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10.1038/bjc.2017.231

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Height, selected genetic markers and prostate cancer risk: results from the PRACTICAL consortium


Background: Evidence on height and prostate cancer risk is mixed, however, recent studies with large data sets support a possible role for its association with the risk of aggressive prostate cancer.

Methods: We analysed data from the PRACTICAL consortium consisting of 6207 prostate cancer cases and 6016 controls and a subset of high grade cases (2480 cases). We explored height, polymorphisms in genes related to growth processes as main effects and their possible interactions.

Results: The results suggest that height is associated with high-grade prostate cancer risk. Men with height > 180 cm are at a 22% increased risk as compared to men with height < 173 cm (OR 1.22, 95% CI 1.01–1.48). Genetic variants in the growth pathway gene showed an association with prostate cancer risk. The aggregate scores of the selected variants identified a significantly increased risk of overall prostate cancer and high-grade prostate cancer by 13% and 15%, respectively, in the highest score group as compared to lowest score group.

Conclusions: There was no evidence of gene-environment interaction between height and the selected candidate SNPs. Our findings suggest a role of height in high-grade prostate cancer. The effect of genetic variants in the genes related to growth is seen in all cases and high-grade prostate cancer. There is no interaction between these two exposures.

Prostate cancer is the second most common cancer in men worldwide. Approximately 1.1 million men were diagnosed with prostate cancer in 2012 and almost 70% of the cases occur in more developed regions (IARC, 2014). The established risk factors include age, ethnicity, family history, and over 100 common genetic variants. There are however other risk factors with less conclusive evidence including height (Key et al, 1997; Hayes et al, 1999; Villeneuve et al, 1999; Hsing et al, 2000; Norrish et al, 2000; Stattin et al, 2000). Height is a phenotypic trait determined by a combination of genetics and environmental factors. The relationship between height and prostate cancer risk has been proposed to act through possible factors including pre-adult nutritional status, androgen and insulin-like growth factor-I (IGF-I; Giovannucci et al, 1997; Calle, 2000; Willett, 2000; Freeman et al, 2001; Emerging Risk Factors Collaboration, 2012; Travis et al, 2016).

Height *per se* is not a cause of cancer but it is a marker for other exposures. It has also been suggested that taller stature may

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60Additional members from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium can be found above the reference list.

Received 11 April 2016; revised 7 June 2017; accepted 23 June 2017; published online 1 August 2017

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Published by Springer Nature on behalf of Cancer Research UK.

indicate increased risk of a number of cancers. The most consistent evidence has been found in relation to breast cancer (Willett, 2000; Gunnell et al, 2001).

In 2008, findings from a large nested case–control study (ProtecT) and meta-analysis (58 studies) suggested a positive association of height with high-grade prostate cancer (OR: 1.23; 95% CI: 1.06–1.43; Zuccolo et al, 2008). In this article, we present results from the international collaboration, the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome consortium (PRACTICAL; http://practical.cge-medschl.cam.ac.uk/). The aim was to explore the effects of height on prostate cancer risk. We were also interested to see if selected candidate SNPs related to height were associated with prostate cancer risk. Finally, we explored possible interactions between the selected SNPs and height.

MATERIALS AND METHODS

PRACTICAL consortium. The PRACTICAL consortium consists of 78 study groups around the world. The consortium was established in September 2008. The co-ordination of PRACTICAL is funded by Cancer Research UK and data have been contributed to the Collaborative Oncology Gene-environment Study (COGGS), a project funded by the European Commission and 7th Framework Programme and the NIH grant. Each study with relevant data contributed an epidemiological data set and blood samples. Data on epidemiological factors for each study were provided in accordance with an assembled data dictionary. We performed quality control checks for each study before merging the data into one combined database. The majority of the samples are of European ancestry (95%). Since we investigated height as our main exposure we only analysed studies that contained subjects with European ancestry in order to minimise variation of height potentially influenced by different ethnic groups.

Blood derived DNA samples were genotyped for 211,155 SNPs on a custom Illumina array (iCOGS) in 25 074 prostate cancer cases and 24 272 controls. Details of genotyping and quality control analysis can be found in previous publication (Eeles et al, 2013).

