

Lack of Association Between *CYP17* MspA1 Polymorphism and Prostate Cancer Risk: A Meta-Analysis of 14 494 Cases and 15 971 Controls

Guoqi Song¹, Ling Gu², Fuliang Tian², Qian Bao², Zhipeng Tang³, Shukui Wang³

¹Department of Hematology, Affiliated Hospital of Nantong University, ²Department of Life Sciences, Nanjing Normal University, ³Central Laboratory of Nanjing First Hospital, Nanjing Medical University, China

Key Words: *CYP17* MspA1 polymorphism; meta-analysis; prostate cancer.

Summary. *Background and Objective.* A T-to-C polymorphism that creates a recognition site for the MspA1 restriction enzyme in the 5' promoter region of *CYP17* has been implicated as a risk factor for prostate cancer. To date, many studies have evaluated associations between the *CYP17* MspA1 polymorphism and prostate cancer risk; however, the results were controversial. Therefore, the aim of this study was to perform a meta-analysis to investigate the association between the *CYP17* MspA1 polymorphism and the risk of prostate cancer.

Material and Methods. By searching the Pubmed, Web of Science, ScienceDirect, EBSCO databases, 36 studies including 14 494 cases and 15 971 controls were collected. Odds ratios (ORs) with their 95% confidence intervals (CIs) were used to assess the strength of the association.

Results. The overall results showed no significant association between the *CYP17* MspA1 polymorphism and the risk of prostate cancer (OR, 1.07; 95% CI, 0.92–1.25 for A2/A2 vs. A1/A1; OR, 1.02; 95% CI, 0.92–1.12 for A1/A2 vs. A1/A1; OR, 1.07; 95% CI, 0.94–1.22 for A2/A2 vs. A1/A2+A1/A1; OR, 1.03; 95% CI, 0.93–1.14 for A1/A2+A2/A2 vs. A1/A1). In the stratified analysis according to ethnicity, no significant associations were observed in Asian, European, and African populations in all genetic models. In the stratified analysis by the source of controls and inpatients were found to have an increased risk of prostate cancer in all genetic models.

Conclusions. The meta-analysis suggests that the *CYP17* MspA1 polymorphism is unlikely to increase the risk of prostate cancer in a wide population.

Introduction

Prostate cancer (PCa) is the most common cancer among men, accounting for 10% of male cancer-related mortality (1). The major risk factors for the development of PCa are advanced age, familial predisposition, ethnicity, and environmental factors (2, 3). The role of steroid hormones in the etiology of PCa has been reported, and several molecules encoded by polymorphic genes (hormones, their receptors, and enzymes involved in hormone biosynthesis and metabolism) have recently been shown to be associated with the risk of PCa (4). The *CYP17* gene maps to chromosome 10q24.3 (5) that encodes the cytochrome P450c17 α enzyme mediating both 17 α -hydroxylase and 17, 20-lyase activities at key points in the testosterone biosynthesis in gonads and adrenals (6). It is conceivable that changes in the activity of the *CYP17* enzyme may have an impact on androgen biosynthesis and, thus, influence susceptibility to the risk of PCa. The 5'-untranslated region of *CYP17* contains a single T-to-C base

transition at position 1931 (rs743572) that creates a recognition site for the MspA1 restriction enzyme that has been used to designate 2 alleles: A1 (wild allele) and A2 (variant allele) (7). This polymorphism may enhance the transcription of the *CYP17* gene and, thus, increases enzyme activity.

A few studies have indicated that the A2 allele may be associated with an increased risk of PCa (8–13). However, other investigations have apparently been inconclusive (14, 15) or have even reported that the A1 allele may increase the risk of PCa (16, 17). To clarify the effect of the *CYP17* MspA1 polymorphism on the risk of PCa, we conducted a meta-analysis of all available studies.

