Null Results in Brief

No Association between a Tetranucleotide Repeat Polymorphism of *CYP19* and Prostate Cancer

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Introduction

The *CYP19* gene encodes the enzyme aromatase, which plays a key role in the conversion of androgen to estrogen. The prostate is influenced by estrogen from peripheral sources as well as through aromatase activity in its stroma (1). There is evidence of elevated levels of aromatase activity and mRNA expression in stromal cells in prostate cancer as well as increasing evidence of cross-talk between estrogens and androgens in regulating gene expression in the prostate (2, 3). Moreover, estrogens compete with androgens for fastening to sex hormone binding protein, and it is believed that sex hormone binding protein synthesis is modulated by, and is a reflection of, estrogen/androgen balance (4). Thus, it is possible that genetic variations in *CYP19* will alter the availability of sex steroid hormones and an individual's risk of prostate cancer.

A tetranucleotide $(TTTA)_n$ repeat polymorphism in intron 4 of the *CYP19* gene is hypothesized to alter aromatase activity, and the $(TTTA)_7$ and $(TTTA)_{11}$ alleles have been associated with risk of prostate cancer in one previous study (5). The role of the *CYP19* $(TTTA)_n$ repeat polymorphism in the etiology of prostate cancer thus remains unclear. We present here the results from a sibling-matched, case-control study to further clarify the potential relation of this genetic polymorphism with prostate cancer.

Materials and Methods

The design of our study has been described in detail elsewhere (6). Briefly, we recruited a study population of 918 brothers (439 cases and 479 controls) from 413 discordant families (i.e., with at least one unaffected

sibling) from the major medical institutions in the greater Cleveland, OH area and from the Henry Ford Health System in Detroit, MI. Institutional review board approval was obtained from the participating institutions and all study participants gave informed consent. Sibling sets consisted of probands with prostate cancer diagnosed at age ≤73 years and at least one brother without prostate cancer who was either older or no more than 8 years younger than the proband's age at diagnosis. The study population was composed of 91% Caucasian, 8% African American, and 1% Hispanic and Asian American. Genotyping was undertaken according to assays described recently elsewhere (5).

We first calculated allele frequencies by disease status and then estimated age-adjusted odds ratios and 95% confidence intervals by conditional logistic regression (matched on family) for the association between the polymorphisms and prostate cancer. The *CYP19* $(TTTA)_n$ repeat was modeled at the genotype and allele levels. In reference to the report by Latil et al. (5), we first used the homozygous $(TTTA)_7/(TTTA)_7$ as our reference for the genotype-level analysis and created the following five genotype categories for comparison: (1) $(TTTA)_{<7}/(TTTA)_{<7}$, (2) $(TTTA)_{<7}/(TTTA)_7$, (3) $(TTTA)_{<7}/CA_{\geq 8}$, (4) $(TTTA)_7/(TTTA)_{\geq 8}$, and (5) $(TTTA)_{\geq 8}/(TTTA)_{\geq 8}$. We further collapsed these five comparison categories by combining those heterozygous for the $(TTTA)_7$ repeat (groups 2 and 4 above) and those without any $(TTTA)_7$ repeats (groups 1, 3, and 5). We also used the homozygous $(TTTA)_{11}/(TTTA)_{11}$ as the reference and carried out similar analysis. At the allele level, we modeled chromosomes as a continuous variable and with the following categorizations: (1) $(TTTA)_7$ (reference), (2) $(TTTA)_{<7}$, and (3) $(TTTA)_{>7}$ or (1) $(TTTA)_{11}$ (reference), (2) $(TTTA)_{<11}$, and (3) $(TTTA)_{>11}$.

To investigate the potential effect of these polymorphisms on prostate cancer aggressiveness, we undertook analyses stratified by the cases tumor stage and grade at diagnosis; men with tumor stage of ≥T2c or Gleason score ≥7 (and their control brothers) were categorized as having high stage/grade; others were considered low stage/grade. In our regression models, we investigated the potential confounding by age, height, and body mass index; the latter two did not materially alter our results, and all results reported here are adjusted for age only.

Table 1. Allele frequency of *CYP19* (TTTA)$_n$ repeat polymorphism by prostate cancer status

CYP19 alleles	Cases (%)	Controls (%)
7− TCT*	303 (34.6)	325 (33.9)
7+ TCT[†]	132 (15.1)	148 (15.4)
8	85 (9.7)	104 (10.8)
9	4 (0.5)	2 (0.2)
10	15 (1.7)	21 (2.2)
11	316 (36.1)	334 (34.8)
12	18 (2.1)	25 (2.6)
13	13 (0.3)	1 (0.1)

NOTE: χ^2 = 5.14, P = 0.74.
*A 3-bp deletion ∼50 bp upstream to the (TTTA)$_n$ repeat.
[†]A 3-bp insertion ∼50 bp upstream to the (TTTA)$_n$ repeat.

Table 2. Relationship between *CYP19* (TTTA)$_n$ repeat polymorphism and prostate cancer risk

CYP19 variant	Odds ratio*	95% Confidence interval	P for trend
(TTTA)$_7$ + TCT			
Two copies	1.0 (reference)		0.84
One copy	0.66	0.27-1.62	
None	0.76	0.30-1.94	
(TTTA)$_{11}$			
Two copies	1.0 (reference)		0.64
One copy	1.33	0.80-2.22	
None	1.03	0.58-1.83	

*Adjusted for age.

Results and Discussion

Genotypes of two cases did not amplify, leaving 436 cases available for our analyses. No noteworthy difference was observed in the frequency of *CYP19* (TTTA)$_n$ repeat polymorphism between cases and controls (Table 1). Logistic regression analyses revealed no association with prostate cancer (Table 2). Specifically, we observed no association between *CYP19* (TTTA)$_n$ repeat polymorphism and prostate cancer regardless of how this was modeled (for brevity sake, we only report results from genotype-level analysis). Stratifying these analyses by the stage/grade of prostate cancer or age at diagnosis of the cases did not materially alter our null results (data not shown). Furthermore, restricting the analyses to Caucasians only did not affect our findings.

By using a sibling-based design, our results are not susceptible to population stratification bias. However, this design can be less efficient than a study of unrelated cases and controls. Nevertheless, our study had >80% power to detect an odds ratio ≥ 1.75 for the poly-

morphisms studied here. In conclusion, this moderately large case-control study did not detect an association between *CYP19* (TTTA)$_n$ repeat polymorphism and risk or aggressiveness of prostate cancer.

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