Analysis of height exposure. During the QC process, any subjects with outlier values were checked directly with the individual study group and subsequently either corrected or excluded. Height data were available in 10 out of 15 studies that submitted data on epidemiological factors. The inclusion criterion for this particular analysis is subjects with European ancestry. The total number of prostate cancer cases and controls were 6207 cases and 6016 controls. The list of studies included in the height exposure analyses are listed in Supplementary Table 1. Meta-analysis was performed using Meta-Analyist software (Wallace et al, 2009). We performed analysis in all PCA cases and high grade cases as compared to controls. The latter is defined by Gleason grade ≥7. Out of 6207 cases, 2480 cases are high grade cases. Meta-analysis was carried out in 9 studies as one of the studies had no controls. Height was fitted as a continuous variable and study heterogeneity was explored. We also performed analysis whereby height was categorised into quartiles using control height values to determine the ranges. Results suggest study homogeneity hence results from a fixed effect model are reported. Pooled analysis was also performed. Tests for trend were carried out to assess possible dose-response relationships. Analyses were performed using IBM SPSS Statistics version 20.0. All analyses were adjusted for age, family history of prostate cancer, and study sites. As the data were derived from various studies with differing sample sizes, the analyses were therefore adjusted for study size to avoid possible confounding effects.

SNPs analyses. We explored the effects of candidate SNPs related to growth factors on prostate cancer risk. We identified 168 candidate SNPs in IGF-1, GH-1, SHOX, FMR1, GHTM, and GHRHR genes related to human growth based on evidence from the literature and these SNPs were genotyped within a custom Illumina array (iCOGS). The full list of 168 candidate SNPs and associated relative risk estimates are shown in Supplementary Table 2. To evaluate effect sizes of these SNPs, we created a data set consisting of individual subjects whose IDs appeared in both the genotype and epidemiological data sets by matching the IDs between the two sets. We included only Caucasian subjects. This resulted in 13 123 controls and 9424 cases. PLINK software was used to explore minor allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE; Purcell et al, 2007). MAF ranges were from 0.017 to 0.496. Out of 155 SNPs, 168 SNPs met HWE (P > 0.05). STATA (version14) was used to obtain risk estimates and R-square (LDscore; Cheng et al, 2006). To quantify risk, the log-additive model was used by including a single variable coded as 0, 1, or 2 based additively on the number of minor alleles. Multiple logistic regression analyses were carried out to obtain the odds ratios of all 168 SNPs. Variables included in the model were age, family history of prostate cancer, study sites, principal components for European ancestry, and SNPs. Twelve SNPs showed significant associations (P-value < 0.05). We then computed the R-square value for these 12 SNPs (Table 1). The results showed that these SNPs fell into 4 regions. SNPs were excluded if $r^2$ value was > 0.8 among them and we kept the most informative SNP based on association and P-value in each region. R-squared values for these 8 SNPs were less than 0.26. After this process, eight SNPs were selected for further analysis. Among these significant SNPs, only two yielded odds ratios (ORs) above 1.15.

Gene and environment interaction analyses. We carried out gene and environment (GE) analyses in 6207 cases and 6016 controls. These are subjects with data on genotype and height. We applied two type of analyses based on the effect sizes of the SNP analyses.

1. For the 8 SNPs that were significantly associated with prostate cancer risk, individual standardised genetic score was computed. First, we multiplied coefficient for each SNP derived from multiple logistic regression (as explained above) with individual risk allele of that particular SNPs. To obtain total genetic risk score, we summed results from each SNP. To compute standardised score, the total score was divided with s.d. value from control group. First, genetic risk scores were analysed as for main effect by comparing subjects in the second and third tertile of the referent category. For GE analysis, both height and genetic risk score were then compared as binary variables. We classified both variables into tertiles with lowest tertile as reference group and highest tertiles as exposed group. We applied empirical-Bayes (EB) method proposed by Mukherjee et al (Mukherjee et al, 2008). Results for all PCA and high grade cases are presented.

2. We also employed the general multifactor dimensionality reduction (GMDR) method (Chen et al, 2011). For this we included the top 2 SNPs with effect sizes >1.15 and fitted these into the model at the same time. This procedure is not possible in the conventional GE methods. Height was fitted as a binary variable. We included subjects with height in the reference (lowest tertile) and top third tertile. Analyses were carried out for all PCA and high grade cases. Age and family history of PCA were fitted as covariates.
RESULTS

Subject characteristics are displayed in Table 2. Family history of prostate cancer is associated with prostate cancer risk. Subjects with a positive family history of prostate cancer had a 12% increase in prostate cancer risk. Mean height for cases and controls was 176.3 and 176.8 cm, respectively. The Student’s t-test suggests a significant difference in the means between the two groups (P-value < 0.05). Results from a meta-analysis of height are presented in Figures 1 and 2. ORs were adjusted for age, family history of prostate cancer, and study site. In all cases and high grade cases, point risk estimates of each study are very similar and are close to 1. None of the estimated relative risks is statistically significant. The heterogeneity P-value of 0.467 in all cases and 0.634 in high grade cases suggests that studies are homogenous. ORs of fixed effect model in all cases and high grade cases are 1.002 (95% CI 0.996–1.009) and 1.003 (95% CI 0.996–1.011) respectively.

