Researc paper

PER3 polymorphisms and their association with prostate cancer risk in Japanese men

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Keywords

Prostate cancer • *PER3* • Polymorphism • Rs2640908 • VNTR

Summary

Introduction. *Prostate cancer (PCa) is one of the most common cancers affecting men globally. Although PER3 has been suggested as a risk factor for cancer development, there are few reports elucidating the relationship between PER3 and PCa. We investigated the association between PER3 polymorphisms (rs2640908 and VNTR) and susceptibility to PCa in the Japanese population.*
Methods. *Eighty three patients with PCa and 122 controls participated in this study. We analyzed rs2640908 and VNTR polymorphisms by using PCR-Restriction Fragment Length Polymorphism (PCR-RFLP).*
Results. *Compared to the C/C genotype with the rs2640908 polymorphism, the T/T (OR: 0.35, 95% CI: 0.15-0.81, P = 0.02) and C/T + T/T (OR: 0.46, 95% CI: 0.24-0.88, P = 0.02) genotypes had a significantly lower risk of PCa. TT (OR: 0.29, 95% CI: 0.10-0.77, P = 0.02) and CT + TT (OR: 0.47, 95% CI: 0.23-0.97, P = 0.04) also had significant protection against PCa in the smoker group. Significantly, we observed an association between smoking and rs2640908 polymorphism in this study. However, no association between the VNTR polymorphisms and PCa was detected.*
Conclusions. *Our results suggest that PER3 rs2640908 polymorphisms influence an individual's susceptibility to PCa.*

Introduction

Prostate cancer (PCa) is the second most common cancer in men and also ranks fifth among the leading causes of death globally. In 2018, 1.3 million new cases of PCa were diagnosed and 359,000 associated deaths were reported globally [1]. In 2015, PCa also became the most common male cancer in the Japanese population [2]. In 2018, 70,654 new cases of PCa were reported and the age-standardized rate was 35.4 per 100,000 [3]. While the causes of PCa remain to be elucidated, many potential risk factors for PCa have been identified. Age, race, a high fat diet, alcohol abuse, exposure to cadmium or agent orange, and family history are major risk factors associated with PCa [4]. Recently, disruption of circadian rhythm has also been suggested to be a risk factor for carcinogenesis, including development of PCa [5]. The incidence of breast and endometrial cancers was higher in shift workers who experienced disruption of the circadian rhythm [6].

Physiological states such as body temperature, and biochemical processes including hormone secretion, metabolism, and sleep/wake cycle are controlled by circadian rhythms in an approximate 24-hour cycle [7, 8]. The suprachiasmatic nucleus (SCN) in the anterior hypothalamus of the brain is thought as a central part that generate circadian rhythms [9-11]. The circadian rhythms are controlled by the genes, including *circadian locomotor output cycles kaput* (*CLOCK*), *period* (*PER*), and *cryptochrome* (*CRY*) [9-11].

Some previous research indicated the association between various circadian genes and PCa. Wendeu-Foyet et al. reported that pathway of 31 circadian genes including 872 SNPs significantly associated with PCa and this association was mainly supported by the circadian core-genes pathway which were *NPAS2* and *PER1* [12]. Yu et al. also indicated that *NPAS2* as a part of circadian genes significantly associated with disease progression of PCa [13]. Other article showed that some circadian genes (*PER1*, *PER2*, *CRY1*, *CRY2*, *CLOCK*, *NPAS2*) were significantly associated with susceptibility to prostate cancer [14]. On the other hand, circadian genes could play a part of role of carcinogenesis or the tumor suppressor through cell proliferation and apoptosis [15]. These findings indicated there was a potential link between genetic variants in circadian genes and PCa.

