CYP19 TCT Tri-Nucleotide Del/Del Genotype Is a Susceptibility Marker for Prostate Cancer in a Taiwanese Population

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OBJECTIVES The *CYP19* gene encodes aromatase—a key enzyme involved in the conversion of androstenedione/testosterone to estrone/estradiol. In this study, we analyzed the association between the TCT insertion (Ins)/deletion (Del) and TTTA repeat polymorphisms of *CYP19* and prostate cancer (PCa).

METHODS Automated sequencer with GeneScan software was used to determine the *CYP19* gene polymorphisms in peripheral blood mononuclear cell DNA from 244 patients with PCa and 261 age-matched healthy male controls. The distribution of Stage I to IV was 3.4%, 23.8%, 19.6%, and 53.2%, respectively. The Gleason score was 2 to 5 in 22.9%, 6 to 7 in 53.2%, and 8 to 10 in 23.8%.

RESULTS The frequency of the TCT Del/Del genotype in the Taiwanese patients with PCa (12.3%) was significantly greater than that in the controls (5.4%; $P = 0.015$, odds ratio [OR] 2.43, 95% confidence interval [CI] 1.23 to 4.80). Individuals with a homozygous A1 (seven TTTA repeats) genotype had a significantly greater risk of developing PCa (OR 1.59, 95% CI 1.04 to 2.44, $P = 0.044$). The frequency of the Ins-A6 (12 TTTA repeats) haplotype was significantly greater in the control group than in the patient group (9.8% versus 6.1%, OR 0.61, 95% CI 0.38 to 0.97). The OR of developing PCa for men with the homozygous Del-A1 diplotype was 2.31 (95% CI 1.10 to 4.83).

CONCLUSIONS The results of our study have shown that the *CYP19* TCT Del/Del genotype might be a susceptibility marker for PCa. Men with the Ins-A6 haplotype had a lower risk of developing PCa. UROLOGY 69: 996–1000, 2007. © 2007 Elsevier Inc.

Prostate cancer (PCa) is a leading cause of illness and death among men in the United States and Western Europe.[1] The incidence of PCa varies widely among differing ethnic populations and nationalities. African-American men have the greatest incidence in the world, and Asians have a much lower incidence, especially among the Chinese.[2] Well-documented risk factors associated with PCa include age, race, and a family history of PCa. Secondary risk factors that have been implicated include diet, androgens, occupational chemicals, smoking, inflammation, and obesity.[2]

The *CYP19* gene encodes aromatase—a key enzyme that converts androstenedione (A)/testosterone (T) to estrone/estradiol (E2). Testosterone has been shown to induce prostate adenocarcinoma, and low levels of E2 have been proposed to be associated with PCa risk.[3,4] The prostate is influenced by estrogen from peripheral sources, as well as by aromatase activity in the stroma.[5] Two genetic polymorphisms—TTTA tetranucleotide repeats and TCT trinucleotide insertion/deletion (Ins/Del) alleles—have been identified in the intron 4 of the human *CYP19* gene.[6,7] The TTTA repeats are located approximately 80 base pairs (bp) downstream from exon 4 of the *CYP19* gene; the TCT Ins/Del allele is located approximately 50 bp upstream of the TTTA repeats.[8,9] Gennari *et al.*[10] reported that in a group of Italian men older than 55 years of age, those with low number of TTTA repeats (fewer than 10 repeats) had significantly lower levels of

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serum E2 and higher levels of testosterone than did those with a high number of TTTA repeats (10 or more repeats). Thus, it is possible that genetic polymorphisms in *CYP19* can alter a man's susceptibility to PCa. However, inconsistent associations among different TTTA repeats alleles of *CYP19* and PCa risk have been reported. Latil *et al.*[11] found that 7 and 11 TTTA repeats alleles were associated with PCa in the French population, but Li *et al.*[12] failed to identify any association between TTTA repeat polymorphism and PCa risk in white men.

Because no such association study has been conducted in the Chinese, we decided to conduct a case-control study to determine whether any association exists between *CYP19* genetic polymorphisms and PCa in a Taiwanese population. We hypothesized that men with lower numbers of *CYP19* TTTA repeats would be more susceptible to PCa and men with a greater number of TTTA repeats would have protection against PCa. Additionally, we analyzed the association of another polymorphism of *CYP19*—TCT Ins/Del allele with PCa risk. The results showed that men with homozygous seven TTTA repeats or TCT-Del genotypes had a significantly greater risk of developing PCa. In addition, the odds ratio (OR) of developing PCa for men with homozygous seven TTTA repeats and the Del diplotype was 2.31 (95% confidence interval [CI] 1.10 to 4.83).