Results from pooled analysis yielded similar risk estimates with OR 1.004, 95% CI 0.996–1.012 in all cases and OR 1.007, 95% CI 0.999–1.015 in high grade cases. We also analysed height as a categorical variable. Results are presented in Table 3. Results also suggest no overall association between height and prostate cancer risk comparing all cases with controls. In the high-grade case group, however, significant results were observed in the fourth quartile as compared to the first quartile (OR 1.15 into the model).

Table 4 shows the ORs of candidate SNPs with statistically significant results. ORs range from 0.90 to 1.32 with P-value from 10^-9 to 10^-3. One SNP in the IGF-1 gene had the highest ORs (1.32).

Table 5 shows the ORs of genetic risk scores and prostate cancer risk. A significant result was observed in the third tertile as compared to reference tertile (OR 1.13 with 95% CI 1.03–1.23) when all prostate cancer cases were included. The P-value for trend is also statistically significant. In the high grade cases, similar results were observed. There is also a trend of increasing risk with increasing genetic risk scores in all prostate cancer cases and in high grade cases.

The interaction results between height and genetic risk scores suggest that there is no GE interaction between height and genetic risk score (Table 6) regardless of type of cases.

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Results of the GE analyses by GMDR method are depicted in Table 7. We fitted 2 SNPs with effect sizes > 1.15 into the model and adjusted for covariates (age and family history of PCA). None of the models yield significant ORs regardless of case type. This is confirmed by cross-validation consistency. Both all and high grade cases, the extended models show consistency across testing sets.

DISCUSSION

This study investigated the effect of height and its possible interaction with selected SNPs from the PRACTICAL consortium in 6207 cases and 6016 controls. The consortium is an international collaboration on PCA and it has had notable successes for example in identifying 100 new genetic loci (Eeles et al, 2008, 2009, 2013; Al Olama et al, 2009, 2012, 2014). These loci confer small to medium risks with highly significant P-values of ≤ 10^-7 (GWAS significance).

There are, however, many polymorphisms with estimated risks less statistically significant which could still play an important role, particularly in the presence of environmental exposure. We therefore created a data set (subjects with epidemiological data and genotype data) which allowed us to investigate such a hypothesis.

Out of the 6207 cases, 2480 cases (40%) are high grade cases defined by Gleason grade ≥ 7. One of the limitations of defining high grade cases is that we did not have data on Gleason grade breakdown hence we have to use combined score data of 7 rather than (4 + 3 or 3 + 4). Age and family history of PCA are confirmed risk factors in our study (Table 2). We investigated height in 3 ways. First, we explored height phenotype as a main exposure. Second, we investigated genetic profile (candidate SNPs) related to height, and third, we determined if there are any potential interactions between the selected SNPs and height. SNPs were deemed ‘related to height’ because they are found in candidate genes for height but they have not necessarily been identified in GWAS as underlying the variability of the height phenotype. We present results for all PCA cases and high grade cases as compared to controls. Although mean height values were very similar between cases and controls the mean difference was statistically significant and is in the opposite direction to that expected. In a multivariate analysis adjusted for age, family history of PCA and
Height, selected genetic markers and prostate cancer risk