Material and Methods

Literature Search. The PubMed, Web of Science, ScienceDirect, and EBSCO databases (the last search was updated on November 5, 2010) were searched with the following key words and terms: *cytochrome P450c17 α* , *CYP17* polymorphism, and *prostate cancer*. All eligible articles were retrieved, and their references were checked for other relevant articles. When more than one publication involved the same patient population, only the most recent or

Correspondence S. Wang, Central Laboratory of Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing, China. E-mail: shukwang@163.com

complete study was included in this meta-analysis.

Inclusion Criteria. The study was included into our meta-analysis only if it met the following criteria: 1) available data on the risk of PCa and the MspA1 polymorphism; 2) published in English or Chinese; 3) case-control studies; 4) sources of cases clearly described; 5) sufficient data to estimate an odds ratio (OR) with its 95% confidence interval (CI); and 6) available genotype frequency. When the publication reported results for more than one population, we considered it as two separate studies.

Information was carefully extracted from all the eligible publications independently by 2 of the authors according to the inclusion criteria listed above. The following information was extracted from the study: the first author's last name, year of publication, ethnicity of subjects, number of patients and controls, source of controls, and genotype frequency.

Statistical Analysis. The strength of association between the *CYP17* MspA1 polymorphism and the risk of PCa was assessed by ORs with 95% CIs. The pooled ORs were estimated for codominant (A2/A2 vs. A1/A1; A1/A2 vs. A1/A1), dominant (A2/A2+

A1/A2 vs. A1/A1), and recessive (A2/A2 vs. A1/A2+A1/A1) models. Stratified analyses were performed by ethnicity and the source of controls. Firstly, the Pearson χ^2 test was used to determine whether the distribution of genotypes in controls was in agreement with the Hardy-Weinberg equilibrium (18). Secondly, the heterogeneity among the studies was evaluated with the Cochran Q test; it was considered significant when $P < 0.05$. The data were combined using both fixed- and random-effects models. The random-effects model was more appropriate when heterogeneity existed (19); otherwise, the fixed-effects model was utilized (20). Finally, publication bias was checked. Publication bias was assessed graphically by using funnel plots and statistically by using the Egger's test (21). Statistical analysis was performed with STATA11.1 and SPSS13.0, and all the P values were two-sided.

Results

Study Characteristics. Based on our search criteria, a total of 53 studies were preliminarily eligible. All the papers were reviewed according to the crite-

Table 1. The Main Characteristics of Studies Included in the Meta-Analysis

First Author	Year	Ethnicity	No. of Patients With PCa	No. of Controls	Source of Controls	A2 allele	P_{HWE}
Wu (22)	2009	Asian	85	82	HB	0.52	0.49
Sobti (23)	2009	Asian	157	170	HB	0.30	0.01
Sobti (24)	2008	Asian	157	170	HB	0.31	0.01
Dos Santos (25)	2008	African	43	50	HB	0.28	0.45
Sarma (26)	2008	African	126	322	PB	0.39	0.00
Setiawan (27)	2007	European	7948	8834	PB	0.40	0.90
Gunes (28)	2007	Asian	148	102	HB	0.28	0.71
Cussenot (29)	2007	European	998	777	PB	0.41	0.10
Onen (30)	2007	Asian	100	105	PB	0.43	0.91
Hamada (31)	2007	European	222	83	PB	0.39	0.44
Sobti (32)	2006	Asian	100	100	HB	0.30	0.63
Guli (33)	2006	Asian	31	104	HB	0.45	0.49
Yang (34)	2006	Asian	163	202	HB	0.59	0.54
Okugi (35)	2006	Asian	102	117	HB	0.47	0.75
Vesovic (36)	2005	European	174	89	NR	0.39	0.09
Forrest (37)	2005	European	262	462	PB	0.36	0.35
Antognelli (38)	2005	European	384	360	NR	0.44	0.06
Antognielli (39)	2004	European	96	18	NR	0.44	0.67
Cicek (40)	2004	African	38	38	FB	0.33	0.17
Cicek (40)	2004	European	397	436	FB	0.40	0.61
Madigan (41)	2003	Asian	174	274	PB	0.61	0.22
Lin (42)	2003	Asian	93	121	HB	0.36	0.02
Stanford (13)	2002	European	560	523	PB	0.40	0.59
Stanford (13)	2002	African	30	15	PB	0.37	0.99
Santos (43)	2002	African	8	72	PB	0.34	0.38
Santos (43)	2002	European	84	128	PB	0.34	0.22
Chang (14)	2001	European	225	182	PB	0.36	0.43
Latil (15)	2001	European	226	156	PB	0.42	0.20
Kittles (12)	2001	African	71	111	PB	0.30	0.93
Haiman (11)	2001	European	590	782	PB	0.39	0.12
Yamada (10)	2001	Asian	101	200	HB	0.45	0.00
Habuchi (17)	2000	Asian	252	333	HB	0.44	0.42
Gsur (9)	2000	European	63	126	NR	0.36	0.09
Wadelius (16)	1999	European	178	160	PB	0.44	0.14
Lunn (8)	1999	African	12	8	HB	0.31	0.72
Lunn (8)	1999	European	96	159	HB	0.34	0.81

