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REGULAR ARTICLE

Associations between estrogen receptor genetic polymorphisms, smoking status, and prostate cancer risk: a case–control study in Japanese men

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Abstract
Objective Prostate cancer (PCa) is one of the major causes of death among men. Our study investigated the association of ESR1 and ESR2 genotypes with susceptibility to PCa in relation to smoking status in Japanese.
Method A case–control study was performed with 750 Japanese prostate cancer patients and 870 healthy controls. After age-matching in case–controls, 352 controls and 352 cases were enrolled in this study. By using logistic regression analysis, the different genotypes from ESR1 and ESR2 were analyzed according to case/control status.
Result ESR2 rs4986938 AG and AG + AA genotypes were associated with significantly decreased risk of PCa (AG: OR = 0.68, 95 % CI 0.47–0.97, $P < 0.05$ and AG + AA: OR = 0.67, 95 % CI 0.47–0.94, $P < 0.05$). However, there was no significant association between ESR1 rs2234693 and PCa risk. When patients were grouped according to smoking status, the ESR2 rs1256049 AA genotype (OR = 0.48, 95 % CI 0.25–0.95, $P < 0.05$) and ESR2 rs4986938 AG + AA genotype (OR = 0.64, 95 % CI 0.41–1.00, $P < 0.05$) showed significantly decreased PCa risk in the ever-smoker group.
Conclusion Our results suggest that the estrogen receptor ESR2 has a very important function to predict PCa and that different SNPs have different predictive values. Smoking may influence estrogenic activity and may influence PCa together with the estrogen receptor.

Keywords Prostate cancer · Estrogen receptor · Polymorphism · Genetic association studies · Smoke

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Introduction

Prostate cancer (PCa), also known as carcinoma of the prostate, is the development of cancer in the prostate, a gland in the male reproductive system [1]. The number of clinical cases has been increasing annually. In Japan, PCa deaths accounted for 3.5–4 % of the total cancer deaths and it is predicted that mortality will increase to 10 % of the total cancer deaths, with more than 80,000 males suffering from PCa in 2020 [2].

One of the hypothesized risk factors of PCa is older age. Almost all prostate cancers are detected in men aged >50 years; asymptomatic patients are usually identified through screening programs and symptomatic individuals present at outpatient clinics. About 70 % of deaths due to prostate cancer are observed in patients ≥75 years old in the USA [3] and Japan [4].

Smoking is also a risk factor for PCa. An association with smoking could have a hormonal basis; male smokers were found to have elevated levels of circulating androsterone and testosterone, which may increase PCa risk or contribute to cancer progression [5]. Twenty-four prospective cohort studies showed increased risk of incident PCa for smokers [6], though five studies found no positive association between smoking and PCa incidence in Japan [7–11].

Although the roles of estrogen in the pathogenesis of PCa remains poorly understood, estrogens have been

implicated in the stimulation of aberrant prostate growth, control of cell growth, and programmed cell death in PCa cells [12, 13]. Despite the controversy surrounding the exact role of estrogens on the prostate epithelium, estrogens have been used in the treatment of PCa because of their growth-inhibitory effects [14]. Sex steroids (estrogen and progesterone) could play a key pathophysiological role in the development PCa. The effects of estrogen are mediated by two estrogen receptors (ERs), the ER-1, and the ER-2 [14]. These belong to a superfamily of nuclear receptors that are ligand-dependent transactivators [15]. The ESR1 gene is located on chromosome 6q25.1 and the ESR2 gene is located on chromosome 14q23.1. The ESR1 gene intron 1 contains a single-nucleotide polymorphisms (SNPs) named the *Pvu*II (T/C) (rs2234693) [16]. The 5′ and 3′ regions of the ESR2 gene have two common SNPs: a silent 1082 G/A transition in exon 5 (*Rsa*I, rs1256049), and G/A exchange at nucleotide 1730 in the 3′ untranslated region in exon 8 (*Alu*I, rs4986938) [17]. Both receptors have been detected in human prostate normal mucosa [16, 17]. The ESR1 gene is expressed in the stroma and at low levels in basal epithelial cells of normal prostate [18, 19]; the ESR2 gene is highly expressed in the prostate epithelium, signifying a direct effect of estrogen on the prostate [20]. Imamov and Cheng's studies have shown antiproliferative and anti-invasion properties of estrogen acting through ERS2 [21, 22]. The correlation between PCa and estrogen receptors ESR1 and ESR2 according to smoking status is unclear.

We studied a common SNP (rs2234693) in the ESR1 gene and two in the ESR2 gene (rs1256049 and rs4986938). To the best of our knowledge, no study has reported the association of ESR1 and ESR2 genotypes with susceptibility to PCa in relation to age and smoking status in Japanese men.