MATERIAL AND METHODS

Patients

From 2000 to 2004, 244 patients with PCa were recruited from the postoperative follow-up clinics at three Taiwanese hospitals: Taipei Veterans General Hospital, Taipei Mackay Memorial Hospital, and Kaohsiung Veterans General Hospital. The PCa diagnosis for all patients was done pathologically using transrectal ultrasound-guided biopsy specimens. The demographic and clinical data, including disease stage, Gleason score, and prostate-specific antigen level, were collected by reviewing the patients' medical records. The disease stage was determined using the definition proposed by the American Joint Committee Against Cancer TNM system (2002). All the patients were Taiwanese descendants, and none were aborigines. In addition, 261 normal adult men, matched by age and ethnic background to the patients, were recruited from the Department of Family Medicine, Taipei Municipal Hospital and Kaohsiung Yuan's General Hospital. All the controls had undergone a physical examination, including a digital rectal examination, and serobiochemical tests to rule out malignancy. Men with an abnormal prostate-specific antigen level (greater than 4.0 ng/mL) were excluded from the control group. The institutional review board of all participating hospitals reviewed and approved this study. All patients and controls participating in this study provided informed consent.

CYP19 Genetic Polymorphism Determination

Genomic DNA was obtained from the peripheral blood mononuclear cells using a conventional phenol/chloroform extraction method followed by ethanol precipitation. The *CYP19* TCT Ins/Del and TTTA repeat alleles were assessed by fragment analysis of the polymerase chain reaction product using primers described in Polymeropoulos *et al.*[13] The forward primer was 5′-labeled with HEX fluorescence dye for automated fragment analysis with an ABI PRISM 377 DNA sequencer (Applied Biosystems, Foster City, Calif) using a GeneScan 400 size standard, GeneScan, and Genotyper analysis software (Applied Biosystems). The TTTA repeat polymorphisms ranged from 7 to 13 repeats, with an allelic size of 169 to 196 bp. TTTA repeat numbers 7 to 13 were designated as A1 to A7 alleles, respectively. The A1 allele (seven TTTA repeats) contained two different alleles, with or without a trinucleotide TCT Ins/Del located 50 bp upstream of the TTTA repeats tract, resulting in base pair products of 169 and 172 bp.[14]

Statistical Analysis

The Pearson chi-square test or Fisher's exact test was used to determine the statistical significance of any differences in allele frequencies of the *CYP19* gene between the patient and control groups. The Monte-Carlo exact test was performed to determine whether the allele frequency of the TTTA repeats was different between the patients and controls.[15] The Hardy-Weinberg equilibrium was tested for each marker using the chi-square test. GENECOUNTING software (version 2.0) was used to estimate the frequencies of the haplotypes of these two loci and to calculate the linkage disequilibrium (r^2 or D′) between two loci.[16,17] The RUNGC program was used to calculate the probability for the haplotype allocations to obtain diplotypes (combinations of haplotypes) for each subject. ORs and 95% CIs were estimated for the genotypes/diplotypes associations with PCa by logistic regression analysis. Statistical analyses were performed using the Statistical Package for Social Sciences software package, version 11.0 (SPSS, Chicago, Ill), and $P < 0.05$ was considered significant.

RESULTS

A total of 244 patients with PCa and 261 controls were recruited for this case-control study. The mean age ± standard deviation at the diagnosis of the patients was 73.1 ± 7.0 years (range 50 to 92) and of the controls was 73.4 ± 7.7 years (range 50 to 89). The mean pretreatment prostate-specific antigen level ± standard deviation of the patients was 299.0 ± 1093.1 ng/mL (range 0.11 to 10,651, median 35.1, n = 228). The distribution of TNM Stage I to IV was 3.4% (8 of 235), 23.8% (56 of 235), 19.6% (46 of 235), and 53.2% (125 of 235), respectively. The Gleason score was 2 to 5 in 53 (22.9%) of 230 patients, 6 to 7 in 123 (53.2%), and 8 to 10 in 55 (23.8%).