PCa, prostate cancer; HWE, Hardy-Weinberg equilibrium; FB, family-based; HB, hospital-based; PB, population-based; NR, not reported.

ria defined above. We excluded 3 reviews, 3 repeated articles, and 15 papers that did not offer full information or were irrelevant to our study. Four studies analyzed different populations. Finally, 36 studies were included in our analysis. There were 16 studies of European, 13 studies of Asian, and 7 studies of African populations. Table 1 summarizes their main characteristics. In the majority of the analyzed studies, genotype distributions were in agreement with the Hardy-Weinberg equilibrium with the exception of 5 studies (10, 23, 24, 26, 42).

Quantitative Synthesis. Table 2 lists the main results of the meta-analysis. When all the 36 studies were pooled into the meta-analysis, there was no evidence for a significant association between the CYP17 MspA1 polymorphism and the risk of PCA. In the subgroup analyses by ethnicity and the source of controls, significant associations were found only in inpatients subjects in all genetic models (Table 2).

Test for Heterogeneity. There was significant heterogeneity across the studies in overall comparisons. In order to clarify the source of the heterogeneity, stratified analyses by the source of controls and ethnicity were performed. As a result, the source of controls was found to contribute to the heterogeneity for dominant ($P_{\text{heterogeneity}} < 0.001$), recessive ($P_{\text{heterogeneity}} = 0.006$), and codominant (A2/A2 vs. A1/A1, $P_{\text{heterogeneity}} = 0.001$; A2/A1 vs. A1/A1, $P_{\text{heterogeneity}} = 0.006$) models. However, ethnicity was not the source of heterogeneity.

Publication Bias. The Begg's funnel plot and the Egger's test were used to assess publication bias. As shown in Fig. 1, the shapes of the funnel plot did not reveal an obvious asymmetry. The Egger's test was used to provide the statistical evidence of funnel plot symmetry. The results did not show any publication bias ($t=1.27$, $P=0.213$, for A2/A2 vs. A1/A2+A1/A1).

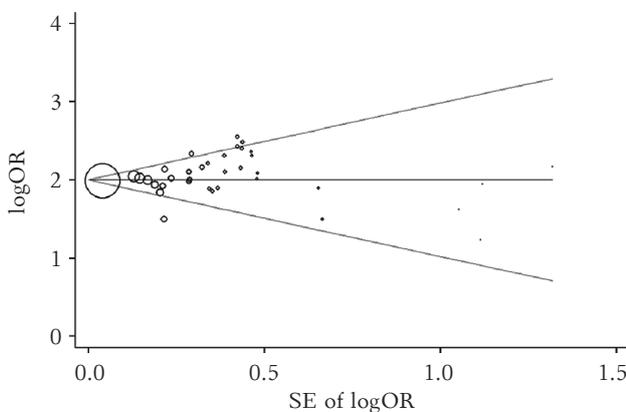


Fig. Begg's funnel plot with pseudo 95% confidence intervals for publication bias testing (CYP17 MspA1 polymorphism for genotypes A2/A2 vs. A1/A2+A1/A1)

