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Advances in Brief

CDKN1A and CDKN1B Polymorphisms and Risk of Advanced Prostate Carcinoma[1]

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Abstract

A multigenic model of prostate cancer susceptibility has been proposed, in which common polymorphic variants of genes, such as the androgen and vitamin D receptor, contribute to tumorigenesis. The discovery of additional genetic factors that contribute to prostate cancer risk should provide opportunities for new approaches to the detection and treatment of this common malignancy. Herein, we examined single nucleotide polymorphic variants in the 3′-untranslated region of *CDKN1A* ($p21^{cip1}$) and in codon 109 of *CDKN1B* ($p27^{kip1}$) for association with advanced prostate cancer in a European-American population. Ninety-six cases and 106 controls were analyzed using PCR amplification and restriction digestion assays. *CDKN1A* genotype was scored as *CC*, *CT*, and *TT* on the basis of the digestion products. The *CDKN1A* genotypes *CT* and *TT* were associated with an increased risk of advanced prostate carcinoma compared with the *CC* genotype [odds ratio (OR), 2.24; 95% confidence interval (CI), 1.02–4.95]. The *CDKN1B* genotype was scored as *VV*, *VG*, or *GG*, again on the basis of the digestion products. The *CDKN1B* genotype *VV* was also associated with an increased risk of advanced prostate carcinoma (OR, 1.95; 95% CI, 1.09–3.47). These associations were particularly strong in those patients with androgen-independent disease [OR = 2.88 (95% CI, 1.19–6.97) and 2.11 (95% CI, 1.05–4.22) for high-risk genotypes of *CDKN1A* and *CDKN1B*, respectively]. In addition, the association of *CDKN1B* was particularly strong in the cohort of patients under the median age of diagnosis (OR, 2.23; 95% CI, 1.08–4.59). These results suggest that in a European-American population, *CDKN1A* and *CDKN1B* variants are associated with advanced prostate cancer. Analysis of *CDKN1A* and/or *CDKN1B* genotypes may prove useful in determining which patients are at risk for developing advanced prostate carcinoma and therefore would gain the most from aggressive screening, prophylaxis, and/or treatment.

Introduction

Prostate cancer is a large and increasing medical problem in most developed countries. In the United States alone, it is estimated that in 2002 approximately 189,000 new cases will be diagnosed, and 30,200 men will die of the disease (1). Major prostate cancer susceptibility genes such as *HPC1* and *HPC2* confer high risk for prostate cancer, and candidates, such as *RNASEL* and *ELAC2*, have been proposed as potential tumor suppressor genes at these loci (2, 3). However, the identification of hereditary prostate cancer genes may be of clinical benefit in a minority of patients because only 9% of all prostate carcinoma is believed to arise in patients with these dominant susceptibility alleles (4). Minor susceptibility genes may play a larger role in prostate cancer risk. These genes do not cause carcinoma, but in certain environments or in concert with other genetic alterations, they influence disease development. Of particular interest would be susceptibility loci for metastatic or lethal prostate carcinoma. Earlier identification of individuals at risk for aggressive disease would allow targeted screening and prophylaxis.

Two genes of interest are $p21^{cip1}$ *(CDKN1A)* and $p27^{kip1}$ *(CDKN1B)*, members of the cip/kip family of cdk[3] inhibitors. The cip/kip family members inhibit phosphorylation of the retinoblastoma protein (Rb) through binding to cyclin-cdk complexes: cyclin E-cdk2; cyclin A-cdk2; and cyclin D-cdk4 (5–7). Failure of cell cycle arrest secondary to alterations in cdk inhibitor expression has been implicated in malignancy in general (5) and prostate carcinoma in particular (8–11).

There are several common SNPs described in *CDKN1A*: a serine to arginine substitution at codon 31; and a single-base substitution of C to T 20 bp 3′ of the stop codon. The two polymorphisms are in strong linkage disequilibrium, and it has been hypothesized that each may alter CDKN1A function (12). High-risk genotypes have been associated with a variety of malignancies including lung, breast, and endometrial carcinomas (12–14). The sole study examining prostate carcinoma found that both variants were associated with prostate carcinoma. However, tumor rather than normal tissue was analyzed, so conclusions about increased susceptibility could not be drawn (13).