The allelic frequencies of the TCT Ins/Del and TTTA repeats of *CYP19* for the patients with PCa and the controls are summarized in Table 1. The TCT Ins/Del and TTTA repeats alleles were in Hardy-Weinberg equilibrium. The allelic distribution of TCT Ins/Del was not significantly different between the two groups. We found six allelic types of the TTTA repeats in our population: A1 (7 repeats), A2 (8 repeats), A4 (10 repeats), A5 (11 repeats), A6 (12 repeats), and A7 (13 repeats). The most frequent allele among all 505 subjects in this study was A1. None of the alleles mentioned had significantly different frequencies between patients and controls, ex-

Table 1. *CYP19* TCT Ins/Del and TTTA repeat allele frequencies among patients with prostate cancer and matched controls

CYP19 Polymorphism	Patients with PCa (%) (n = 244; 488 alleles)	Controls (%) (n = 261; 522 alleles)	*P* Value
TCT Ins/Del alleles			
Ins	328 (67.2)	376 (72.0)	0.110*
Del	160 (32.8)	146 (28.0)	
TTTA repeat alleles† (*P* = 0.155‡)			
A1	273 (55.9)	279 (53.4)	0.464
A2	2 (0.4)	3 (0.6)	0.940
A3	0 (0)	0 (0)	—
A4	10 (2.0)	4 (0.8)	0.141
A5	173 (35.5)	184 (35.2)	0.999
A6	30 (6.1)	51 (9.8)	0.045
A7	0 (0)	1 (0.2)	—

Ins = insertion; Del = deletion.
* Calculated by chi-square test.
† TTTA repeat numbers for A1 to A7 alleles were 7 to 13, respectively.
‡ Calculated by Monte-Carlo exact test.

Table 2. Distribution of common haplotypes of *CYP19* TCT Ins/Del and TTTA repeat in patients with prostate cancer and matched controls

Haplotype*	Patients with PCa (%) (n = 244; 488 alleles)	Controls (%) (n = 261; 522 alleles)	OR (95% CI)†	OR (95% CI)‡
TCT Ins/Del-TTTA repeat§				
Del-A1	160 (32.8)	144 (27.6)	1.28 (0.98–1.68)	1.18 (0.87–1.61)
Ins-A1	113 (23.2)	135 (25.9)	0.86 (0.65–1.15)	0.89 (0.64–1.23)
Ins-A5	173 (35.5)	184 (35.2)	1.01 (0.78–1.31)	1.00 (Ref)
Ins-A6	30 (6.1)	51 (9.8)	0.61 (0.38–0.97)¶	0.63 (0.38–1.03)
Others‖	12 (2.4)	8 (1.5)	1.62 (0.66–4.00)	1.60 (0.64–4.00)

OR = odds ratio; CI = confidence interval; other abbreviations as in Table 1.
* Only haplotypes with estimated frequencies ≥5% listed.
† All others haplotypes as reference.
‡ Most common haplotype as reference.
§ TTTA repeat numbers for A1 to A7 alleles were 7 to 13, respectively.
‖ Haplotypes with estimated frequencies <5% pooled into "others" category.
¶ $P < 0.05$.

cept for the A6 allelic type of the TTTA repeats. Compared with the controls, the patients with PCa had a significantly lower frequency of the A6 allelic type (6.1% versus 9.8%, $P = 0.045$; Table 1).

In addition, we estimated the linkage disequilibrium between the TCT Ins/Del and TTTA repeats polymorphisms using the GENECOUNTING software package. The results showed complete linkage disequilibrium between the TCT Ins/Del and TTTA repeat polymorphism ($P < 0.00001$). Subsequently, we compared the frequencies of different TCT Ins/Del-TTTA repeat haplotypes between the two groups. As shown in Table 2, four haplotypes had a frequency of 5% or more, and they accounted for 97.6% and 98.5% of all haplotypes in the patients and controls, respectively. The Del allele of the Ins/Del polymorphism occurred only in the A1 allelic type, and the Ins allele co-segregated with all the TTTA repeat alleles. When we compared the frequencies of the different haplotypes between the two groups, the results showed that the frequency of the Ins-A6 haplotype was significantly greater in the control group than in the patient group (9.8% versus 6.1%, OR 0.61, 95% CI 0.38 to 0.97). Therefore, persons with the Ins-A6 haplotype might have a lower risk of developing PCa.