Table 2. Stratified Analyses of CYP17 MspA1 Polymorphism and Prostate Cancer Risk

Study Subgroups	No. of Studies	Sample Size (No. of Cases/No. of Controls)	A2/A2 vs. A1/A1		A1/A2 vs. A1/A1		A2/A2 vs. A1/A2+A1/A1		A1/A2+A2/A2 vs. A1/A1	
			OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Overall	36	14 494/15 971	1.07 (0.92-1.25)*	<0.001	1.02 (0.92-1.12)*	0.001	1.07 (0.94-1.22)*	0.001	1.03 (0.93-1.14)*	<0.001
Ethnicity										
Asian	13	1663/2080	1.38 (0.97-1.98)*	0.001	1.15 (0.92-1.46)*	0.012	1.22 (0.96-1.55)	0.053	1.20 (0.93-1.55)*	0.001
European	16	12 503/13 275	0.93 (0.78-1.11)*	0.002	0.95 (0.86-1.05)	0.099	0.97 (0.82-1.14)*	0.002	0.94 (0.85-1.04)*	0.037
African	7	328/616	1.42 (0.90-2.23)	0.564	1.31 (0.76-2.28)*	0.024	1.40 (0.88-2.23)	0.375	1.27 (0.82-1.99)	0.095
Source of controls										
Hospital-based	14	1540/1918	1.56 (1.10-2.20)*	0.012	1.31 (1.06-1.61)	0.066	1.31 (1.05-1.63)	0.266	1.36 (1.09-1.71)*	0.017
Population-based	16	11 802/12 986	0.98 (0.90-1.05)	0.718	0.93 (0.82-1.05)*	0.012	0.99 (0.92-1.06)	0.639	0.94 (0.84-1.05)*	0.039
Family-based	2	435/474	0.87 (0.59-1.29)	0.698	1.17 (0.60-2.29)	0.154	0.88 (0.61-1.26)	0.897	1.07 (0.63-1.82)	0.199

P_h : P values for heterogeneity from Q test; OR, odds ratio; CI, confidence interval. *The random-effects model was used when a P value for heterogeneity test was <0.05; otherwise, the fixed-effects model was used.

Discussion

The present meta-analysis of 36 studies, including 14 494 cases and 15 971 controls, provided the most comprehensive analysis on the association of the *CYP17* MspA1 polymorphism with the risk of PCa. The results indicated that the *CYP17* MspA1 polymorphism was not associated with an increased risk of PCa in the overall studied population. These findings were consistent with most of the studies that were included into our meta-analysis.

A study by Zmuda et al. reported that white men with the A2/A2 genotype had a higher bioavailable testosterone level than men with the A1/A1 genotype. A1/A2 heterozygotes had intermediate testosterone values (44). However, there was no evidence of a consistently increased androgen concentration in A2 allele carriers demonstrated. Additionally, the *CYP17* genotype was not reported to be associated with the different levels of testosterone, other androgens and their metabolites (dehydrotestosterone, androstanediol glucuronide) (11, 45). Furthermore, genome scans had typically not identified significant linkage to the 10q24.32 chromosomal region where the *CYP17* gene was located (46, 47).

In the stratified analysis according to ethnicity, no significant associations were observed in Asian, European, and African populations in all genetic models suggesting that ethnic differences in genetic backgrounds and the environment they lived did not play an obvious role in the association between the *CYP17* MspA1 polymorphism and the risk of PCa.

