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Research Paper

A single nucleotide polymorphism in *CYP1B1* leads to differential prostate cancer risk and telomere length

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Abstract

BACKGROUND: Cytochrome P450 1B1 (CYP1B1) is a key enzyme in its oestrogen metabolism pathway, giving rise to hydroxylation and conjugation. Functionally relevant genetic variants within *CYP1B1* may affect the telomere length and subsequently lead to prostate carcinogenesis.

METHODS: We evaluated 8 *CYP1B1* tag single nucleotide polymorphisms (SNPs) in 1015 men with prostate cancer (PCa) and 1052 cancer-free controls, and calculated odds ratios (ORs) and 95% confidence intervals (CIs) to estimate their association with risk of PCa. The influence of *CYP1B1* SNPs on the relative telomere lengths was then appraised in peripheral blood leukocytes using real-time PCR.

RESULTS: *CYP1B1* rs1056836 variant was associated with decreased risk of PCa [odds ratio (OR): 0.80; 95% confidence interval (CI): 0.68–0.99, $P = 0.041$]. Longer telomere length showed a significantly higher proportion of the *CYP1B1* rs1056836 CG/GG genotypes, compared with that of the CC genotype (OR: 1.60, 95% CI: 1.04-2.45).

CONCLUSION: Our findings suggest that genetic variants within *CYP1B1* may confer genetic susceptibility to PCa by altering telomere length.

Key words: CYP1B1; prostate cancer; single nucleotide polymorphism; susceptibility.

Introduction

Telomeres are specialised hexanucleotide repeats complexed to proteins. They are located at ends of linear chromosomes and protect their structural integrity[1]. Telomere length reduces with increasing chronological age and with accumulation of age-related comorbidities. Given that telomere shortening contributes to cellular senescence, telomere length represents a cellular marker of biological aging. A large number of studies suggest that telomere length is a marker of cancer risk and short leukocyte telomere length are believed to be causative events in malignant transformation[1].

The hypothesis that estrogen influences telomere length came from several preclinical, observational and interventional studies[2].This phenomenon was explained by the finding that estrogen stimulates telomerase via estrogen response element present in the TERT promoter region. Additional protective effect of estrogen on telomere length is thought to be mediated through its reduction in oxidative stress[3]. Despite the well-known antioxidant role of estrogen, estrogen metabolites, on the other hand, may paradoxically lead to increased oxidative stress through the formation of depurinating DNA adducts and release of surplus amount of superoxide radicals[4]. Several single nucleotide polymorphisms (SNPs) within the estrogen metabolic pathway have been described to have functional effects on the corresponding enzymes, thereby compromising conjugation and redox buffering capacity of cells[5].

Candidates include *CYP1B1*, which catalyze the conversion of estrogens to reactive catechol estrogens. Furthermore, we described that a *CYP1B1* SNP rs1056836 was significantly associated with biochemical recurrence after radical prostatectomy and relative *CYP1B1* mRNA expression[6].

Encouraged by such findings we have now tested *CYP1B1* SNPs for associations with risk of PCa in a case-control study. In addition, a real-time PCR based telomere assay was performed to investigate whether leukocyte telomere was in relation to *CYP1B1* SNPs.

Materials and Methods

Study Design and Population

The study subjects were mostly from previously published case-control study[7]. Briefly, 1115 eligible patients recruited into this study were newly diagnosed and histopathologically confirmed primary prostate adenocarcinoma from Fudan University Shanghai Cancer Center (FUSCC) between January 2005 and January 2012, of whom 1015 (92%) agreed to participate in this study. All cases had received no prior chemotherapy or radiotherapy upon recruitment. The tumor stage was determined according to criteria established by the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system [AJCC Staging Manual, sixth edition, 2002]. Histopathological grading of the specimens was performed according to the Gleason score system. The clinical information including Gleason score, serum PSA level at diagnosis and disease stage were abstracted from the archival medical records. In addition, 1143 age-(± 5yr) and geographical regions-matched cancer-free ethnic Han Chinese controls were recruited from the Taizhou longitudinal (TZL) study conducted during a similar time period. TZL study was a large prospective cohort initiated to explore the environmental and genetic risk factors for common non-communicable diseases. Individuals with a known test of serum PSA > 4 ng/mL present with or without abnormal digital rectal examination were excluded from the control group and those without response to the study participation were excluded (n = 91). All of the participants were interviewed with a questionnaire after a written informed consent was obtained. Blood samples were collected and processed as a routine practice by the FUSCC Tissue Bank (for cases) and the TZL study (for controls). This study was approved by the Institutional Review Board of FUSCC.