A second member of this family is *CDKN1B*. A SNP at codon 109 results in a glycine (G) for valine (V) substitution (V109G; Ref. 15). The V109G SNP has not been evaluated for an association with prostate carcinoma. An earlier study examining germ-line DNA of patients with metastatic prostate carcinoma demonstrated that 16 of 19 (84%) were homozygous (*VV*), 1 of 19 (5%) was heterozygous (VG), and 2 of 19 (11%) were homozygous (*GG*) (16); this distribution of *CDKN1B* genotypes was not in Hardy-Weinberg equilibrium ($P = 0.012$, Haldane exact test). In addition, the *VV* genotype was overrepresented in this patient cohort compared with historical controls reported by Cave *et al.* (OR, 4.66; 95% CI, 1.3–16.4; Ref. 15). This raised the possibility that the valine allele was associated with an increased risk of advanced prostate carcinoma.

In the present study, we evaluated the association of the V109G polymorphism of *CDKN1B* and the C to T SNP in the 3′-UTR of *CDKN1A* with the risk of advanced prostate carcinoma in a European-American population. We hypothesized that individuals with the *CDKN1B VV* genotype and the *CT* and *TT CDKN1A* genotype would be at increased risk of advanced prostate carcinoma. We undertook a case-control study using 96 patients with advanced prostate cancer and 106 patients without evidence of prostate cancer specifically to determine whether polymorphisms in these two genes are associated with advanced disease.

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[3] The abbreviations used are: cdk, cyclin-dependent kinase; SNP, single nucleotide polymorphism; UTR, untranslated region; OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen.

Table 1 *Characteristics of 96 cases*

Pelvic lymph node metastasis	5 (5%)
PSA >50 ng/ml only	12 (13%)
Metastatic disease	23 (24%)
Androgen-independent disease	35 (36%)
Dead from prostate carcinoma	21 (22%)
Total	96 (100%)
Treated with curative intent	50 (52%)
Mean age at diagnosis (yrs)	66.0 ± 9.5
Median age at diagnosis (yrs)	66.0
Family history of prostate cancer	19 (20%)

Materials and Methods

Subjects and Controls. Prostate cancer patients were identified from the urology and oncology clinics at our institution from May 2000 to March 2002. Criteria for inclusion of cases with advanced disease were as follows: (*a*) patient must be receiving androgen ablation therapy for prostate carcinoma; and (*b*) patient must have either pathological or radiological evidence of metastasis *or* a PSA of greater than 50 ng/ml. These criteria were designed to ensure that all patients had advanced disease. Family history was defined as any first- or second-degree relative with a history of prostate carcinoma.

The control group was identified from the urology and medicine clinics at our institution during the same period of time. The control population consisted of male patients > 75 years old with no history of prostate carcinoma, PSA < 4.0 ng/ml, and a benign digital rectal examination. These criteria were designed to ensure that all controls had minimal risk of having or ever developing prostate carcinoma.

All study subjects and controls provided informed consent under a protocol approved by the Committee for the Studied Involving Human Subjects. All patients and controls were of European descent and were residents of the metropolitan area. Genomic DNA was obtained from peripheral blood leukocytes and extracted using standard protocols.

CDKN1A. Genotypes were determined using a PCR amplification and digestion assay. A 868-bp PCR amplification product was generated using the primers 5′-GAATTTGCCGTTGGGTCAAG-3′ and 5′-AGGAGAACACGGGATGAGGAG-3′. The reaction mix contained 20 ng of genomic DNA, 1.5 μM deoxynucleoside triphosphate, and 60 nM of forward and reverse primer. Thirty-five PCR cycles were performed (94°C for 15 s, 64.8°C for 30 s, and 72°C for 60 s). The PCR product was digested with *Pst*I, and the fragments were resolved on a 7% nondenaturing polyacrylamide gel. The T allele lacks a *Pst*I site that is present in the C allele. Therefore, digestion results in fragments of 133 and 735 bp (T allele) or 133, 256, and 479 bp (C allele). Individuals were classified as CC, CT, or CC. Selected samples from each gel were repeated to confirm the results.

CDKN1B. Genotypes were determined using similar PCR amplification and restriction digestion assay. A 540 bp PCR amplification product was produced using the primers 5′TGCAGACCCGGGAGAAAG3′ and 5′CCGCTAACCCCGTCTGG3′. The reaction mix contained 20 ng of genomic DNA, 1.5uM deoxynucleoside triphosphate and 80 nM of forward and reverse primer. Thirty-five PCR cycles were performed (94°C for 15 s, 58°C for 30 s, and 72°C for 60 s). The product was digested with *Bgl*I, and the fragments were resolved on a 7% nondenaturing polyacrylamide gel. The valine allele lacks a *Bgl*I site present in the glycine allele. Therefore, digestion results in fragments of 76 and 464 bp (V allele) or 76, 199, and 265 bp (G allele). Individuals were classified as VV, VG, or GG. Again, selected samples from each gel were repeated to confirm the results.