PER is one of the main mediators of the circadian rhythm, and has a function in the negative feedback loop where it is translocated from the cytoplasm to the nucleus to regulate their expression by an inhibit transcription [16, 17]. *PER* has three paralogs, *PER1*, *PER2*, and *PER3*. Disruption of the circadian genes, including that of *PER3*, affects carcinogenesis related cellular processes, including proliferation, cell cycle regulation, and apoptosis [18]. *PER3* expression was decreased in chronic myeloid leukemia [19], and expression of *PER3* in colorectal cancer tissue was lower than in healthy mucosa [18, 20]. Polymorphisms of *PER3* have also been associated with various cancers [14, 21, 22].

The rs2640908 polymorphism is a *PER3* single nucleotide polymorphism (SNP) associated with cancer

development [23-25]. The rs2640908 polymorphism has an association with patient overall survival in hepatocellular carcinoma and colorectal carcinoma. Another polymorphism of *PER3* is a variable number tandem repeat (VNTR) consisting of 4-5 repeat 54-bp sequences in exon 18 encoding 18 amino acids [26]. Individuals with a variant of 5 VNTR repeats experience delayed sleep phase syndrome and extreme diurnal preference [27, 28]. A relationship between VNTR polymorphism and elevated levels of serum cytokine IL-6 has also been reported [29]. This suggested that *PER3* polymorphisms could have an influence on the carcinogenesis through cell cycle regulation. However, the relationship between both rs2640908 and VNTR polymorphisms and PCa in the Japanese population is yet to be studied in detail. Thus, the aim of this study was to evaluate the relationship between rs2640908 and VNTR polymorphisms and PCa carcinogenesis within the Japanese population.

Methods

Study subjects

A total of 83 patients with PCa and 122 healthy controls were recruited from the Japanese population. Patients were diagnosed at the University of Occupational and Environmental Health (UOEH) Hospital and University of Miyazaki Hospital in Japan, and all diagnoses were confirmed by histology. The control subjects were recruited from UOEH Hospital, University of Miyazaki Hospital, and a hospital located near UOEH Hospital.

All subjects were surveyed with self–questionnaires that collected information on history of illness, occupation, and smoking status. Participants who had been exposed to carcinogenic agents, heavy metals, and radiation in their occupational history were excluded. The included subjects were classified into two groups according to smoking status. The non-smokers were grouped into the "Never" group, and both current and previous smokers were classified as "Smoker". All participants were briefed about the study, and written informed consent was obtained from each participant. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Miyazaki.

Genotyping

Peripheral blood samples were collected from each subject, and genomic DNA was extracted by proteinase K digestion and phenol/chloroform extraction method [30].

Genotyping of the rs2640908 polymorphism was carried out using PCR-Restriction Fragment Length Polymorphism (PCR-RFLP). The sequence of PCR primers used for amplification were 5'-CTGTTTAACACACGAAGTTGAAGA-3' (forward) and 5'-GTTCTGGATGGGGATTCGCT-3' (reverse). PCR was performed using a KAPATaq EXtra PCR Kit (NIPPON Genetics Co., Ltd., Tokyo, Japan) following manufacturer's instructions. The thermocycler conditions were: initial denaturation at 94˚C for 2 min, followed by 35 cycles of denaturation at 94˚C for 30 s, annealing at 55˚C for 30 s, and extension at 72˚C for 45 s, with final extension at 72˚C for 7 min. PCR products were digested with *AgeI* restriction enzyme (New England Biolabs Inc., Ipswich, MA, USA) and incubated at 37˚C overnight, before being resolved by 2% agarose gel electrophoresis. For genotyping, two digestion products of size 798 and 265 bp were expected for C/C genotype (homozygous wild-type), three products of size 1,063, 798, and 265 bp were expected for C/T genotype, and only a single product sized 1,063 bp was expected for T/T genotype. The electrophoretic image of each genotypes is shown in Figure 1.

PCR genotyping for VNTR polymorphisms was similarly performed with primer sequences:

5'–CAAAATTTTATGACACTACCAGAATGGCTGAC–3' (forward)

and 5'–AACCTTGTACTTCCACATCAGTGCCTGG–3' (reverse).