Between-study heterogeneity may be attributed to many factors including the selection of publications and differences in population characteristics, sample sizes, and source of controls. We also ex-

plored the ethnicity and source of controls as the possible causes of heterogeneity. First, controls in the studies were not uniformly defined. Although most of the controls were mainly selected from healthy populations, a few controls had benign prostatic hyperplasia. Nondifferential misclassification bias was possible because these studies might have included controls that had different risks for developing PCa. Second, the detailed information on patients' age, smoking habits, and environmental factors could not be traced. Therefore, our unadjusted estimates should be confirmed by further studies. Third, we should also admit the possibility of publication bias. Some studies on the relationship between the *CYP17* MspA1 polymorphism and the risk of PCa may not have been indexed online or may be unpublished so far.

In summary, this meta-analysis did not provide the evidence of an association between the *CYP17* MspA1 polymorphism and the risk of PCa in a pooled worldwide population. Future studies should use standardized, unbiased, homogenous groups of cancer patients and well-matched controls. Studies of the combined effects of gene and environment contribution would lead to more comprehensive understanding of the association between the *CYP17* MspA1 polymorphism and the risk of PCa.

Conclusions

The meta-analysis demonstrated that the *CYP17* MspA1 polymorphism was not associated with an increased risk of prostate cancer in a worldwide population.

Statement of Conflicts of Interest

The authors state no conflict of interest.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71-96.
- Abate-Shen C, Shen MM. Molecular genetics of prostate cancer. *Genes Dev* 2000;14:2410-34.
- Taylor JD, Holmes TM, Swanson GM. Descriptive epidemiology of prostate cancer in metropolitan Detroit. *Cancer* 1994;3:1704-7.
- Ntais C, Polycarpou A, Tsatsoulis A. Molecular epidemiology of prostate cancer: androgens and polymorphisms in androgen-related genes. *Eur J Endocrinol* 2003;149:469-77.
- Fan YS, Sasi R, Lee C, Winter JS, Waterman MR, Lin CC. Localization of the human *CYP17* gene (cytochrome P450(17 alpha)) to 10q24.3 by fluorescence in situ hybridization and simultaneous chromosome banding. *Genomics* 1992;14:1110-1.
- Picado-Leonard J, Miller WL. Cloning and sequence of the human gene for P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): similarity with the gene for P450c21. *DNA* 1987;6:439-48.
- Carey AH, Waterworth D, Patel K, White D, Little J, Novelli P, et al. Polycystic ovaries and premature male pattern baldness are associated with one allele of the steroid metabolism gene *CYP17*. *Hum Mol Genet* 1994;3:1873-6.
- Lunn RM, Bell DA, Mohler JL, Taylor JA. Prostate cancer risk and polymorphism in 17 hydroxylase (*CYP17*) and steroid reductase (*SRD5A2*). *Carcinogenesis* 1999;20:1727-31.
- Gsur A, Bernhofer G, Hinteregger S, Haidinger G, Schatzl G, Madersbacher S, et al. A polymorphism in the *CYP17* gene is associated with prostate cancer risk. *Int J Cancer* 2000;87:434-7.
- Yamada Y, Watanabe M, Murata M, Yamanaka M, Kubota Y, Ito H, et al. Impact of genetic polymorphisms of 17-hydroxylase cytochrome P-450 (*CYP17*) and steroid 5alpha-reductase type II (*SRD5A2*) genes on prostate-cancer risk among the Japanese population. *Int J Cancer* 2001;92:683-6.
- Haiman CA, Stampfer MJ, Giovannucci E, Ma J, Decalo NE, Kantoff PW, et al. The relationship between a polymorphism in *CYP17* with plasma hormone levels and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:743-8.
- Kittles RA, Panguluri RK, Chen W, Massac A, Ahaghotu C, Jackson A, et al. *Cyp17* promoter variant associated with prostate cancer aggressiveness in African Americans. *Cancer Epidemiol Biomarkers Prev* 2001;10:943-7.

