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# The correlation between PER3 rs2640908 polymorphism and colorectal Cancer in the Japanese population

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## Abstract

**Background:** Colorectal cancer (CRC) is one of the most common cancers in Japan. Many factors influence this cancer, one of which is circadian rhythm disruption. Our research investigated the correlation between single-nucleotide polymorphisms (SNPs) in the *Period 3* (*PER3*) (rs2640908), which is one of the circadian genes, and colorectal cancer in the Japanese population.

**Methods:** The study participants consisted of 121 cases and 197 controls. DNA was extracted from participants' peripheral blood cells, and polymerase chain reaction—restriction fragment length polymorphism analysis (PCR-RFLP) was performed to detect genotypes of *PER3*.

**Results:** Participants with T/T genotype were at lower risk of developing colorectal cancer than participants with C/C genotype (adjusted ORs = 0.32 (95% CI: 0.15–0.63)). When stratified by gender and smoking status, T/T genotype were associated with a decreased susceptibility to cancer in males only (adjusted ORs: 0.23 (95% CI: 0.09–0.59)), T/T genotype were also associated with a decreased susceptibility to cancer among both smokers and non-smokers.

**Conclusions:** A significant association was found between the T allele of *PER3* polymorphism and a reduced risk of colorectal cancer, especially in males. Smoking status showed no association with the relationship between *PER3* genotype and CRC carcinogenesis.

**Keywords:** Circadian gene, PER3, Colorectal cancer, Japanese

## Background

Gastrointestinal tract cancers, including stomach, oesophageal and colorectal cancers, comprise 20 % of cancers worldwide. Among gastrointestinal tract cancers, 50% are colorectal cancers [1]. According to a 2012 World Health Organization (WHO) report, colorectal cancer was the second most common cancer in women and the third most common cancer in men [2]. Colorectal cancer was the fourth-largest cause of cancer deaths worldwide as well as in Japan in particular [2]. It is estimated that in Asia, the number of deaths due to colorectal cancer (CRC) will reach approximately 376,700 annually by 2020 [2, 3]. In Japan, the age-standardized incidence and mortality of CRC were, respectively, 17.2 and 8.2 per 100,000 population [4, 5].

The risk factors of CRC are thought to be multifactorial and to be related to environmental and genetic factors as well as lifestyle. According to a report from the World Cancer Research Fund/ American Institute for Cancer Research (WCRF/AICR), high body mass index (BMI), smoking, drinking alcohol and eating red meat, and night shift work are correlated with high risk of CRC [6, 7]. A Japanese study indicated that 31–33% of CRC were related to these factors [5]. High levels of physical activity and high consumption of fibre, fish, vegetables, and fruits were shown to be associated with a lower risk of CRC [5].

Sleep quality is important to the maintenance of general health. Epidemiological studies have demonstrated that temporally altered body organisation due to circadian disruption could be a factor in cancer risk. Nurses working at night, for

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example, have a higher tendency to contract various cancers such as breast cancer and colorectal cancer [8–10]. Nurses who have worked night shifts for more than 15 years are more likely to develop colon cancer than those who have never worked night shifts [10]. However, the actual pathophysiological mechanism is not yet understood [11, 12].

Sleep quality relates to sleep rhythm, which is controlled by some circadian clock genes. Several circadian clock genes are expressed in the suprachiasmatic nucleus (SCN). SCN is thought to be the centre that controls circadian rhythm in the human body [13]. Typical genes controlling circadian rhythm are the circadian locomotor output cycles kaput (*CLOCK*), neuronal PAS domain protein 2 (*NPAS2*), brain and muscle Arnt-like protein 1 (*BMAL1)*, periods 1, 2, and 3 (*PER1, PER2, PER3*), and cryptochromes 1 and 2 (*Cry1,Cry2*) [13–15]. The molecular mechanism controlling the circadian rhythm has been reported to be based on positive and negative transcriptional and translational loops with those circadian clock genes [16].