The thermocycler conditions were: initial denaturation at 94˚C for 2 min, followed by 35 cycles of denaturation at 94 ˚C for 30 s, annealing at 60˚C for 30 s, and extension at 72˚C for 45 s with at final extension at 72˚C for 7 min. A 4/4 genotype (homozygous for 4 repeats) had an expected product size of 581 bp, 4/5 (heterozygotes) had expected product sizes of 635 and 581bp, 5/5 (homozygous for 5 repeats) had an expected product size of 635 bp (Fig. 1). PCR products were resolved and visualized using 2% agarose gel electrophoresis.

Statistical analysis

A t-test was used to compare the continuous variables, and a χ^2 test was used to compare categorical data and to determine probability of allele frequencies being in Hardy–Weinberg equilibrium [31]. Odds ratio (OR) and 95% confidence interval (95% CI) were estimated using a multiple logistic regression analysis with adjustment for age and smoking status. Stratified analysis by smoking status was also performed. The level of statistical significance was set at P value < 0.05. All statistical analyses were performed using R ver. 3.6.1.

Results

Clinical characteristics of patient and control subjects, including age and smoking status, are summarized in Table I. The mean age was 69.2 years (SD: 10.4) for control group and 71.6 years (SD: 8.6) for the patient group. Incidentally, a significantly higher percentage of the control group (83.6%) was classified as "Smoker" compared to the patient group (67.5%, P = 0.01).

Distribution of rs2640908 and VNTR polymorphisms for patient and control groups are shown in Table II. Allele frequencies for rs2640908 and VNTR polymorphisms in the control group were in Hardy-Weinberg equilibrium (P = 0.86 and 0.76, respectively). For rs2640908

Tab. I. Characteristics of the controls and cases.

Variable	Controls (n = 122)	Cases (n = 83)	P-value
Age			
Mean (SD)	69.2 (10.4)	71.6 (8.6)	0.08
Smoking status (%)			
Never	20 (16.4)	27 (32.5)	0.01
Smoker	102 (83.6)	56 (67.5)	

t-test and χ^2 test were used for age and smoking status, respectively.

Tab. II. Associations between the PER3 genotype (rs2640908 and VNTR) and PCa.

Genotype	Controls (n = 122)	Cases (n = 83)	Crude OR (95% CI)	Adjusted OR (95% CI)
rs2640908				
C/C (%)	26 (21.3)	29 (34.9)	Ref	Ref
C/T (%)	63 (51.6)	40 (48.2)	0.57 (0.29-1.10)	0.52 (0.26-1.03)
T/T (%)	33 (27.0)	14 (16.9)	0.38 (0.16-0.85)*	0.35 (0.15-0.81)*
C/T + T/T (%)	96 (78.7)	54 (65.1)	0.50 (0.27-0.94)*	0.46 (0.24-0.88)*
VNTR				
4/4 (%)	82 (67.2)	56 (67.5)	Ref	Ref
4/5 (%)	37 (30.3)	25 (30.1)	0.99 (0.53-1.82)	0.94 (0.50-1.76)
5/5 (%)	3 (2.5)	2 (2.4)	0.98 (0.13-6.07)	1.28 (0.16-8.69)
4/5 + 5/5 (%)	40 (32.8)	27 (32.5)	0.99 (0.54-1.79)	0.96 (0.52-1.77)

χ^2 test and multiple logistic regression were used for crude OR and adjusted OR for age and smoking status, respectively. 95% CI: 95% confidence interval; OR: odds ratio; Ref: reference; *: P < 0.05.

Tab. III. Associations between the PER3 genotype (rs2640908 and VNTR) and PCa when stratified by smoking status.