13. Stanford JL, Noonan EA, Iwasaki L, Kolb S, Chadwick RB, Feng Z, et al. A polymorphism in the CYP17 gene and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2002;11:243-7.
14. Chang B, Zheng SL, Isaacs SD, Wiley KE, Carpten JD, Hawkins GA, et al. Linkage and association of CYP17 gene in hereditary and sporadic prostate cancer. *Int J Cancer* 2001;95:354-9.
15. Latil AG, Azzouzi R, Cancel GS, Guillaume EC, Cochan-Priollet B, Berthoni PL, et al. Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways. *Cancer* 2001;92:1130-7.
16. Wadelius M, Andersson AO, Johansson JE, Wadelius C, Rane E. Prostate cancer associated with CYP17 genotype. *Pharmacogenetics* 1999;9:635-9.
17. Habuchi T, Liqing Z, Suzuki T, Sasaki R, Tsuchiya N, Tachiki H, et al. Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect. *Cancer Res* 2000;60:5710-3.
18. Schaid DJ, Jacobsen SJ. Biased tests of association: comparisons of allele frequencies when departing from Hardy-Weinberg proportions. *Am J Epidemiol* 1999;149:706-11.
19. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
20. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol* 2005;28:123-37.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
22. Wu YJ, Liang CH, Zhou FJ, Gao X, Chen LW, Liu Q. A case-control study of environmental and genetic factors and prostate cancer in Guangdong. *Zhonghua Yu Fang Yi Xue Za Zhi* 2009;43:581-5.
23. Sobti RC, Gupta L, Thakur H, Seth A, Singh SK, Kaur P. CYP17 gene polymorphism and its association in north Indian prostate cancer patients. *Anticancer Res* 2009;29:1659-63.
24. Sobti RC, Gupta L, Singh SK, Seth A, Kaur P, Thakur H. Role of hormonal genes and risk of prostate cancer: gene-gene interactions in a North Indian population. *Cancer Genet Cytogenet* 2008;185:78-85.
25. Dos Santos RM, de Jesus CM, Trindade Filho JC, Trindade JC, de Camargo JL, Rainho CA, et al. PSA and androgen-related gene (AR, CYP17, and CYP19) polymorphisms and the risk of adenocarcinoma at prostate biopsy. *DNA Cell Biol* 2008;27:497-503.
26. Sarma AV, Dunn RL, Lange LA, Ray A, Wang Y, Lange EM, et al. Genetic polymorphisms in CYP17, CYP3A4, CYP19A1, SRD5A2, IGF-1, and IGFBP-3 and prostate cancer risk in African-American men: the Flint Men's Health Study. *Prostate* 2008;68:296-305.
27. Setiawan VW, Schumacher FR, Haiman CA, Stram DO, Albanes D, Altshuler D, et al. CYP17 genetic variation and risk of breast and prostate cancer from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). *Cancer Epidemiol Biomarkers Prev* 2007;16:2237-46.
28. Gunes S, Bagci H, Sarikaya S, Bilen CY, Kara N. Prostate-specific antigen and 17-hydroxylase polymorphic genotypes in patients with prostate cancer and benign prostatic hyperplasia. *DNA Cell Biol* 2007;26:873-8.
29. Cussenot O, Azzouzi AR, Nicolaiew N, Fromont G, Mangin P, Cormier L, et al. Combination of polymorphisms from genes related to estrogen metabolism and risk of prostate cancers: the hidden face of estrogens. *J Clin Oncol* 2007;25:3596-602.
30. Onen IH, Ekmekci A, Eroglu M, Polat F, Biri H. The association of 5alpha-reductase II (SRD5A2) and 17 hydroxylase (CYP17) gene polymorphisms with prostate cancer patients in the Turkish population. *DNA Cell Biol* 2007;26:100-7.