In terms of genotype, the patients had a significantly greater rate of the homozygous TCT deletion (Del/Del) genotype than did the controls (12.3% versus 5.4%, $P = 0.015$; Table 3). When we used the patients with the TCT Ins/Ins genotype as a reference group, the OR for patients with the Del/Del genotype to develop PCa was 2.43 (95% CI 1.23 to 4.80). A comparison of the Gleason score for the patients with different TCT Ins/Del genotypes showed that a Gleason score greater than 7 was found more often in patients with the Del/Del genotype (27.6%) than in those with the Ins/Ins (24.8%) or Del/Ins (20.7%) genotype. However, the differences were not statistically significant. In addition, the patients had a significantly greater rate of the homozygous A1 genotype than did the controls (34.8% versus 26.4%, $P = 0.044$). When we used the patients with the most common genotype A1/A5 as the reference group, the OR for developing PCa among those carrying the A1/A1 genotype was 1.59 (95% CI 1.04 to 2.44). Finally, the frequency for the homozygous Del-A1 diplotype was 12.3%

Table 3. Distribution of different *CYP19* TCT Ins/Del and TTTA repeat genotypes and diplotypes in patients with prostate cancer and matched controls

CYP19	Patients with PCa (%) (n = 244)	Controls (%) (n = 261)	OR (95% CI)*	OR (95% CI)†
Genotype				
TCT Ins/Del				
Ins/Ins	114 (46.7)	129 (49.4)	0.90 (0.63–1.27)	1.00 (Ref)
Del/Ins	100 (41.0)	118 (45.2)	0.84 (0.59–1.20)	0.96 (0.67–1.38)
Del/Del	30 (12.3)	14 (5.4)	2.47 (1.28–4.79)‡	2.43 (1.23–4.80)‡
TTTA repeat‖				
A1/A1	85 (34.8)	69 (26.4)	1.49 (1.02–2.18)‡	1.59 (1.04–2.44)‡
A1/A5	83 (34.0)	107 (41.0)	0.74 (0.52–1.07)	1.00 (Ref)
A1/A6	15 (6.1)	28 (10.7)	0.55 (0.28–1.05)	0.69 (0.35–1.38)
A5/A5	37 (15.2)	30 (11.5)	1.38 (0.82–2.31)	1.59 (0.91–2.79)
A5/A6	12 (4.9)	16 (6.1)	0.79 (0.37–1.71)	0.97 (0.43–2.16)
Others§	12 (4.9)	11 (4.2)	1.18 (0.51–2.72)	1.41 (0.59–3.35)
Diplotype‖				
TCT Ins/Del and TTTA repeat				
Del-A1/Del-A1	30 (12.3)	14 (5.4)	2.47 (1.28–4.79)‡	2.31 (1.10–4.83)‡
Del-A1/Ins-A1	39 (16.0)	43 (16.5)	0.96 (0.60–1.55)	0.98 (0.55–1.74)
Del-A1/Ins-A5	52 (21.3)	56 (21.5)	0.99 (0.65–1.52)	1.00 (Ref)
Del-A1/Ins-A6	7 (2.9)	16 (6.1)	0.45 (0.18–1.12)	0.47 (0.18–1.24)
Ins-A1/Ins-A1	16 (6.6)	12 (4.6)	1.46 (0.67–3.14)	1.44 (0.62–3.32)
Ins-A1/Ins-A5	31 (12.7)	51 (19.5)	0.60 (0.37–0.97)	0.66 (0.37–1.17)
Ins-A5/Ins-A5	37 (15.2)	30 (11.5)	1.38 (0.82–2.31)	1.33 (0.72–2.45)
Ins-A5/Ins-A6	12 (4.9)	16 (6.1)	0.79 (0.37–1.71)	0.81 (0.35–1.87)
Others§	20 (8.2)	23 (8.8)	0.92 (0.49–1.73)	0.94 (0.46–1.90)

Abbreviations as in Tables 1 and 2.
* All others genotypes/diplotypes as reference.
† Most common genotype/diplotype as reference.
‡ $P < 0.05$.
§ Genotype and diplotype frequencies <5% pooled into "others" category.
‖ TTTA repeat numbers for A1 to A7 alleles were 7 to 13, respectively.

and 5.4%, respectively, for the patient and control groups compared with the most common diplotype Del-A1/Ins-A5; the OR for developing PCa among patients with the homozygous Del-A1 diplotype was 2.31 (95% CI 1.10 to 4.83).