SNP Selection and Genotyping

Tagging SNPs were selected in the *CYP1B1* gene using the Tagger algorithm with $r^2 \geq 0.8$, and minor-allele frequencies > 0.05 based on the HapMap population data for Han Chinese in Beijing. There were 9 tagging SNPs (rs1056836, rs10916, rs162562, rs2551188, rs9341250, rs9341266, rs9341248, rs162549, rs1056827).

All these nine SNPs were genotyped by the TaqMan real-time PCR method as described previously[8, 9]. Briefly, DNA isolation was performed by using the Qiagen Blood DNA Mini KIT (Qiagen Inc., Valencia, CA) with the buffy-coat fraction of the blood samples donated by the participants. The results with > 99% call rates and 100% concordance for duplicated specimens were acceptable for further genotyping data analysis. SNP rs9341248 was removed because it did not conform to Hardy–Weinberg equilibrium (HWE) ($P < 0.05$). Thus, a total of 8 SNPs were included for subsequent analysis.

Measurement of Relative Telomere Length

Relative telomere length measurements were available in 426 patients as described previously[9]. Briefly, telomere length as represented by the telomere repeat copy number to single copy gene (i.e., *36B4*) copy number (T/S) ratio was measured using real-time quantitative PCR method on an Applied Biosystems 7900HT. The PCR reaction mixture consisted of SYBR Green Mastermix (Applied Biosystems), 100 nmol/L Tel-1, 900 nmol/L Tel-2, 400 nmol/L 36B4d, 400 nmol/L 36B4u, and 7ng of genomic DNA. The thermal cycling profile was 95°C for 10 min followed by 40 cycles of 95°C for 15 sec and at 56°C (for telomere) or 58°C (for *36B4*) for 1 min. Following amplification, a dissociation curve confirmed the specificity of the reaction. During each run, negative and positive controls, a calibrator DNA sample, and a standard curve were included. For each standard curve, 2-fold serial dilutions of a reference DNA sample were used to produce a standard curve in each reaction. Two main steps were involved in telomere length quantification: first, the T/S ratio was determined for each sample based on the standard curve. Second, the ratio for each sample was normalized to the calibrator DNA to standardize sample values across all reaction plates. The laboratory personnel were blinded to disease status. R^2 for each standard curve was ≥ 0.99.

Statistical Analysis

For all subjects, the χ^2 test was used to assess differences in the frequency distributions of the selected demographic variables and genotypes of 8 SNPs between the cases and controls. The HWE for genotype distribution in controls was tested by a goodness-of-fit χ^2 test. Odds ratios (ORs) and 95%

confidence intervals (CIs) were calculated by univariable and multivariable unconditional logistic regression models to evaluate associations between the genotypes and risk of PCa without and with adjustment for confounding factors, respectively. Further stratification analyses were conducted to calculate the associations of SNP genotypes with PCa risk by demographic and clinicopathologic variables, followed by the homogeneity Q-tests. Spearman rank correlation was used to investigate associations between telomere length and age. Telomere length was categorized into dichotomies, tertile and quartile based on the distribution. To account for chance associations from multiple comparisons, we used the false-positive report probability (FPRP) to assess the false-positive association findings. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC).

Results

Characteristics of the study subjects

The distributions of demographic characteristics of the subjects are shown in **Table 1**. Briefly, there were no statistical differences in the distributions of age and smoking status between two groups.