Genotype	Controls (n = 122)	Cases (n = 83)	Crude OR (95% CI)	Adjusted OR (95% CI)
Never				
rs2640908				
C/C (%)	3 (15.0)	8 (29.6)	Ref	Ref
C/T (%)	11 (55.0)	12 (44.4)	0.41 (0.07-1.83)	0.39 (0.07-1.76)
T/T (%)	6 (30.0)	7 (25.9)	0.44 (0.07-2.34)	0.53 (0.08-3.02)
C/T + T/T (%)	17 (85.0)	19 (70.4)	0.42 (0.08-1.72)	0.43 (0.08-1.79)
VNTR				
4/4 (%)	12 (60.0)	20 (74.1)	Ref	Ref
4/5 (%)	8 (40.0)	6 (22.2)	0.45 (0.12-1.60)	0.40 (0.10-1.46)
5/5 (%)	0 (0)	1 (3.7)	-	-
4/5 + 5/5 (%)	8 (40.0)	7 (25.9)	0.53 (0.15-1.81)	0.48 (0.13-1.70)
Smoker				
rs2640908				
C/C (%)	23 (22.5)	21 (37.5)	Ref	Ref
C/T (%)	52 (51.0)	28 (50.0)	0.59 (0.28-1.25)	0.57 (0.27-1.21)
T/T (%)	27 (26.5)	7 (12.5)	0.28 (0.10-0.76)*	0.29 (0.10-0.77)*
C/T + T/T (%)	79 (77.5)	35 (62.5)	0.49 (0.24-0.99)*	0.47 (0.23-0.97)*
VNTR				
4/4 (%)	70 (68.6)	36 (64.3)	Ref	Ref
4/5 (%)	29 (28.4)	19 (33.9)	1.27 (0.62-2.57)	1.22 (0.60-2.48)
5/5 (%)	3 (2.9)	1 (1.8)	0.65 (0.03-5.27)	0.81 (0.04-6.97)
4/5 + 5/5 (%)	32 (31.4)	20 (35.7)	1.22 (0.61-2.41)	1.19 (0.59-2.37)

χ^2 test and multiple logistic regression were used for crude OR and adjusted OR for age, respectively. 95% CI: 95% confidence interval; OR: odds ratio; Ref: reference; *: P < 0.05.

genetic variants, risk for PCa was significantly lower for T/T genotype (adjusted OR: 0.35, 95% CI: 0.15-0.81, P = 0.02), and C/T + T/T genotype (adjusted OR: 0.46, 95% CI: 0.24-0.88, P = 0.02) relative to the C/C genotype, with no significant difference observed for C/T genotype (adjusted OR: 0.52, 95% CI: 0.26-1.03, P = 0.06). In contrast, no significant association was observed between any of the VNTR variants and PCa.

Table III shows the analysis stratified by smoking status. For rs2640908 polymorphisms in the "Smoker" group, there was a significantly lower risk of PCa in T/T genotype (adjusted OR: 0.29, 95% CI: 0.10-0.77, P = 0.02) and C/T + T/T (adjusted OR: 0.47, 95%

CI: 0.23-0.97, P = 0.04) compared to the C/C genotype. Again, no relationship was observed between VNTR genotypes and PCa.

Discussion

In this study, we studied the relationship between the *PER3* polymorphisms, rs2640908 and VNTR, and risk of PCa in the Japanese population. We demonstrated that for the rs2640908 polymorphism, the T/T and C/T + T/T genotypes are associated with a lower risk of PCa. However, we were unable to find a significant association between VNTR variants and PCa.

Disruption of the circadian rhythm is linked to an increased risk of several diseases, including cancer [18-20, 32]. Disruption can arise from different factors, such as shift work and exposure to light at night (LAN exposure) [33]. Shift work influences body temperature, energy allocation, and disrupts circadian rhythm, resulting in damage to health. The circadian rhythm is a physiological fluctuation that takes place in approximately 24-hour cycles, and is involved in the health and survival of most living organisms. Some reports have described auto–regulatory transcriptional and translational feedback loop mechanisms for circadian genes, with both positive and negative regulators [34]. Circadian genes have also been linked to carcinogenesis through DNA repair, apoptosis, and cell proliferation [15, 35, 36].