COMMENT

In this study, we found evidence suggesting a link between the *CYP19* TCT Del/Del genotype and susceptibility to PCa in the Taiwanese population (OR 2.43, 95% CI 1.23 to 4.80). To our knowledge, this is the first report of such an association. When we compared the allelic frequencies of TCT Ins/Del of our controls with the data of the white controls reported by Li *et al.*,[12] we found that the white controls had a significantly greater frequency of the *CYP19* Del allele than did our Taiwanese controls (33.9% versus 28.0%, $P = 0.024$).

As shown in Table 3, an association was found between the homozygous *CYP19* 7 TTTA repeat genotype (A1/A1) and PCa (OR 1.59, 95% CI 1.04 to 2.44). Additionally, we found that patients with PCa had a significantly lower frequency of the A6 allelic type than did the controls (Table 1). The frequency of the Ins-A6 haplotype was also significantly lower in the patient group than in the control group (6.1% versus 9.8%, OR 0.61, 95% CI 0.38 to 0.97). Because it has been shown that adult men with high TTTA repeat genotypes have greater aromatase activity, those with the Ins-A6 haplotype may convert androgens to estrogens more efficiently.[10] Therefore, these results fit with our hypothesis. We also compared the allelic frequencies of the TTTA repeats between our Taiwanese control group and the white control group reported by Li *et al.*[12] Compared with the Taiwanese population, the allelic frequency of A6 was significantly lower in the white men (9.8% versus 2.6%, $P < 0.0001$). Furthermore, Suzuki *et al.*[18] reported that 26 (11.2%) of 232 Japanese men had the A6 allele. Therefore, the identified discrepancy of the frequencies of the A6 allele between whites and Asians could partially explain why white men have a greater incidence of PCa than do Asian men.

In this study, we found that the Del allele of the Ins/Del polymorphism co-segregates with the A1 allele but that the Ins allele co-segregates with all alleles of the TTTA repeat marker. It has been reported that complete linkage disequilibrium was present between the Del allele of the TCT Ins/Del and 7 TTTA repeat allele.[8,14,19,20] In addition, when we analyzed the TCT Ins/Del and TTTA repeat diplotypes, the results indicated that the OR for individuals carrying a homozygous TCT Del and A1 diplotype was 2.31 (95% CI 1.10 to 4.83). In contrast, the OR for those carrying a homozygous TCT Ins and A1 was 1.44 (95% CI 0.62 to 3.32). Therefore, the Del/Del genotype of TCT Ins/Del polymorphism, rather than the

A1/A1 genotype of the TTTA repeats, is the key factor determining the susceptibility to PCa. This is the first study reporting a positive association between the *CYP19* TCT Del/Del genotype and the susceptibility to PCa.

Previously, Gennari *et al.*[10] reported that in a group of men older than 55 years of age, those with a low number of TTTA repeats (fewer than 10 repeats) had a significantly lower level of serum E2 and a greater level of testosterone than did those with a high number of TTTA repeats (10 or more repeats). In addition, Dunning *et al.*[21] found that the Del/Del genotype is associated with a reduced E2/testosterone ratio in a group of postmenopausal women in the United Kingdom. These findings can be explained by the strong disequilibrium in the linkage among TCT Ins/Del, TTTA repeats, and a C/T SNP in exon 10 of *CYP19*.[21,22] Because the C/T SNP in exon 10 is in the 3′UTR of the mRNA, it could have functional significance by affecting mRNA stability or regulation of termination translation.[22] The findings from these reports could provide mechanistic explanations for the results we obtained in this study.

The main limitation of this study was the small sample size. Future studies with a larger number of subjects are needed to confirm these findings. Another limitation was that of all the known polymorphisms of *CYP19*, we only tested a small subset. It is uncertain whether the polymorphisms we tested play a causal role in PCa or whether they are merely in linkage disequilibrium with other functional polymorphism sites within or flanking the *CYP19* gene.

CONCLUSIONS

The results of our study suggest that the *CYP19* TCT Del/Del genotype may be a susceptibility marker for PCa. Men with the Ins-A6 haplotype had a lower risk of developing PCa in our study.

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