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Prostate Cancer

Polymorphisms of Genes Involved in Glucose and Energy Metabolic Pathways and Prostate Cancer: Interplay with Metformin

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Abstract

Background: Energy metabolism is important in cancer proliferation and progression, but its role in prostate cancer (PCa) remains unclear.
Objective: We explored whether single-nucleotide polymorphisms (SNPs) of genes involved in energy metabolic pathways are associated with PCa risk and prognosis, and whether antidiabetic treatment modifies any such association.
Design, setting, and participants: The PRACTICAL Consortium genotyped 397 SNPs among 3241 screened participants (including 801 PCa cases) in the Finnish Prostate Cancer Screening Trial and 1983 hospital-based PCa cases. Information on medication use was obtained from a national prescription database.
Outcome measurements and statistical analysis: Genetic risk scores were calculated in terms of SNPs associated with PCa incidence or survival at a significance level of $p < 5 \times 10^{-3}$. Hazard ratios for PCa and disease-specific death were calculated via Cox regression modelling. The predictive value of the genetic risk score was evaluated using receiver operating characteristic and Harrell's c-index analyses.
Results and limitations: A total of 30 SNPs were associated with PCa risk and ten SNPs with survival. The genetic risk score was consistently associated with PCa survival. The risk association was non-significantly weaker in metformin users. The genetic risk score did not improve prediction of PCa risk, but slightly improved the ability to predict PCa survival when added to conventional predictors (c-index improved from 87.4 to 87.9; $p < 0.001$). A limitation is that information on diabetes apart from medication use was unavailable for the study population.
Conclusions: SNPs of genes involved in energy metabolic pathways are associated with PCa survival. This suggests an important role of glucose metabolism in PCa progression, which could point to new avenues for prevention of PCa death.
Patient summary: Genetic changes in glucose and energy metabolic pathways are associated with a higher risk of high-risk prostate cancer and adverse outcomes.

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1. Introduction

Factors affecting prostate cancer (PCa) progression are not well understood, and further knowledge is needed.

Cancer progression requires energy, and the central role of metabolic reprogramming towards anaerobic glycolysis in cancer cells has long been recognised [1]. However, the role of glucose and energy metabolism in PCa development and progression is unclear, although PCa mutations are more common in the mitochondrial genome than in autosomal chromosomes [2].

Diabetes mellitus, a condition affecting systemic glucose and energy balance, is inversely correlated with overall PCa risk [3], but diabetic men may have more poorly differentiated cancer [4]. This supports claims of the importance of glucose metabolism in PCa. The antidiabetic drug metformin inhibits PCa cell growth in vitro, and its use may decrease PCa mortality [5,6].

Polymorphisms in genes involved in glucose metabolism have not been evaluated as a PCa risk factor before, although polymorphisms in mitochondrial genes [7] and insulin-like growth factors [8] may not be associated with a higher risk of PCa.

We evaluated associations between single-nucleotide polymorphisms (SNPs) in the genes of glucose metabolism pathways and the PCa risk and prognosis. Furthermore, we explored whether these SNPs predict PCa risk and death better than conventional predictive factors do, and we examined the possible modification of effect exerted by metformin and other antidiabetic drugs.

2. Patients and methods

2.1. Study population

Two previously described study cohorts [9] were used. The screening trial cohort consisted of a randomly selected sample of 3241 men among 32 000 men randomised to the screening arm of the Finnish Prostate Cancer Screening Trial (FinPCST) followed during 1996–2013. The trial protocol has been described previously [10]. The men were invited to prostate-specific antigen (PSA) screening at 4-yr intervals. Among the genotyped men, 801 new PCa cases were identified during a median follow-up of 16 yr.

The hospital cohort comprised 1983 PCa cases diagnosed outside systematic screening protocols. The patients were treated at Tampere University Hospital between 1990 and 2010 and followed until 2013.

The clinical data included diagnosis date, clinical TNM stage, Gleason grade, and date and cause of death. For the hospital cohort, the date of disease progression after primary treatment was also obtained. This was defined as two consecutive increases in PSA after reaching the nadir or radiographic disease progression in patients managed with endocrine treatment (258 progressions; 33% within the treatment subgroup), PSA >0.2 ng/ml in patients treated with radical prostatectomy (148; 34.9%), or a rising PSA level >2 ng/ml above the nadir in radiation-treated men (91; 39.6%).

Deaths for which PCa (ICD10 code C61) was the official underlying cause as obtained from Statistics Finland and death certificates were considered to be PCa deaths.

2.2. SNP genotypes

In all, 397 SNPs distributed across 80 genes (Supplementary Table 1) involved in the glucose metabolic pathway were genotyped as part of an international PRACTICAL Consortium effort using a custom SNP panel (iCOGs). The SNPs were selected via the UCSC genome browser (http://genome.ucsc.edu/).

2.3. Use of antidiabetic medication

The screening trial cohort was linked to the national prescription database of the Social Insurance Institution of Finland (SII) [11] via a unique personal identification number. Information on antidiabetic medication use was available for 1995–2009.

2.4. Statistical analysis

Associations between individual SNPs and PCa risk and death were tested using the genome association analysis software PLINK. Permutation analysis and Bonferroni correction were used to correct p values for multiple testing.

SNPs meeting the a priori defined significance criterion (association with PCa risk or death at a significance level of $p \leq 0.005$) were further tested using multivariate-adjusted regression models. SNPs associated with PCa risk or mortality at $p \leq 0.001$ in a Cox regression model including all SNPs were selected for further analysis.

A genetic risk score was calculated after obtaining of a correlation coefficient for each significant SNP from the multivariate-adjusted Cox regression for PCa risk and death. Individual coefficients were summed to compose a polygenic risk score as described previously [12].

Hazard ratios (HRs) with 95% confidence intervals (CIs) for PCa diagnosis and death were calculated via the Cox proportional hazards regression method. The time metric was years since the screening trial randomisation (incidence analysis in the screening trial cohort) or years since PCa diagnosis (survival analysis considering both cohorts).

We applied adjustment for age (age-adjusted model; analyses of PCa risk and mortality) and for PSA level at diagnosis, Gleason score, and the presence of distant metastases (multivariate-adjusted model; analyses of disease recurrence and survival after PCa diagnosis).

Receiver operating characteristics were used to compare the predictive accuracy of the genetic risk score (area under the curve, AUC) for PCa grade and stage together with age and PSA level. Harrell's c-index analysis was used to compare prediction for PCa survival between Cox regression models including conventional predictors of PCa death (PSA at diagnosis, tumour stage, Gleason grade) and a model also including the genetic risk score. Graphical model comparison was performed using decision curve analysis.

To estimate the effect of antidiabetic drug usage on the SNP-cancer association, we stratified the analysis by metformin usage overall and for men with cumulative amount of use above the median (>2100 g in total), and by non-metformin antidiabetic drug usage. Interaction related to metformin use was evaluated via addition of an interaction term with genetic risk score to the analysis.

Adjusted means for PSA concentrations were determined for the baseline value (PSA measured at the first screening) and for all PSA values measured during the screening trial. Adjusted means were calculated by fitting the natural logarithm of PSA into an age-adjusted or multivariate-adjusted (for age and use of 5α-reductase inhibitors and antidiabetic drugs) linear regression model.

Cox regression and ROC analyses were performed using SPSS v.20 statistical software (IBM, Chicago, IL, USA). Adjusted means for PSA values were estimated via Stata v.12 (StataCorp, College Station, TX, USA). Harrells's c-index and decision curve analysis were performed using R version 3.1.2 R Project for Statistical Computing, Vienna, Austria).