Table 1. Characteristics of PCa Cases and Controls

Variables	Cases (%) N = 1015	Controls (%) N = 1052	*P*
Age	69.1 ± 8.2	68.6 ± 8.9	0.828
≤ 64	291 (28.7)	308 (29.3)	
65-75	496 (48.9)	500 (47.5)	
> 75	228 (22.5)	244 (23.2)	
Smoking status			
Never	406 (40.0)	412 (39.2)	0.697
Ever	609 (60.0)	640 (60.8)	
PSA value (ng/ml)			
< 10	180 (19.4)		
10-20	195 (21.0)		
> 20	552 (59.6)		
Missing	88 (8.7)		
Gleason score			
≤ 7 (3+4)	317 (31.2)		
≥ 7 (4+3)	606 (59.7)		
Missing	92 (9.1)		
Stage of disease			
I	5 (0.5)		
II	434 (42.8)		
III	142 (14.0)		
IV	356 (35.1)		
Missing	78 (7.7)		

PSA: prostate-specifc antigen

Associations of *CYP1B1* SNPs with PCa Risk

The genotype frequencies of 8 *CYP1B1* SNPs and their associations with PCa risk are summarized in **Table 2**. The observed genotype frequencies of 8 SNPs in controls agreed with the Hardy-Weinberg equilibrium. Furthermore, the genotype distribution of *CYP1B1* rs1056836 was significantly different between the cases and controls. . In multivariate logistic regression analysis, *CYP1B1* rs1056836 was associated with PCa risk. Compared with CC genotype, rs1056836 variant CG/GG genotype was associated with a decreased risk of PCa (OR: 0.80, 95% CI = 0.66-0.97). However, no associations between the other 7 SNPs and PCa risk were observed.

Table 2. Association of *CYP1B1* SNPs with PCa Risk

SNP	Cases, No. (%) n = 1015	Controls, No. (%) n = 1052	OR (95% CI)	*P*[a]
rs9341266				
GG	774 (76.3)	816 (77.6)	1.00	
AG	218(21.5)	215 (20.4)	1.07 (0.87-1.32)	0.533
AA	23 (2.3)	21 (2.0)	1.15 (0.63-2.10)	0.649
AG/AA vs. GG			1.08 (0.88-1.32)	0.477
GG/AG vs. AA			1.13 (0.62-2.06)	0.683
rs162549				
TT	787 (77.5)	811 (77.1)	1.00	
AT	209 (20.6)	222 (21.1)	0.95 (0.77-1.18)	0.636
AA	19 (1.9)	19 (1.8)	1.01 (0.53-1.93)	0.971
AT/AA vs. TT			0.96 (0.78-1.17)	0.660
TT/AT vs. AA			1.02 (0.54-1.95)	0.944
rs10916				
TT	808 (79.6)	856 (81.4)	1.00	
GT	192 (18.9)	183 (17.4)	1.12 (0.89-1.40)	0.333
GG	15 (1.5)	13 (1.2)	0.75 (0.50-1.11)	0.152
GT/GG vs. TT			1.13 (0.91-1.40)	0.289
TT/GT vs. GG			1.21 (0.57-2.56)	0.617
rs162562				
AA	695 (68.5)	711 (67.6)	1.00	
AC	287 (28.3)	305 (29.0)	0.97 (0.80-1.17)	0.719
CC	33 (3.3)	36 (3.4)	0.96 (0.59-1.55)	0.854
AC/CC vs. AA			0.96 (0.80-1.16)	0.700
CC/AC vs.CC			0.97 (0.60-1.56)	0.887
rs2551188				
CC	541 (53.3)	558 (53.0)	1.00	
CT	423 (41.7)	421 (40.0)	1.05 (0.88-1.26)	0.564
TT	51 (5.0)	73 (6.9)	0.72 (0.49-1.05)	0.086
CT/TT vs. CC			1.00 (0.84-1.19)	0.964
CC/CT vs.TT			0.70 (0.49-1.02)	0.060
rs9341250				
CC	955 (94.1)	985 (93.6)	1.00	
AC	58 (5.7)	64 (6.1)	0.96 (0.66-1.38)	0.806
AA	2 (0.2)	3 (0.3)	0.66 (0.11-3.94)	0.644
AC/AA vs. CC			0.94 (0.66-1.35)	0.741
CC/AC vs. AA			0.66 (0.11-3.95)	0.646
rs1056827				
CC	668 (65.8)	679 (64.5)	1.00	
AC	303 (29.9)	327 (31.1)	0.94 (0.78-1.14)	0.543
AA	44 (4.3)	46 (4.4)	0.98 (0.64-1.50)	0.908
AC/AA vs. CC			0.95 (0.79-1.14)	0.555
CC/AC vs. AA			0.99 (0.65-1.52)	0.976
rs1056836				
CC	728 (71.7)	705 (67.0)	1.00	
CG	274 (27.0)	323 (30.7)	0.82 (0.68-0.99)	0.041
GG	13 (1.3)	24 (2.3)	0.54 (0.27-1.07)	0.079
CG/GG vs. CC			0.80 (0.66-0.97)	0.020
CC/CG vs. GG			0.57 (0.29-1.14)	0.111

HWE: Hardy-Weinberg equilibrium. [a]Adjusted for age and smoking status. The results were in bold if $P < 0.05$.