...study sites, height as a continuous variable did not show associations with PCA risk in either all PCA cases or high grade PCA cases. However, height categorised in quartiles did show significantly increased risk in high grade cases. Subjects with a height > 180 cm are at 22% increased risk compared with subjects with height < 173 cm. We did not observe any association between height and low grade cases ((Gleason grade < 7) results are not presented in the paper). Our findings suggest taller subjects are at increased risk of high grade PCA risk. A previous report from a large nested case–control study (ProtecT) reported the OR of prostate-specific antigen–detected high-grade PCA per 10 cm increase in height was 1.23; 95% CI: 1.06–1.43. In a meta-analysis of 58 studies, a smaller effect was reported (random-effects OR: 1.12; 95% CI: 1.05–1.19) (Zuccolo et al, 2008). Findings from The Early Stage Prostate Cancer Cohort Study which looked at the relationship between height and prostate cancer grade in various...
subpopulations of men with potentially different risk of high-grade PCA also suggested that participants in the highest quartile of height were more than twice as likely to have a Gleason score \( \geq 7 \) \((4 + 3)\) at biopsy than participants in the lowest quartile of height \((\text{OR} \ 2.14 \ (95\% \ CI \ 1.11, \ 4.14); \ \text{Farwell et al,} \ 2011)\). Two other studies presented results exclusively on cases with advanced stage PCA and both supported a positive association between height and PCA risk \((\text{Hayes et al,} \ 1999; \ \text{Norrish et al,} \ 2000)\). Hayes and colleagues observed a two-fold increased risk in white men with height \(\geq 1.75\) metres compared to height \(\leq 1.67\) metres. The association was absent among black men \((\text{Hayes et al,} \ 1999)\). Norrish and colleagues investigated the role of height and PCA risk in both

<table>
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<th>SNP</th>
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<th>Odds ratios*</th>
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<td>1.02</td>
<td>1.15</td>
<td>0.013</td>
</tr>
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Abbreviations: CI = confidence interval; SNP = single-nucleotide polymorphism.

*Multiple logistic regression adjusted for age, family history of prostate cancer, study site and Principal Components of EU ancestry.
sporadic cancer cases and familial cancer cases. The study used the Gleason grading score to characterise the cases. Advanced PCA cases were defined by combined Gleason score ≥7 and localised PCA cases by combined Gleason score ≤6. Results on sporadic advanced cancer showed an indication of risk increasing across the quintiles (P for trend = 0.07) which is similar to our high grade cases. Moreover the risk was greater among those with a positive family history of PCA (OR for height > 179 cm compared to <170 cm = 7.41, 95% CI 1.68–32.67, P for trend = 0.02). A null association was reported in localised cases. Not only is height potentially associated with PCA risk but it also shows association with PCA mortality. A recent publication including more than 1 million subjects investigated adult height and the risk of cause-specific death and vascular morbidity suggested that hazard ratios per 6.5 cm greater height were 1.04 (1.03–1.06) for death from cancers and 1.07 (1.02–1.11) for death from PCA (Emerging Risk Factors Collaboration, 2012). In contrast, the results form a large cohort of 10,501 PCA cases and 10,831 controls within the NCI Breast and Prostate Cancer Cohort Consortium (BPC3) suggested that height was not associated with PCA risk both as a continuous variable (OR: 1.001, 95% CI: 1.000–1.002 per cm increase, P = 0.12) or as in tertiles (OR: 1.02, 95% CI: 0.99–1.06, P = 0.24) (Lindstrom et al, 2011). A null association was reported in the study also using PRACTICAL genotype data set and investigated the effect of height and prostate cancer incidence and mortality using Mendelian randomisation approach (Davies et al, 2015). The authors analysed genetic variants associated with height from published genome-wide association studies and reported that these genetic variants are strong instrument for the variable. There are some limitations in that GWA studies will not explain a majority of the estimated 80% contribution of genetic factors to variation in height (Lango Allen et al, 2010).