Data Analysis. Data were analyzed using Stata 5.0 (College Station, TX). Fisher's exact test was used to calculate ORs with 95% CIs to determine whether *CDKN1A* or *CDKN1B* genotypes were associated with disease. In addition, patients were stratified by age at presentation and aggressiveness of disease to determine whether an association existed between genotype and young age of onset or between genotype and development of androgen-independent disease.

Results and Discussion

In this study, *CDKN1A* and *CDKN1B* genotypes were evaluated in patients with aggressive prostate cancer and healthy controls to determine whether an association existed between genotype and aggressive prostate carcinoma. The study was designed to examine extreme phenotypes (individuals with potentially lethal prostate cancer and individuals with minimal risk of developing prostate cancer). Patient characteristics are listed in Table 1. As evidence of the advanced disease that characterizes this cohort, 22% of the patients have died of metastatic prostate carcinoma, and an additional 36% have androgen-independent disease. Patients have an average age at presentation with prostate carcinoma of 66.0 years (age range, 41–90 years), a median age at presentation of 66 years, and an average age at enrollment in the study of 75.4 years (age range, 46–91 years).

As outlined in "Materials and Methods," controls were deliberately selected who had survived most of their natural lives without any clinical evidence of prostate carcinoma. Using young patients, who are still at substantial risk of developing prostate carcinoma during their lifetime, could bias results. As a result, cases and controls are deliberately not matched by age. Average age of controls is 79.1 years (age range, 75–90 years), median age is 78 years, average PSA is 1.07 ± 0.61 ng/ml, and all had a negative digital rectal exam.

The distribution of genotypes was statistically significantly different between cases and controls (Tables 2 and 3). The genotypes *CDKN1B VV* and *CDKN1A CT* and *TT* were observed more frequently in cases than controls (OR = 1.95 (95% CI, 1.09–3.47) and 2.24 (95% CI, 1.02–4.95), respectively]. The association did not appear to be the result of a nonrepresentative genotype distribution in the control population. First, the frequency of the *CDKN1A* and *CDKN1B* genotypes within the control population was in Hardy-Weinberg equilibrium, (χ^2 goodness of fit, P = not significant). Second, the frequency of these genotypes in the control population was comparable with that seen in previous studies of Caucasian populations (12, 15).

Whereas all patients had advanced disease, some had more aggressive disease as demonstrated by development of androgen-independent disease and eventual death from prostate cancer. Stratification of the patients into those with more aggressive metastatic disease (androgen-independent disease or death from metastatic prostate carcinoma) and less aggressive metastatic disease (documented metastasis or PSA > 50 ng/ml but controlled with hormone ablation) demonstrated that *CDKN1A* high-risk genotypes (*CT* and *TT*) and *CDKN1B* high-risk genotype (VV) were more strongly associated with androgen-independent disease [OR = 2.88 (95% CI, 1.19–6.97) and 2.11 (95% CI, 1.05–4.22), respectively].

Another marker of clinically important prostate carcinoma is the age at onset. Stratification of patients into a cohort younger and older than median age of diagnosis revealed that the *CDKN1B* high-risk

Table 2 *CDKN1A genotype analysis*

	CC	CT	TT	OR CC *vs.* CT, TT
Cases (n = 92)[a]	73 (79%)	18 (20%)	1 (1%)	2.24 (95% CI, 1.02–4.95)
Androgen dependent disease (n = 40)	34 (85%)	6 (15%)	0 (0%)	1.52 (95% CI, 0.52–4.44)
Androgen independent disease (n = 52)	39 (75%)	12 (23%)	1 (2%)	2.88 (95% CI, 1.19–6.97)
Age ≤ median (n = 47)	37 (78%)	9 (19%)	1 (2%)	2.33 (95% CI, 0.92–5.96)
Age > median (n = 45)	36 (80%)	9 (20%)	0 (0%)	2.16 (95% CI, 0.83–5.65)
Controls (n = 106)	95 (90%)	9 (8%)	2 (2%)	1.0 (reference)

[a] CDKN1A genotype was not determined for four cases.