Table 3. Association between *CYP1B1* SNPs and RTL

SNP	Genotype	Short RTL, n (%)	Long RTL, n (%)	OR (95% CI)[a]	*P*
rs9341266	GG	58 (27.9)	64 (29.4)	1.00	
	AG/AA	150 (72.1)	154 (70.6)	1.08 (0.71-1.64)	0.737
rs162549	TT	44 (21.2)	48 (22.0)	1.00	
	AT/AA	164 (78.8)	170 (78.0)	1.05 (0.66-1.67)	0.828
rs10916	TT	35 (16.8)	54 (24.8)	1.00	
	GT/GG	173 (83.2)	164 (75.2)	1.63 (1.01-2.62)	0.045
rs162562	AA	60 (28.8)	66 (30.3)	1.00	
	AC/CC	148 (71.2)	152 (69.7)	1.07 (0.71-1.62)	0.747
rs2551188	CC	82 (39.4)	103 (47.2)	1.00	
	CT/TT	126 (60.6)	115 (52.8)	1.38 (0.94-2.02)	0.104
rs9341250	CC	13 (6.2)	17 (7.8)	1.00	
	AC/AA	195 (93.8)	201 (92.2)	1.27 (0.60-2.68)	0.533
rs1056827	CC	67 (32.2)	69 (31.7)	1.00	
	AC/AA	141 (67.8)	149 (68.3)	0.98 (0.65-1.47)	0.901
rs1056836	CC	67 (32.2)	50 (22.9)		
	CG/GG	141 (67.8)	168 (77.1)	1.60 (1.04-2.45)	0.033

RTL: Relative telomere length [a]Adjusted for age and smoking status.

In the stratified analysis, the decreased risk was also observed in men who were ever smokers, Gleason score ≥7 (4 + 3), and stage III/IV (**Supplementary Table 1**). Further homogeneity tests suggested, however, that there were no differences in the risk estimates between these strata.

Genetic variations and telomere length

To investigate whether the telomere length had prognostic significance, 426 patients were categorized into dichotomies, tertile and quartile based on their telomere length distribution (range, 0.06-2.06) (**Supplementary Table 2**). Telomere length was inversely associated with age (r = -0.40, $P < 0.001$). When participants were dichotomized according to the median telomere length value, significant differences in telomere length by genotype of *CYP1B1* rs1056836 and rs10916 were observed (**Table 3**). Longer telomere length showed a significantly higher proportion of the CG/GG genotypes, compared with that of the CC genotype (OR: 1.60, 95% CI: 1.04-2.45).

FPRP Values for Associations between PCa Risk and *CYP1B1* SNPs

The FPRP values at different prior probability levels for all significant findings are summarized in the Supplementary Table 3. When the assumption of prior probability was 0.01, no association was noteworthy in all subgroups for rs1056836 as well as rs10916. In contrast, some greater FPRP values for the other significant associations between *CYP1B1* variants and PCa risk suggested some possible false-positive results in the findings, which need further validation in larger studies.

Discussion

In the current study we found a *CYP1B1* inherited variation rs1056836 associated with PCa risk and further showed its biologic association with leukocyte telomere length. Findings on *CYP1B1* polymorphisms and susceptibility to PCa have proved inconsistent across different ethnic groups[8-14]. However, previous studies were conducted in small-sized populations, and require confirmation in larger studies.