Human height is well known as a polygenic trait with a number of genes that contribute to height (Chial, 2008). Recent GWAS studies have identified strong and moderate effects of genes related to human height (Weedon and Frayling, 2008; McEvoy and Viesscher, 2009). Single SNPs with small effects in aggregate form can be applied to assign individuals to their height distribution (Lettre, 2009). We applied a candidate SNPs approach and identified SNPs in genes that had been genotyped in our consortium that were related to growth processes. These SNPs were in the genes IGF-I, GH-1, SHOX, FMR1, GHTM, and GHRHR (Gunnell, 2000; Ellis et al, 2001; Gunnell et al, 2001). Twelve SNPs in these genes show significant associations. We computed r² and kept the 8 SNP based on association and P-value in each region. Only one SNP (rs6503691) showed a small protective effect. This SNP is reported to associate with significantly decreased risk of breast cancer (Johansson et al, 2007; Zhao et al, 2015). Polymorphisms in the IGF signalling pathway have been shown to associate with PCA mortality (Cao et al, 2014). Other studies reported null associations (Gu et al, 2010; Nalisini et al, 2013). We also explored association between aggregated SNPs score as main effect; results support that individuals with genetic risk scores in the third tertiles are at increased risk of high grade PCA at 15% and of all PCA cases at 13% as compared with the lowest tertile. A test for trend also supports a dose-response relationship (P-value <0.05 in both case groups). These findings support that a genetic risk score in the growth pathway are associated with high grade PCA. IGF genes have been previously linked with PCA (Cheng et al, 2006; Johansson et al, 2007; Cao et al, 2014; Gan et al, 2014; Qian et al, 2014; Takeuchi et al, 2014; Travis et al, 2016). GHSR genes are also previously reported to associate with prostate cancer risk (Dresen, 2007). We also investigated possible gene-environment interactions using two approaches. The first approach uses combined genetic risk scores and a binary variable of height with the first tertile as the reference group and the third tertile as the ‘exposed’ group. Analyses were done in both PCA and high grade case group using the Bayesian method proposed by (Mukherjee et al, 2008). Results of the GE analyses however suggested no interaction between genetic risk scores and height. In the second approach, we selected the top 2 SNPs with the strongest effect sizes and fitted a model using the GMDR method (Chen et al, 2011). The GMDR method allows adjustment for discrete and quantitative covariates and is applicable to both dichotomous and continuous phenotypes. The GMDR with covariate adjustment had a power of > 80% in a case–control design with a sample size of ≥2000. We applied the GMDR method because it differs from the traditional GE method in that it allows more than 1 SNP in the model (traditional method-based on the concept of single-factor-based approaches; Lou et al, 2007). The results also showed no interactions. None of the main effect (height) and extended models showed any significant results.

In summary, our findings suggest that height and genetic variants related to the human growth pathway are associated with high grade PCA risk. Taller men of >1.80 m are at increased risk of high grade PCA. Genetic variants in genes that relate to growth pathways are associated with prostate cancer risk. The estimated risk is evident amongst subjects in the highest score group when combined genetic risk scores were used. There is, however, no GE interaction between selected genetic variants and height.

ACKNOWLEDGEMENTS

This study would not have been possible without the contributions of the following: Per Hall (COGS); Douglas F Easton, Paul Pharoah, Kyriaki Michailidou, Manjeeet K Bolla, Qin Wang (BCAC), Andrew Berchuck (OCAC), Rosalind A Eles, Douglas F Easton, Alii Alin Al Olama, Zsofia Kote-Jarai, Sara Benlloch (PRACTICAL), Georgia Chenexis-Trench, Antonis Antoniou, Lesley McGuffog, Fergus Couch and Ken Offit (CIMBA), Joe Dennis, Alison M Dunning, Andrew Lee, and Ed Dicks, Craig Luccarini and the staff of the Centre for Genetic Epidemiology Laboratory, Javier Benitez, Anna Gonzalez-Neira, and the staff of the CNIO genotyping unit, Jacques Simard and Daniel C Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissière and Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre, Stig E Bojesen, Sune F Nielsen, Borge G Nørgaard, and the staff of the Copenhagen DNA laboratory, and Julie M Cunningham, Sharon A Windebank, Christopher A Hilker, Jeffrey Meyer and the staff of Mayo Clinic Genotyping Core Facility. Funding for the iCOGS infrastructure came from: the European Community’s Seventh Framework Programme under grant agreement no 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A10710, C12292/A11174, C1281/A2014, C5047/A8384, C5047/A15007, C5047/A11174, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112–the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. Funding for ICESS (‘This work was also supported by CRUK (grant number C18281/A19169’). Funding for the CRUK study and PRACTICAL consortium: this work was supported by the Canadian Institutes of Health Research, European Commission’s Seventh Framework Programme grant agreement no 223175 (HEALTH-F2-2009-223175), Cancer Research UK Grants C5047/A7357, C1287/A10118, C5047/A3354, C5047/A10692, C6913/A6135, and The National Institute
of Health (NIH) Cancer Post-Cancer GWAS initiative grant: No. 1 U19 CA 148357-01 (the GAME-ON initiative). We acknowledge support from the NIH to the Biomedical Research Centre at The Institute of Cancer Research and Royal Marsden NHS Foundation Trust.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

THE PRACTICAL CONSORTIUM

(In addition to those named in the author list) Information on the consortium can be found at http://practical.ccg.e.medschl.cam.ac.uk/.


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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)