Materials and methods

Study subjects

DNA samples were obtained from participants at Jikei University Hospital (Tokyo, Japan) and Mitsui Memorial Hospital (Tokyo, Japan), the ethical approval and informed consent of this study were obtained from all participants. Case subjects in this study were 750 men of Japanese ancestry who were diagnosed with histologically confirmed PCa at Jikei University Hospital from April 1, 2005 to December 31, 2006. Men of Japanese ancestry who were undergoing health screening at Mitsui Memorial Hospital during the same period were asked to participate as control subjects. Although a total of 870 subjects were included, due to the fact that age can have a great impact on prostate cancer, we selected an age-adjusted control group using the case group's average age. Thus, we enrolled 352 controls and 352 cases in this study. All subjects were classified into two groups according to smoking status by self-report: the "never" group composed of non-smokers and the "ever" group composed of both current smokers and ex-smokers.

The blood samples were collected during the protocol period before each procedure was performed. We stored buffy coats immediately after blood collection at −80 °C until we isolated DNA for genotyping of all case patients and control subjects. The Ethic Review boards at both Miyazaki University and Kumamoto University approved this study on April 1, 2005 (approval number 180) and April 26, 2012 (approval number 209). All participants were given an explanation of the nature of this study.

Genotyping

Common SNPs in ESR1 (rs2234693: T>C) and ESR2 (rs4986938: G>A, rs1256049: G>A) genes, previously associated with alteration in receptor expression were selected for the purpose of the current study. Pre-validated allelic discrimination TaqMan real-time PCR assays (Applied Biosystems, USA) were used for detection of the respective SNPs in ESR1 and ESR2 genes. The reaction solution (9 μL) was placed into each well of a 48-well reaction plate (the remainder of the reaction solution was used to prevent experimental errors), and 1 μL of DNA sample or water control was added to each tube. DNA samples with homozygous ESR1 mutant T/T and ESR2 mutant G/G were used as control samples in each array plate.

Statistical analyses

The Student's *t* test and Chi-squared test were used to compare genotype and smoking status between the patients and control subjects. The Pearson's Chi-squared test was also used for evaluating the probability of Hardy–Weinberg equilibrium. Relative associations between the two groups were assessed by calculating odds ratios (ORs) from contingency tables. In logistic regression analysis, the OR with corresponding 95 % confidence intervals (CI) were calculated. All statistical tests were based on two-tailed probability and *P* values of <0.05 were considered to be significant. Statistical analyses were carried out using SPSS Ver. 20 (SPSS Inc., Chicago, IL).

Results

The general characteristics of the cases and the controls are shown in Table 1. This study involved 352 patients with pathologically confirmed PCa and 352 controls, aged from

Table 1 Demographic characteristics of prostatic cancer cases and controls

Characteristics	Controls $N = 352$ (%)	Case $N = 352$ (%)	P value
Age at reference (years)			
≤65 (%)	176 (50.0 %)	180 (51.1 %)	
≥66 (%)	176 (50.0 %)	172 (48.9 %)	0.76[a]
Smoking status			
Never	113 (32.1 %)	127 (36.1 %)	
Ever	239 (67.9 %)	225 (63.9 %)	0.27[a]
Current smoker	69 (19.6 %)	56 (15.9 %)	0.14[a]
Ex-smoker	170 (48.3 %)	169 (48.0 %)	0.47[a]
Mean age (years), mean ± SD	65.0 (± 6.5)	65.0 (± 6.5)	0.98[b]

[a] P values were calculated form chi-square test

[b] P values were calculated form t test

Table 2 Associations between the ESR1 and ESR2 genotype and prostatic cancer

Genotype	Control $N = 352$ (%)	Case $N = 352$ (%)	OR (95 % CI)
rs2234693 ESR1			
TT (Ref)	80 (22.7 %)	67 (19.0 %)	1.00
CT	175 (49.7 %)	191 (54.3 %)	1.08 (0.77–1.52)
CC	97 (27.6 %)	94 (26.7 %)	0.76 (0.49–1.18)
CT + CC	272 (77.3 %)	285 (81.0 %)	0.99 (0.71–1.36)
rs1256049 ESR2			
GG (Ref)	167 (47.4 %)	185 (52.6 %)	1.00
AG	146 (41.5 %)	142 (40.3 %)	0.88 (.64–1.20)
AA	39 (11.1 %)	25 (7.1 %)	0.58 (0.34–1.00)*
AG + AA	185 (52.6 %)	167 (47.4 %)	0.82 (0.61–1.10)
rs4986938 ESR2			
GG (Ref)	254 (72.1 %)	280 (79.5 %)	1.00
AG	90 (25.6 %)	67 (19.1 %)	0.68 (0.47–0.97)*
AA	8 (2.3 %)	5 (1.4 %)	0.57 (0.18–1.76)
AG + AA	98(27.9 %)	72 (20.5 %)	0.67 (0.47–0.94)*

ORs were estimated using Chi-square statistic and multivariate logistic regression, respectively

Ref reference group, 95 % *CI* 95 % confidence interval, *OR* odds ratio

* $P < 0.05$

50 to 79. The average ages of the case and control groups were both 65.0 years. No significant differences were observed between the cases and controls in terms of smoking status and pack-year status.