Table 3 *CDKN1B genotype analysis*

	VV	VG	GG	OR VV *vs.* VG, GG
Cases (n = 96)	67 (70%)	24 (25%)	5 (5%)	1.95 (95% CI, 1.09–3.47)
Androgen-dependent disease (n = 40)	27 (68%)	11 (27%)	2 (5%)	1.75 (95% CI, 0.81–3.76)
Androgen-independent disease (n = 56)	40 (72%)	13 (23%)	3 (5%)	2.11 (95% CI, 1.05–4.22)
Age ≤ median (n = 51)	37 (73%)	12 (23%)	2 (4%)	2.23 (95% CI, 1.08–4.59)
Age > median (n = 45)	30 (67%)	12 (27%)	3 (6%)	1.68 (95% CI, 0.81–3.50)
Controls (n = 105)[a]	57 (54%)	38 (36%)	10 (10%)	1.0 (reference)

[a] CDKN1B genotype was not determined for one control.

genotype was more strongly associated with younger age of diagnosis (OR, 2.23; 95% CI, 1.08–4.59). *CDKN1A* high-risk genotypes approached statistical significance in this cohort of patients (OR, 2.33; 95% CI, 0.92–5.96). The loss of statistically significance for *CDKN1A* probably reflects the small size in this subgroup. Whereas these results are interesting, dividing the case cohort into tertiles by age at diagnosis failed to demonstrate a trend for either gene, indicating that age of onset may not be associated with either of these high-risk variants.

Lastly, our data did not support an interaction between high-risk *CDKN1A* and *CDKN1B* genotypes. Ten cases and 8 controls had both high-risk genotypes, whereas 82 cases and 97 controls had ≤1 high-risk genotypes (OR, 1.48; 95% CI, 0.56–3.92). In contrast, the presence of at least one high-risk genotype was associated with advanced disease. Seventy-two cases and 60 controls had one or more high-risk genotypes, whereas 20 cases and 45 controls had none (OR, 2.72; 95% CI, 1.44–5.04).

CDKN1B is rarely mutated in malignancies and has not been linked to any hereditary tumor syndrome (17). However, *CDKN1B* has been implicated as a tumor suppressor gene because overexpression inhibits cell entry into S phase (7). Evidence of CDKN1B involvement in prostate carcinoma was initially limited to studies measuring protein expression by immunohistochemistry in tumor samples (8, 9). In general, decreased expression was associated with unfavorable tumor features and poor patient outcome. Subsequent studies have demonstrated in animal models that subtle changes in CDKN1B levels, in concert with loss of other tumor suppressor genes, increase the risk of malignancy (18).

This polymorphism (V109G) lies within the $p38^{jab1}$ binding domain. $p38^{jab1}$ functions as a negative regulator of CDKN1B by promoting degradation (19). The absence of mutations, coupled with multiple studies demonstrating decreased CDKN1B protein expression in malignancy, has led to speculation that decreased CDKN1B levels in malignancy are secondary to alterations in degradation. It is possible that the V allele may alter CDKN1B affinity for $p38^{jab1}$ and thereby modify CDKN1B degradation. V109G had not been studied previously in any malignancy.

Like *CDKN1B*, *CDKN1A* has not been linked to any hereditary tumor syndrome and is rarely mutated in malignancies (20). Nonetheless, CDKN1A has been implicated as a tumor suppressor gene based on its ability to induce cell cycle arrest (6). There is evidence that CDKN1A plays a role in prostate tumorigenesis because some studies demonstrate a correlation between altered expression of CDKN1A in tumor specimens and decreased cancer-specific survival (10, 11).

CDKN1A genotypes have been associated with a variety of malignancies (12, 14) including prostate carcinoma (13). Facher *et al.* (13) demonstrated that the high-risk 3′-UTR variant was present in 9.1% of controls and 16.7% of tumor samples. However, this difference did not reach statistical significance, possibly because of the small sample size. It is important to note that the controls were not matched by race or sex, both of which are clearly important variables in prostate carcinoma. Furthermore, the DNA samples analyzed were derived from tumor rather than normal tissue, so conclusions about increased susceptibility cannot be drawn (13).

The 3′ polymorphism may increase the risk of prostate carcinoma by altering mRNA stability and, in doing so, increase intracellular levels of CDKN1A. Alternatively, association may be caused by linkage disequilibrium with another variant of CDKN1A or a gene in close proximity. The codon 31 variant, for example, is in strong linkage disequilibrium with the 3′-UTR SNP (12) and lies within the zinc finger motif. Therefore, this serine to arginine substitution may alter CDKN1A function (12).

In conclusion, the *CDKN1B* codon 109 *VV* genotype and the *CDKN1A* 3′-UTR *CT, TT* genotype are both associated with advanced prostate cancer in a Caucasian population. This was particularly true in patients with young age of onset and androgen-independent disease. Analysis of these genotypes could be potentially useful in determining which patients are at risk for developing and dying of metastatic prostate carcinoma. Early identification of patients at increased risk for lethal prostate carcinoma would allow targeted, aggressive screening, prophylaxis, and/or treatment in this patient population.

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