PER is a circadian gene, with 3 subtypes (*PER1*, *PER2*, and *PER3*) [14]. A previous study has suggested that heterozygosity of a *PER3* polymorphism could be a risk factor for breast cancer among premenopausal women [26]. *PER3* also plays an important role in regulating cell proliferation and apoptosis [37]. Deletion and reduced expression of *PER3* results in upregulation of the estrogen receptors, and is associated with an increased recurrence of breast cancer [38], suggesting that the *PER3* may also play a role in homeostasis for reproductive hormones.

There are two polymorphisms described for *PER3*, rs2640908 and VNTR. At least one variant allele of the rs2640908 polymorphism is associated with a significantly lower risk of death among patients with hepatocellular carcinoma when compared to homozygous wild-type patients [24]. The T/T genotype of the rs2640908 polymorphism also has a protective effect in colorectal cancer compared to the C/C genotype [25]. We found a similar effect for PCa. However, the biological mechanisms that underlie this protection against carcinogenesis remain to be elucidated. The rs2640908 polymorphism is found in the exonic splicing enhancer (ESE) region, which can affect or alter translation initiation sites and translation efficiencies through mRNA splicing, and destabilize the binding of the serine/arginine-rich (SR) protein [39]. The rs2640908 polymorphism may therefore reduce exon recognition and define an alternative splice site [40]. This would affect cell proliferation, cell cycle regulation, and apoptosis, potentially leading to cancer [25].

In our study, no correlation was observed between VNTR polymorphisms and PCa. Varying relationships between VNTR polymorphism and carcinogenesis have been reported previously. The VNTR variant with 5 repeats is associated with increased risk of prostate cancer in men with high levels of insulin resistance [41] and with colorectal adenoma [21]. In contrast, a meta-analysis could not identify any significant relationships between VNTR polymorphisms and breast, prostate, and colon cancers [42]. The 5 repeats sequence of the VNTR polymorphism play an essential role as it is a phosphorylation site, and the 5/5 genotype plays a crucial role in the circadian process compared to the 4/4 genotype [43]. Heritable chronotypes may be polygenic, and variants of several genes may be required for full phenotypic expression [43]. That may explain why no association was observed between VNTR polymorphism and PCa in this study.

There relation between circadian genes and PCa was inconsistent. Markt et al. did not find the consistent association between 96 SNPs across 12 circadian-related genes and fatal prostate cancer risk using three patient cohorts [44]. On the other hand, the study on EPICAP study showed the evidence supporting hypothesis of a link between circadian genes and PCa [12]. Since circadian rhythms were produced by multiple molecular interactions of protein, and PCa was a complex polygenic trait, a single-SNP approach may not be sufficient to investigate the association between circadian genes and PCa [12]. Therefore, further investigation will be need to evaluate the relation between circadian genes and carcinogenesis of PCa with more samples and various genes including *PER3* gene, especially for Japanese population.

We also evaluated the association between rs2640908 polymorphisms and susceptibility to PCa in smokers. We found that the T/T and C/T + T/T genotypes conferred lower risk of PCa compared to the C/C genotype within the "Smoker" group, but not the "Never" group. This result suggests that there is an association between smoking and *PER3* polymorphisms, as previously observed in colon cancer [25]. Cigarette exposure changes DNA binding by modulating the redox potential of cells and tissues [45], and therefore affects transcriptional activity. Binding of transcriptional circadian genes, including *BMAL1*, *CLOCK*, and *NPAS2,* is dependent on the redox ratio [46]. Circadian genes and smoking may therefore interact in a synergistic manner. However, the possibility of association between gene polymorphisms and smoking remains controversial. Jin et al has advocated that genetic differences in risk tend to be smaller at high doses of carcinogens, including tobacco, when the environmental effect may overpower any genetic predisposition [47]. However, this was disputed by Kuroda et al, who reported that the Pro/Pro genotype of a *TP53* polymorphism in smokers was significantly higher in patients with urothelial cancer compared with that in the control [48]. Polymorphisms for the metabolic genes *GSTT1*, *GSTM1*, and *CYP1A1* are not associated with the smoking status in onco-hematological diseases [49].