31. Hamada A, Danesi R, Price DK, Sissung T, Chau C, Venzon D, et al. Association of a CYP17 polymorphism with overall survival in Caucasian patients with androgen-independent prostate cancer. *Urology* 2007;70:217-20.
32. Sobti RC, Onsory K, Al-Badran AI, Kaur P, Watanabe M, Krishan A, et al. CYP17, SRD5A2, CYP1B1, and CYP2D6 gene polymorphisms with prostate cancer risk in North Indian population. *DNA Cell Biol* 2006;25:287-94.
33. Guli MR, Wang JQ, Zhang JX, Deng D. Association between the polymorphism of CYP17 gene and risk of prostate cancer in chinese vigurs men. *Zhonghua Nan Ke Xue* 2006;12:120-2.
34. Yang J, Wu HF, Zhang W, Gu M, Hua LX, Sui YG, et al. Polymorphisms of metabolic enzyme genes, living habits and prostate cancer susceptibility. *Front Biosci* 2006;11:2052-60.
35. Okugi H, Nakazato H, Matsui H, Ohtake N, Nakata S, Suzuki K. Association of the polymorphisms of genes involved in androgen metabolism and signaling pathways with familial prostate cancer risk in a Japanese population. *Cancer Detect Prev* 2006;30:262-8.
36. Vesovic Z, Herkommer K, Vogel W, Paiss T, Maier C. Role of a CYP17 promoter polymorphism for familial prostate cancer risk in Germany. *Anticancer Res* 2005;25:1303-7.
37. Forrest MS, Edwards SM, Houlston R, Kote-Jarai Z, Key T, Allen N, et al. Association between hormonal genetic polymorphisms and early-onset prostate cancer. *Prostate Cancer Prostatic Dis* 2005;8:95-102.
38. Antognelli C, Mearini L, Talesa VN, Giannantoni A, Mearini E. Association of CYP17, GSTP1, and PON1 polymorphisms with the risk of prostate cancer. *Prostate* 2005;63:240-51.
39. Antognelli C. Association of CYP17, GSTP1, PON1-55 and PON1-192 polymorphisms with prostate cancer risk. *European Urology* 2004;3(Suppl):217.
40. Cicek MS, Conti DV, Curran A, Neville PJ, Paris PL, Casey G, et al. Association of prostate cancer risk and aggressiveness to androgen pathway genes: SRD5A2, CYP17, and the AR. *Prostate* 2004;59:69-76.
41. Madigan MP, Gao YT, Deng J, Pfeiffer RM, Chang BL, Zheng S, et al. CYP17 polymorphisms in relation to risks of prostate cancer and benign prostatic hyperplasia: a population-based study in China. *Int J Cancer* 2003;107:271-5.
42. Lin CC, Wu HC, Chen WC, Chen HY, Tsai FJ. CYP17 gene promoter allelic variant is not associated with prostate cancer. *Urol Oncol* 2003;21:262-5.
43. Dos Santos A, Ribeiro ML, Mesquita JC, Carvalho-Salles AB, Hackel C. No association of the 5' promoter region polymorphism of CYP17 gene with prostate cancer risk. *Prostate Cancer Prostatic Dis* 2002;5:28-31.
44. Zmuda JM, Cauley JA, Kuller LH, Ferrell RE. A common promoter variant in the cytochrome P450c17alpha (CYP17) gene is associated with bioavailability testosterone levels and bone size in men. *J Bone Miner Res* 2001;16:911-7.
45. Allen NE, Forrest MS, Key TJ. The association between polymorphisms in the CYP17 and 5alpha-reductase (SRD5A2) genes and serum androgen concentrations in men. *Cancer Epidemiol Biomarkers Prev* 2001;10:185-9.
46. Ostrander EA, Stanford JL. Genetics of prostate cancer: too many loci, too few genes. *Am J Hum Genet* 2000;67:1367-75.
47. Stanford JL, Ostrander EA. Familial prostate cancer. *Epidemiol Rev* 2001;23:19-23.

Received 20 March 2012, accepted 28 January 2013