The genotype frequency distributions are shown in Table 2; SNP genotyping completion rates were 100 %. Hardy–Weinberg equilibrium was confirmed for the ESR1 rs2234693 genotype ($P = 0.95$), ESR2 rs1256049 genotype ($P = 0.41$), and ESR2 rs4986938 genotype ($P = 0.99$) in the controls. For the ESR1 rs2234693 SNP, there were no statistically significant differences in risk for PCa between the case and control groups according to genotype. On the other hand, for the ESR2 rs1256049 SNP, the AA carriers showed decrease risk of PCa (OR = 0.58, 95 % CI 0.34–1.00, $P < 0.05$). For the ESR2 rs4986938 SNP, AG and AG + GG genotypes also showed decrease risk of PCa (OR = 0.68, 95 % CI 0.47–0.97, $P < 0.05$ and OR = 0.67, 95 % CI 0.47–0.94, $P < 0.05$, respectively).

In order to check the PCa risk associated with genotypes in combination with smoking status, we classified all individuals in this study group as either never smokers or ever-smokers (Table 3). In the never-smoker group, there was no significant association between different genotypes and risk of PCa. In the ever-smoker group, the ESR2 rs1256049 AA genotype (OR = 0.48, 95 % CI 0.25–0.95, $P < 0.05$) and the *ESR2* rs4986938 AG + AA genotype

Table 3 Associations between the ESR1 and ESR2 genotype and prostatic cancer when stratified by smoking status

Smoking status	Genotype	Control $N = 113$ (%)	Case $N = 127$ (%)	OR (95 % CI)
Never ($N = 240$)	rs2234693 ESR1			
	TT (Ref)	31 (27.4 %)	37 (29.1 %)	1.00
	CT	57 (50.4 %)	63 (49.6 %)	0.93 (0.51–1.68)
	CC	25 (22.1 %)	27 (21.3 %)	0.91 (0.44–1.87)
	CT + CC	82 (72.6 %)	90 (70.9 %)	0.92 (0.52–1.62)
	rs1256049 ESR2			
	GG (Ref)	58 (51.3 %)	68 (53.5 %)	1.00
	AG	45 (39.8 %)	49 (38.6 %)	0.93 (0.54–1.59)
	AA	10 (8.8 %)	10 (7.9 %)	0.85 (0.33–2.19)
	AG + AA	55 (48.7 %)	59 (46.5 %)	0.92 (0.55–1.52)
	rs4986938 ESR2			
	GG (Ref)	78 (69.0 %)	97 (76.4 %)	1.00
	AG	34 (30.1 %)	28 (22.0 %)	0.66 (0.37–1.19)
	AA	1 (0.9 %)	2 (1.6 %)	1.61 (0.14–18.07)
	AG + AA	35 (31.0 %)	30 (23.6 %)	0.69 (0.39–1.22)
Smoking status	Genotype	Control $N = 239$ (%)	Case $N = 225$ (%)	OR (95 % CI)
Ever	rs2234693 ESR1			
($N = 464$)	TT (Ref)	49 (20.5 %)	30 (13.3 %)	1.00
	CT	118 (49.4 %)	128 (56.9 %)	1.17 (0.77–1.77)
	CC	72 (30.1 %)	67 (29.8 %)	0.66 (0.38–1.16)
	CT + CC	190 (79.5 %)	195 (86.7 %)	1.02 (0.68–1.51)
	rs1256049 ESR2			
	GG (Ref)	109 (45.6 %)	117 (52.0 %)	1.00
	AG	101 (42.3 %)	93 (41.3 %)	0.86 (0.58–1.26)
	AA	29 (12.1 %)	15 (6.7 %)	0.48 (0.25–0.95)*
	AG + AA	130 (54.4 %)	108 (48.0 %)	0.77 (0.54–1.12)
	rs4986938 ESR2			
	GG (Ref)	176 (73.6)	183 (81.3 %)	1.00
	AG	56 (23.4 %)	39 (17.3 %)	0.67 (0.42–1.06)
	AA	7 (2.9 %)	3 (1.3 %)	0.41 (0.11–1.62)
	AG + AA	63 (26.3 %)	42 (18.6 %)	0.64 (0.41–1.00)*

ORs were estimated using Chi-square statistic and multivariate logistic regression, respectively

Ref reference group, 95 % *CI* 95 % confidence interval, *OR* odds ratio

* $P < 0.05$

(OR = 0.46, 95 % CI, 0.41–1.00, $P < 0.05$) were associated with significantly lower risk of PCa.

