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Original article

Apoptosis gene polymorphisms and risk of prostate cancer: A hospital-based study of German patients treated with brachytherapy

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Abstract

Background and objectives: Prostate cancer has a genetic component, and single nucleotide polymorphisms (SNPs) can contribute to the risk. We aimed to investigate the role of polymorphisms in 10 candidate genes with a key function in apoptosis.

Methods and materials: Eight coding SNPs were chosen in *ATM* (Ser49Cys), *BID* (Ser56Cys), *CASP8* (Asp302His), *CASP10* (Val410Ile), *LGALS3* (Pro64His), *RASSF1* (Ser133Ala), *TP53* (Arg72Pro), and *TP53AIP1* (Ala7Val), and two non-coding SNPs were selected in *BCL2* (-938C/A) and *HDM2* (SNP309). A hospital-based case-control series of 510 prostate cancer patients and 490 healthy males from Northern Germany were genotyped for these polymorphisms.

Results: SNP rs4644 in *LGALS3* showed evidence for a protective effect of the minor allele, encoding the His64 variant (OR 0.82, 95% CI 0.69;0.99, $P = 0.04$). Carriers were underrepresented among cases under a dominant model (OR 0.71; 95% CI 0.54;0.92; $P = 0.01$), and the effect appeared more pronounced in patients diagnosed before the age of 60 years (OR 0.52; 95% CI 0.31;0.85, $P = 0.01$). The other nine polymorphisms did not vary significantly between cases and controls, though subtle trends were noted for *BCL2* ($P = 0.07$) and *CASP10* ($P = 0.08$). The Asp302His variant of *CASP8* tended to associate with a protective effect in the group with higher Gleason score under a dominant model ($P = 0.03$). Carriers of either the *CASP8* or the *CASP10* variants were underrepresented in the prostate cancer series ($P = 0.02$).

Conclusions: These results provide first evidence to implicate the functional Pro64His variant of galectin-3 (*LGALS3*) in the genetic susceptibility towards prostate cancer. The potential role of polymorphisms in *BCL2*, *CASP8*, and *CASP10* merits further investigation.

Keywords: Prostate cancer; Apoptosis; Programmed cell death; Genetic susceptibility; Genetic risk; Single nucleotide polymorphism

1. Introduction

Prostate cancer is a leading cancer in men, with about 1 in 6 U.S. citizens being diagnosed with prostate cancer during his lifetime [1]. Its aggregation in families indicates a heritable susceptibility, and single nucleotide polymorphisms (SNPs) have emerged as a potentially important part of the genetic predisposition [2–4]. The identification of molecular markers specific to early and late events in prostate cancer progression can aid the development of improved detection and prognostication strategies [5].

Previous studies have indicated a possible role for genes that are involved in apoptosis. Rare truncating mutations in a few genes that regulate apoptosis, such as

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CHEK2, NBN, or *TP53AIP1*, appear to confer a moderately increased risk for prostate cancer [3,6–9]. Furthermore, a prostate cancer susceptibility locus uncovered by recent genome-wide association studies on chromosome 8q24 appears to regulate the expression of MYC, an oncoprotein governing cell proliferation and apoptosis [10,11]. Several prognostic markers for prostate cancer progression have also been implicated in apoptosis, including BCL2, BID, RASSF1A, or galectin-3, the product of the *LGALS3* gene [12–17].

Apoptosis is a natural biological mechanism that has evolved to eliminate highly damaged cells through the means of a programmed cell death, and impairment of apoptosis can result in both the development of cancer cells and their resistance to cytotoxic drugs [18,19]. Apoptosis can be triggered via several pathways. Following chromosomal damage, for instance, this process can be induced via the ATM kinase and its phosphorylation targets, including the tumor suppressor TP53 and its inhibitor HDM2 [20–22]. The ATM kinase also phosphorylates BID, a member of the BCL2 family of apoptotic proteins that exerts a proapoptotic function after cleavage by CASP8 [23]. The BCL2 protein is itself a central mediator of the mitochondrial apoptosis pathway and is antagonized by TP53AIP1 [24]; both genes are under the transcriptional control of TP53 [25,26]. LGALS3, a galactoside-binding lectin, shares some structural features with BCL2 and exerts dual functions on apoptosis in its intracellular or secreted forms [27,28]. RASSF1A mediates pro-apoptotic functions through activation of the BCL2 family member BAX in response to death receptor or oncogenic K-ras signaling [29]. Different pathways to apoptosis merge into the cleavage of several proteins to activate the downstream demolition machinery that is executed by cysteine proteases such as the initiator caspases CASP8 or CASP10 [30–32].

The present study aimed to investigate the potential role of common genetic variants in apoptosis genes for prostate cancer susceptibility in a German case-control study. We chose 10 candidate genes based on their above-described biological role in apoptosis, and we selected polymorphisms in these genes that had been associated with functional dysregulation and/or with cancer susceptibility in previous reports. Allele and genotype distribution of these genetic variants and their influence on the age at diagnosis of prostate cancer were then tested in a hospital-based series of 510 German brachytherapy patients.

2. Materials and methods

2.1. Study population

A hospital-based series of 510 unselected patients with prostate cancer who were brachytherapy-treated between 10/2000 and 06/2007 at our institution, were enrolled for this study. All patients had biopsy-proven adenocarcinoma of the prostate. Sextant biopsies at least were performed in all patients. Indications for permanent brachytherapy was clinically localized low risk early prostate cancer (cT2a or less with a PSA serum level <10 ng/ml and a Gleason score < 7) following the ESTRO/EAU/EORTC recommendations. The median age at diagnosis was 66.3 years in this patient series (range 42–82 years). A summary of clinical characteristics of the patient group is provided in Table 1. Written informed consent was obtained from each patient. For comparison, a series of 490 genomic DNA samples was established from ethnically matched adult male blood donors at our hospital in the period from 2006 to 2007. The median age of these population controls was 39 years (range 20–71 years).

Table 1
Clinical characteristics of patients in the Hannover Prostate Cancer Study (HaPCS)

Mean age at diagnosis (years)	66.3
Range (years)	42–82 years
T classification	
cT1c	57
cT2a	324
cT2b	89
cT2c	16
Unknown	24
Median Gleason sum	6
Range	3–8
3	6
4	29
5	76
6	363
7	27
8	1
Unknown	8
Mean PSA level at diagnosis (ng/ml)	7.0
Range (ng/ml)	0–55
<4	39
4–10	392
10–20	66
>20	2
Unknown	11

Distribution of clinical parameters for 510 patients of the HaPCS, undergoing brachytherapy at Hannover Medical School and chosen for the prostate cancer case-control association study. Note that study entry for brachytherapy was restricted to patients with low Gleason score and T stage.

This case-control series has previously been tested for variants in the *ATM* and *TGFB1* genes and for polymorphic sites at the 8q24 locus [33–35], and has also been part of genetic association studies performed by the international PRACTICAL Consortium [36,37]. The present study received institutional reviewer board approval at Hannover Medical School.

2.2. Genotyping

Genomic DNA was extracted from peripheral white blood cells by a routine proteinase K digest and phenol-