PROSTATE CANCER, AGGRESSIVENESS AND RED MEAT CONSUMPTION-A NUTRIGENOMICS PERSPECTIVE

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Introduction

Approximately 15% of all patients with prostate cancer (PCa) are diagnosed with high-risk for this disease[1]. Current definitions of high risk prostate cancer are given below.

The current definitions of high-risk PCa, however, include a wide range of patients with various prognoses. Hence, there is a need for refined classification scheme in order to enable the early and better identification of high-risk disease so that more-effective treatment paradigms can be developed[1].

The current study is an attempt to understand whether there is a genotypic link to this cause and to further evaluate whether genotype and lifestyle factors including red meat consumption have an effect.

Common definitions of high-risk prostate cancer [1]

❖ ***American Urological Association***
Preoperative PSA >20 ng/ml, and/or preoperative Gleason score of 8–10, and/or clinical stage ≥ T2c
❖ ***European Association of Urology***
Preoperative PSA >20 ng/ml, and/or preoperative Gleason score of 8–10, and/or clinical stage ≥T3a
❖ ***Radiation Therapy Oncology Group***
High risk: T1–2 and Gleason 8–10, or T3 or N1 with Gleason 7
Very high risk: T3 or N1 with Gleason 8–10
❖ ***National Comprehensive Cancer Network***
High risk: Preoperative PSA >20 ng/ml, preoperative Gleason score of 8–10, or clinical stage T3a
Very high risk: T3b–T4
❖ ***Cancer of the Prostate Risk Assessment (CAPRA)***
Includes age, PSA, clinical stage, Gleason score, and percentage of positive biopsy cores.
Abbreviations: PSA, prostate-specific antigen, T (1-4)-tumour, stages, N-nodal metastatic stage

Materials and Samples

41 single nucleotide polymorphisms (SNPs) reported in 24 genes and one intergenic region associated with risk and progression of PCa were identified through an extensive literature search using Pubmed database published between years 2011 and 2013. Genes employed for this study were identified by referring to Genome-Wide Association Studies, following a strict selection criteria (table 1).

446 patients (between the ages of 40-81 years and self-reported European ancestry) with proven diagnoses of PCa, were recruited for this study between the years 2006 to 2014. BMI, past or present smoking status, alcohol intake, red meat consumption frequency and serum PSA and Gleason score were also collected from this cohort.

Patients with Gleason score of ≤7 (3+4) were considered as having non-aggressive PC, and patients with Gleason score of ≥7 (4+3) were considered as having aggressive PC, for this study[2].

Genotyping for these SNPs was carried out by using SEQUENOM MassARRAY iPLEX assay (SEQUENOM Inc., San Diego, CA)[3].

Table 1: Selection criteria for the SNPs

	SELECTION CRITERION	LIST OF GENES
1	Mismatch repair	*MLH1*
2	Tumour suppression and growth arrest	*PTEN*
3	Transcriptional repression	*ZBTB38, JAZF1, MYRF*
4	Tumour progression and Metastatic pathways	*MYEOV*
5	Genes encoding PSA	*KLK3, KLK2*
6	Regulation of cell growth, oxido-reductase activity and microtubule formation	*IGF1, ELAC2, FADS2, FADS3, FGF10,TUBA1C*
7	Androgen pathway	*AR, CYP17, MSMB, HNF1b*
8	Angiogenesis pathway	*MMP9*
9	Genomic stability	*BRCA1*
10	Cholesterol breakdown pathway	*CCHCRI, CTBP2*
11	Posttranslational modification & Chromosomal repair	*GGCX, TERT*

References available upon request

Results

Table1: Lifestyle and Demographics parameters for patients with aggressive and non-aggressive PCa

Lifestyle parameters	Variations	Aggressive PCa	Non-Aggressive PCa	p
Age at diagnosis	Mean (SD) age in years	67.8 (8.4)	64.5 (7.9)	< .0001
Tobacco Smoking status	Current	10 (6.3%)	26 (9.3%)	0.46
	Former smoker	87 (54.7%)	156 (55.7%)	
	Never smoked	62 (39%)	98 (35%)	
Alcohol Consumption	Yes	95 (53.7%)	194 (59.9%)	0.18
	No	82 (46.3%)	130 (40.1%)	
BMI	Mean (SD)	27.5 (3.7)	27.1 (3.8)	0.21

Key Findings

- The aggressive disease was significantly associated with age at diagnosis.
- No significant associations were noted with BMI, smoking status, and alcohol consumption.
- The PSA level between the two groups was also not significantly different (data not shown)

Table 2: Interaction of SNPs with red meat consumption and aggressive PCa

Aggressive PCa	Non-Aggressive PCa	Gene	SNP	Tested Allele	OR (95% CI)	p
59	222	CTBP2	rs4962416	T	2.312 (1.326-4.033)	0.0031
57	221	CCHCR1	rs130067	C	1.734 (1.057-2.845)	0.0293

Key Findings

Out of the 41 tested SNPs none showed significant associations with aggressive disease. However, two SNPs interacting with red meat consumption produced a significant association with aggressive disease. However, the significance was lost after adjusting for multiple corrections.

Inference

Age was a significant factor in differentiating aggressive PCa, as expected. The current finding of no statistical significant association of SNP data between aggressive and non-aggressive PCa could be due to the use of only Gleason score data in our classification of the two groups. Therefore, a re-analysis of data is required using standard classification criteria that uses Gleason score together with tumour stage and PSA level for aggressiveness.
Red meat consumption interacting with two SNPs (from cholesterol metabolism pathway) showed significant associations with aggressive disease before multiple testing corrections were made. This could be an indication that cholesterol from red meat has a role to play in aggressive disease.

References

1- Chang *et al*-High-risk prostate cancer—classification and therapy. Nature Reviews Clinical Oncology 11, 308-232 (2014)

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