Discussion

In the last decade, a large number of studies have attempted to unravel the genetic basis of PCa. Evidence points to genetic factors, such as variations in genes involved in hormone pathways, as the key players in PCa development [14, 23]. In this study, we investigated the associations between genetic polymorphisms of the ESR1 and ESR2 estrogen receptors, smoking status, and PCa risk in a case–control study in Japanese men.

Comparison of ESR1 rs2234693 genotype frequencies between the PCa patient and control groups did not show statistically significant differences. In previous studies, however, further subgroup analyses based on country suggested that ESR1 rs2234693 (C/T) may be associated with increased risk of PCa among Indian and Iranian populations (ORs ranging from 1.93 to 4.46) [14, 24]. Another study failed to confirm these findings among American or Japanese populations [25] and our findings are consistent with this study.

Regarding the ESR2 rs1256049, those with the AA genotype had significantly reduced risk for PCa. Chen et al. reported that the ESR2 rs1256049 was not associated with PCa risk in either all subjects (Prostate Cancer Cohort

Consortium) or only Caucasians [26], but to our knowledge, there were no data regarding the ESR2 rs1256049 SNP and PCa in Japanese men. Another finding of this study was a significant association between ESR2 rs4986938 and PCa; men with ESR2 rs4986938 AG and AG + AA genotypes were less likely to have PCa. Although no significant association was observed for the AA genotype, there was a trend towards decreased chance of having PCa, which is consistent with some previous studies [24, 27–30].

Bergner et al. tested the ESR1 and ESR2 genes in two human PCa cell lines. In their study, polymorphisms were found in both ESR1 and ESR2 genes and these may contribute to the genetic factors that influence the risk for developing PCa [31]. In another study, the author reported that high intake of phytoestrogens substantially reduced PCa risk among men with specific polymorphic variation in the promoter region of the ESR2 gene [32]. In a large population-based case–control study (1415 cases and 801 controls), 28 SNPs spanning the entire ESR2 gene were evaluated [33]. There was a statistically significant difference in allele frequency between cases and controls only for one of the typed htSNPs (rs2987983). Different ESR1 and ESR2 genotypes may exert their effects on PCa via different serum levels of reproductive hormones. Both androgens and estrogens play significant roles in the prostate. Specifically, it is a balance between their actions that is critically important in maintaining normal prostate growth [14]. All of these experimental studies and our results suggest that the ESR1 and ESR2 genetic polymorphisms examined in this study have functional significance, and thus modulate PCa risk.

In terms of smoking status, there was no significant difference observed between the cases and the controls in terms of smoking status ($P = 0.37$) and we also found no significant association between different genotypes in the never-smoker group. In the ever-smoker group, however, the ESR2 rs1256049 AA genotype and the ESR2 rs4986938 AG + AA genotype carriers showed significantly decreased PCa risk. Our findings agree with a study by Takamura et al. [34], which demonstrated that smoking may influence estrogenic activity and that these two factors may influence PCa together. Dai et al. found an association with smoking could also have a hormonal basis. Male smokers were found to have elevated levels of circulating androsterone and testosterone, which may increase PCa risk or contribute to cancer progression [5]; however, they did not report on the possible interaction between smoking and ESR genotype.

In interpreting the results of the current study, some limitations need to be addressed. First, the sample size was relatively small and may not provide sufficient power to estimate the association between gene polymorphisms and prostate cancer risk. Second, we did not account for the potential effects of diet in our study; for instance, some studies have reported that high intake of isoflavone, which is mainly found in soybeans and soy products, may reduce the risk of PCa. Third, all subjects were classified into either the "never" group, composed of non-smokers, or the "ever" group, composed of both current smokers and ex-smokers; thus, we could not analyze the impact of smoking burden in terms of either the number of cigarettes smoked or pack-years. In spite of these limitations, our study still had some merits and values. To the best of our knowledge, this is the first study to analyze the relationship between estrogen receptor gene polymorphisms, smoking status, and PCa risk in Japanese men.

In summary, our results demonstrated that the ESR2 rs1256049 and rs4986938 genotypes, but not ESR1 rs2234693 genotype, had significant associations with risk for PCa in Japanese men. Our findings suggest that estrogen receptor genotype may be an independent risk factor for PCa and may also play a modulatory role in the metabolism of tobacco smoke components. The genotypes of estrogen receptor SNPs may differentially predict PCa risk.

Conflict of interests The authors have declared that no competing interests exist.

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