approximately 250 kb from the gene lysophospholipase-1 (LYPLA1). This SNP is also 100 kb from the SNP.
rs2605100 ($r^2 = 0.64, D' = 0.83$), which was previously discovered to be a female-specific WHR SNP (57), and is 93 kb from rs11118316 ($r^2 = 0.29, D' = 0.94$) which is a determinant of the ratio of visceral to subcutaneous adiposity (58). *LYPLAL1* is thought to function as a triglyceride lipase and is upregulated in subcutaneous adipose tissue in obese participants (59). Gene variants in *LYPLAL1* have been associated with triglyceride levels in men (60). Other SNPs, independent of the WHR SNPs, in the 1q41 region were recently reported to be associated with colorectal cancer at genome-wide significance (61, 62). The minor allele at rs4823006 within the WHR-GRS was marginally protective for high-grade prostate cancer ($P = 0.058$). This SNP is near zinc ring finger 3 and kremen 1 (*ZNRF3-KREMEN1*) and aside from an association with centralized fat deposition involved in Wnt signaling and may act as a tumor suppressor (63). Attempts to replicate the WHR GRS with prostate cancer have been hampered by a lack of existing large prostate studies with both genetic data and measured waist–hip data.

### Table 4. Overall ORs comparing BMI GRSs and WHR GRSs with prostate cancer risk among participants from NMHS

<table>
<thead>
<tr>
<th>Obesity scores</th>
<th>Cases/controls</th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI GRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unweighted BMI allele score$^a$</td>
<td>863/876</td>
<td>1.00 (0.97, 1.04)</td>
<td>0.94</td>
</tr>
<tr>
<td>Weighted BMI allele score$^b$</td>
<td>863/876</td>
<td>1.07 (0.91, 1.25)</td>
<td>0.41</td>
</tr>
<tr>
<td>WHR GRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unweighted WHR allele score$^c$</td>
<td>863/876</td>
<td>1.01 (0.97, 1.06)</td>
<td>0.52</td>
</tr>
<tr>
<td>Weighted WHR allele score$^d$</td>
<td>863/876</td>
<td>1.10 (0.91, 1.32)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**NOTE:** All models adjusted for age, BMI, or WHR, respectively, natural log of prostate volume and 10 principal components. Information on prostate volume was missing for 30 controls and 8 cases; results for multivariable analyses are thus based on 876 controls and 863 cases.

$^a$Unweighted BMI allele score represents the summation of the number of BMI increasing alleles per individual.

$^b$Weighted BMI allele score represents the summation of the number of BMI increasing alleles per individual after weighting with each SNP’s respective beta coefficient for BMI increase.

$^c$Unweighted WHR allele score represents the summation of the number of WHR increasing alleles per individual.

$^d$Weighted WHR allele score represents the summation of the number of WHR increasing alleles per individual after weighting with each SNP’s respective beta coefficient for BMI increase; per 0.3 increase in score (weighted WHR score range: 0.19–1.49).

### Table 5. ORs comparing BMI GRS and WHR GRS with prostate cancer risk stratified by severity of prostate cancer among participants from NMHS

<table>
<thead>
<tr>
<th>BMI-GRS</th>
<th>Low-aggression PC vs. controls (442/876)</th>
<th>High-aggression PC vs. controls (421/876)</th>
<th>High-aggression PC vs. low-aggression PC (421/442)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Un-weighted BMI allele score$^a$</td>
<td>OR (95% CI)</td>
<td>$P$</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>1.01 (0.97–1.05)</td>
<td>0.78</td>
<td></td>
<td>0.99 (0.95–1.04)</td>
</tr>
<tr>
<td>Weighted BMI allele score$^b$</td>
<td>1.07 (0.89–1.28)</td>
<td>0.48</td>
<td>1.04 (0.85–1.27)</td>
</tr>
<tr>
<td>WHR GRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Un-weighted WHR allele score$^c$</td>
<td>0.98 (0.94–1.03)</td>
<td>0.53</td>
<td>1.05 (1.00–1.11)</td>
</tr>
<tr>
<td>Weighted WHR allele score$^d$</td>
<td>1.08 (0.88–1.34)</td>
<td>0.45</td>
<td>1.10 (0.88–1.39)</td>
</tr>
</tbody>
</table>

**NOTE:** All models adjusted for age, BMI, or WHR, respectively, natural log of prostate volume and 10 principal components. Information on prostate volume was missing for 30 controls and 8 cases; results for multivariable analyses are based on 876 controls and 863 cases.

$^a$Unweighted BMI allele score represents the summation of the number of BMI increasing alleles per individual.

$^b$Weighted BMI allele score represents the summation of the number of BMI increasing alleles per individual after weighting with each SNP’s respective beta coefficient for BMI increase.

$^c$Un-weighted WHR allele score represents the summation of the number of WHR increasing alleles per individual.

$^d$Weighted WHR allele score represents the summation of the number of WHR increasing alleles per individual after weighting with each SNP’s respective beta coefficient for BMI increase; per 0.3 increase in score (weighted WHR score range: 0.19–1.49).
Strengths of our study population included prostate cancer cases with measured body size, a large sample of high-grade prostate cancer cases, and exclusion of latent prostate cancer from the control group. Indeed, there are few prostate cancer studies with systematically collected obesity measures, detailed pathology data, and DNA for genetic analyses. Nevertheless, the power for this study was low to detect effects at individual SNPs, where we had 80% power to detect an OR of 1.92 at a SNP with an MAF of 0.1 and an OR of 1.53 at a SNP with an MAF of 0.5 at an α of 1 × 10^{-7}, and no SNP achieved this level of evidence. That these observations occurred due to chance is possible; however, our investigation of obesity genetics with prostate cancer is based on a priori hypothesis developed over years of past research suggesting an association between obesity and high-grade prostate cancer. This study was able to evaluate a very fine map of variation in known metabolic genes for an influence on prostate cancer risk and grade, thus assessing pleiotropy between genetic risk factors for known metabolic traits with prostate cancer risk and grade. A more targeted hypothesis-driven approach assessed pleiotropy between GRS for WHR or BMI with prostate cancer, as BMI and WHR are the common metrics used in most epidemiologic studies. This analysis featured fewer tests, a relatively high-variance predictor to increase power, and distinct and easily testable null hypotheses, compared with the traditional agnostic scan of variation using individual SNPs. Our results were consistent with the overall literature in finding an association restricted to high-grade prostate cancer. We recommend a cautious interpretation, as our results do not meet strict statistical significance thresholds for multiple testing and provide these tentative results to prostate cancer investigators for replication in independent prostate cancer studies with obesity, pathology, and genetic data.

In conclusion, a genetic risk score to redefine WHR was significantly associated with high-grade prostate cancer, independent of measured WHR. While the literature carefully documents these phenomena, this is the first demonstration of pleiotropy of known WHR genes on prostate cancer aggression in a genetic association study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: T.L. Edwards, J.H. Fowke

Development of methodology: T.L. Edwards, J.H. Fowke

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.L. Edwards, A. Giri, J.H. Fowke

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