Considering these contradictory findings, further studies are warranted to clearly elucidate the relationships between gene polymorphisms and smoking.
There were some limitations to this study. First, our small sample may have induced a sampling bias and affected the results of the stratified analysis. Secondly, we had no information regarding the history of shift work, alcohol consumption, BMI, sleep time, clinical characteristics, smoking period and number of cigarettes. The lack of these data also induced information bias, and introduced the influence to our results. Especially, since circadian genes polymorphism could influence sleep condition and shift work tolerance [50], the interaction with circadian genes and sleep condition (sleep duration and sleep quality) could influence the carcinogenesis of PCa. Therefore, additional study will be needed to evaluate the relation between *PER3* gene polymorphisms and carcinogenesis of PCa with considering sleep condition. We could not use smoking condition (smoking period and number of cigarettes), but used the status of smoking. We found that the rate of smoking was higher in the control than in the patient group. We estimated the interaction with smoking and *PER3* polymorphism (rs2640908) by multiple logistic regression analysis. Therefore, smoking condition (smoking period and number of cigarettes) could be important factor. It would be necessary to evaluate the relation between smoking condition and *PER3* polymorphism stratified by smoking condition. Despite these limitations, we believe our findings provide a basis for future studies investigating the association between prostate cancer and circadian gene polymorphisms.

Conclusions

In conclusion, this is the first study that focused on associations between *PER3* polymorphisms (rs2640908 and VNTR) and PCa risk. For rs2640908, the T/T and C/T + T/T genotypes had a significant protective effect against PCa in the Japanese population. However, no relationship between VNTR polymorphisms and PCa could be detected. Our finding suggests that the rs2640908 polymorphism may be a useful marker for prostate cancer and contributes to further understanding of the molecular mechanisms underlying PCa pathogenesis.

List of abbreviations

PCa: Prostate cancer.
SNP: Single Nucleotide Polymorphism.
VNTR: Variable Number Tandem Repeat.
PCR: Polymerase Chain Reaction.
PCR-RFLP: Polymerase Chain Reaction - Restriction Fragment Length Polymorphism.
CLOCK: Circadian Locomotor Output Cycles Kaput Gene.
PER: Period Gene.
CRY: Cryptochrome Gene.
PER1: Period 1.
PER2: Period 2.
PER3: Period 3.
IL-6: Interleukin-6.
UOEH: University of Occupational and Environmental Health.
AgeI: Restriction Enzyme.
χ^2 test: Chi-square test.
OR: Odds Ratio.
95% CI: 95% Confidence Interval.
SD: Standard Deviation.
LAN exposure: Light at Night Exposure.
IARC: The Agency for Research on Cancer.
DNA: Deoxyribonucleic Acid.
ESE: Exonic Splicing Enhancer.
mRNA: Messenger Ribonucleic Acid.
SR: Serine/Arginine-Rich.
BMAL1: Brain and Muscle Arnt - Like 1.
NPAS2: Neuronal PAS domain 2.
TP53: Tumor Protein 53.
GSTT1: Glutathione S - transferase theta 1.
GSTM1: Glutathione S - transferase Mu 1.
CYP1A1: Cytochrome P450 Family 1 Subfamily A Member 1.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

TH contributed to experimental work and designed the experiments and analyzed the results. SM and TK contributed in the data collection. YK contributed on interpreted, reviewed the experiment design, and critically reviewed the manuscript. All authors reviewed the manuscript and approved the final draft.

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