The SNP rs1056836 is a non-synonymous polymorphism in exon 3, which encodes the heme binding domain, and results in a G-to-C and subsequent amino acid substitutions of Valine-to-Leucine[15].The SNP has documented functional consequences on transcription, protein structure, and enzyme action[16, 17]. A number of studies have reported a decreased risk of PCa for carriers of the rs1056836 G allele, but the results were inconsistent in different ethnic groups. Meta-analysis results showed that rs1056836 is significantly associated with PCa susceptibility among Asians[18, 19] and our findings support this association. These inconclusive results may have several causes. First, it may result from the distribution of allele frequencies among different ethnicities or between different case sources. We found that the frequency of rs1056836 G allele was significantly lower in Asian controls than in Caucasian or mixed population controls. Second, the sample sizes of the cases and controls in the Asian populations were both noticeably smaller than those in Caucasians or mixed population subjects[18, 19]. The current study has sufficient power confirm the positive associations in Asians. Moreover, the mechanism of PCa development is similar to other cancers and is dependent on the interactions of genetic factors and environmental agents[20]. Environments and lifestyles are very different among individuals of different races. Thus, the aetiology of PCa is unlikely to be explained solely by genetic polymorphisms because hereditary variation alone

cannot affect the risk of any disease. *CYP1B1* rs1056836 was associated with *CYP1B1* mRNA expression[6] and overlapped with PCa risk in the expected opposite direction suggesting potential biological consequences. Furthermore, a recent study showed that overexpression of CYP1B1 stimulated proliferative, migratory and invasive potential of non-tumorigenic PCa cells[21].

However, exact mechanisms of how CYP1B1 polymorphism contributes to PCa susceptibility requires further illustration. The present dataset offers an attractive possibility to address interactions between telomere length and genotypes. We hypothesized that genetic factors implicated in estrogen metabolism pathways contribute to increased oxidative stress and thereby influence telomere length. Oxidative stress causes telomere attrition by several potential pathways. Reactive oxygen species can directly damage the sensitive triple-G containing telomeres[22], or indirectly, act by inhibiting telomerase activity and increasing the load of pro-inflammatory cytokines that accelerate immune cell turnover and hence telomere loss[23]. Since estrogen metabolism is a well-known source of reactive oxygen species formation, aberrations in this pathway could compromise the redox buffering capacity of cells[4], which may in turn lead to increased oxidative burden and telomere attrition. Accordingly, in our study, we show for the first time that functionally relevant SNP in *CYP1B1* gene impacts telomere length in PCa patients. CYP1B1 participates in the first step of estrogen metabolism, i.e., the conversion of estrogens to 2- or 4-hydroxyestrogens, and specifically catalyzes the 4-hydroxylation of estrogens. 4-hydroxyestradiol is, in sharp contrast to 2-hydroxyestradiol, inactivated by COMT at a slower rate, and undergoes metabolic redox cycling to generate free radicals and reactive semiquinone and quionone intermediates[24]. The *CYP1B1* 1056836 variant allele codes for the enzyme with 2-fold higher mRNA compared to wild-type allele[6], leading to increased 4-hydroxyestradiol production. Consistent with this notion, telomere length was found significantly shorter in individuals carrying the CYP1B1 rs1056836 wild type allele.

A large number of intrinsic and extrinsic factors , such as heredity, epigenetics, aging, stress, immune components, and hormones are all states have been previously associated with shorter telomere length[25]. As such, limitations of the study are mainly related to the scarcity of the relevant exposure data and nature of retrospective study design. The current study was based on the leukocytes telomere length only and not on the prostate tissue telomere length. Because there is an intra-individual synchrony in telomere length across the somatic tissues of humans as evidenced by the strong correlations between the telomere lengths in all tissue types[26]. Moreover, the rates of telomere shortening are similar in the somatic tissues. However, future work aims to directly describe the relationships between prostate tissue, leukocytes telomere lengths and PCa cases. Strengths of the study include a significant number of patients, a candidate gene approach, the high plausibility of the association based on the biologic function of selected candidate genes and an impact on telomere length associated with positive markers.

In summary, significant association with PCa risk for CYP1B1 rs1056836 with telomere length may provide a biological basis for the results obtained in various studies investigating the impact of *CYP1B1* SNPs on PCa risk. With these implications, further investigation of SNP-cancer risk associations in specific subsets of patients with particular environmental or genetic backgrounds, as well as more detailed *in vitro* and *in vivo* biological functional studies will be helpful to elucidate how exactly the *CYP1B1* genetic variations influenced PCa development.

Abbreviations

PSA: prostate-specific antigen; SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval.

Supplementary Material

Supplementary tables.
http://www.jcancer.org/v09p0269s1.pdf

Competing Interests

The authors have declared that no competing interest exists.

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