Null Results in Brief

An Intrinsic Variant in PTEN Is Not Associated with Prostate Cancer Risk

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Introduction

Loss of heterozygosity at chromosome 10q23–25 and allelic loss of the PTEN gene is frequently observed in prostate tumors, which suggests that this locus is a target of inactivation. PTEN, a tumor suppressor gene, encodes a dual-specificity phosphatase whose primary function appears to be the dephosphorylation of the second messenger PIP3 (1). The absence of PTEN expression in prostate tumors is highly correlated with Gleason score and advanced stage and appears to play a role in prostate cancer progression (2). Germ-line mutations in PTEN cause the autosomal dominant Cowden and Bannayan-Riley-Ruvalcaba syndromes (3). Cancer predisposition in Cowden syndrome is limited primarily to breast and thyroid cancers. However, mice deficient in PTEN develop prostate cancer (4). Therefore, germ-line mutations in PTEN primarily predispose to breast cancer, but somatic mutations in PTEN are more commonly observed in prostate cancer (3).

No common polymorphisms in the coding region of PTEN have been reported. However, several intrinsic variants have been identified, including a 5-bp insertion (CTCTTA) at IVS4+109. IVS4 immediately precedes exon 5, which contains the phosphatase core domain, and is a “hot spot” for germ-line mutations. This 5-bp insertion has been associated with earlier age of breast cancer onset in variant homozygotes compared with wild-type heterozygotes or homozygotes (5). This variant has been found at higher frequencies in tumors of various organs than in germ-line samples (5, 6). Because PTEN is somatically mutated in prostate tumors and the 5-bp intronic insertion polymorphism is more commonly found in tumor than in germ-line specimens, we hypothesized that it could be involved in the etiology of prostate cancer.

Materials and Methods

We undertook a case-control study using 248 incident prostate cancer cases identified through Urological Oncology Clinics in the UPHS between September 1994 and December 1999. Case status was confirmed by medical records review. The mean age of diagnosis was 61.0 years. The 293 controls studied here were men attending UPHS general medicine clinics. These clinics see a patient population that is demographically similar to those seen in the UPHS Urological Oncology clinics. These men were ascertained concurrently with the prostate cancer cases (i.e., between September 1994 and December 1999). Controls were excluded from this study if they ever had an abnormal prostate-specific antigen test (i.e., ≥4 ng/dl), if they had ever had an abnormal digital rectal examination, if they had a previous cancer diagnosis, or if they reported having had exposure to finasteride (Proscar) at the time of study ascertainment. Controls were frequency-matched to cases on age and race. The mean age of these men at the time of their clinic visit was 61.4 years. All of the study subjects provided informed consent for participation in this research under a protocol approved by the Committee for Studies Involving Human Subjects at the University of Pennsylvania. The 5-bp insertion in PTEN was characterized using CSGE, as described previously (5). At least four samples, one normal and three heterozygous or homozygous variants, were sequenced from each gel to confirm the CSGE results.

Genotype-disease associations were undertaken using unconditional logistic regression. Analyses considered the effect of genotype adjusted for potential confounders including age (at time of diagnosis in cases or time of study ascertainment in controls) and race (coded as a discrete variable with three levels: Caucasian, African American, or other).

Results and Discussion

There was no difference in the frequency of the homozygous insertion variant between the prostate cancer cases (16.4%) and controls (19.4%). The age- and race-adjusted OR for prostate cancer for those who do not carry the 5-bp insertion allele was 1.14 (95% confidence interval, 0.91–2.28). We also evaluated the relationship of the PTEN polymorphism and dichotomized Gleason grade (OR, 1.03), seminal vesicle invasion (OR, 1.46), margin positivity (OR, 0.79), serum prostate-specific antigen levels at diagnosis (OR, 0.92), and extracapsular extension (OR, 1.13), but found no significant association with any of these characteristics.

The loss of PTEN expression appears to play an important role in the progression of prostate tumors. In the present study, both cases and controls had a lower rate of the insertion variant (35–42%) than previously published series of tumors (53%; reviewed in Refs. 6–8), consistent with a role of PTEN in tumor progression. The present study was designed to detect an OR of 1.8 with 80% power. However, the magnitude of the OR detected here is substantially smaller than this value. It is unlikely that the OR effect seen here would be of clinical significance, even if a large enough study could be undertaken to detect an OR effect of ~1.1. Our data indicate that the intrinsic PTEN variant is not involved in the predisposition to develop prostate cancer.
References