The *PER* genes are a family of genes that influence cell cycle as well as cellular growth and differentiation [17]. *PER* genes have immunomodulatory and tumour-suppressing properties [18]. The *PER* family consists of *PER1, PER2* and *PER3*. Mutation and disruption of *PER3* expression have been observed in some cancers [19–21]. An in vitro study revealed that overexpression of PER3 genes significantly inhibited cell proliferation and invasion and promoted apoptosis in colorectal tissue [22]. Another study showed that there are significantly fewer *PER3* expression in CRC tissues than in healthy mucosa [23, 24]. Deletion and reduced expression of the *PER3* gene on human chromosome 1p36 has been found to be associated with breast cancer recurrence, proving the *PER3* gene to be a tumour suppressor in breast cancer [25]. Recent studies have shown that polymorphism of the *PER3* gene might increase the risk of adenoma formation [19], prostate cancer [26], and breast cancer [27] and also influence the survival rates of patients with resection surgery in cases of hepatocellular carcinoma [28, 29] and gastric cancer [20]. Interestingly, the *PER3* single nucleotide protein (SNP) (rs2640908) is a genetic variant of the human *PER3* that has been associated with the development of various cancers [20, 28]. *PER3* (rs2640908) plays an important role in the development of portal vein thrombosis, which affects prognoses in hepatocellular carcinomas [28]. However, the role of *PER3* polymorphism in colorectal cancer has not yet been explained in detail. Therefore, in this study, we investigate the association of *PER3* (rs2640908) polymorphism and susceptibility to CRC in conjunction with gender and smoking status.

## Methods

### Study population

One hundred twenty-one Japanese CRC cases and 197 Japanese noncancerous clinical controls were the materials in this study. The cases were consecutive patients treated at the University of Miyazaki Hospital and the University of Occupational and Environmental Health Hospital (UOEH) in Japan. The controls were recruited from among patients suffering from non-cancerous diseases in hospitals near UOEH Hospital. The CRC cases were diagnosed histologically. Cancer sites included the ascending, transverse, and descending colon as well as the rectum. Information regarding illnesses, residence, occupation, and smoking status was collected by means of a self-questionnaire. Persons who had been exposed to carcinogens, heavy metals or radiation in their occupational history were excluded from the study.

The cases and controls were classified into two groups according to smoking status: the 'never' group, composed of non-smokers, and the 'smoker' group, composed of both current smokers and former smokers. The nature of the study was explained to all cases and controls, and written informed consent was obtained from all participants. The Ethical Committee of the University of Miyazaki Faculty of Medicine approved this study procedure (Approval Number: 239).

### Polymerase chain reaction (PCR) amplification and genotyping

Genomic DNA was extracted from peripheral blood lymphocytes using the conventional method [30]. Detection of single nucleotide polymorphisms (SNPs) of *PER3* (rs2640908) was performed using the restriction fragment length polymorphism (PCR-RFLP) technique. The PCR-RFLP assay used in this study was referred to in a previous report [28]. The primers for the polymorphisms in *PER3* (rs2640908) were as follows: forward 5'CTGT TTAACACACGAAGTTGAAGA-3′ and reverse 5′ GTTCTGGATGGGGATTCGCT-3′. The DNA was denatured at 94 °C for 30s, followed by 35 cycles of 94 °C for 30s, 55 °C for 30s, 72 °C for 45 s and final extension at 72 °C for 5 min.

The length of the PCR product of the *PER3* was 1063 bp. The digesting fragments of the product of the *PER3* with BsrFI restriction enzyme were measured at 798 bp and 265 bp. These fragments were detected by electrophoresis.

### Statistical analysis

All statistical analyses were performed using R ver. 3.2.3. The results are provided as mean ± SD. Categorical variables analysis was conducted using Pearson's chi-square test ($x^2$ test), and evaluation of the possibility of Hardy-Weinberg equilibrium was also conducted using the $x^2$ test. Two categorical numerical analyses applied t-test analysis. The multivariate analyses used multiple logistic regression. In the analysis, gender and smoking status were adjusted to reduce the confounding effect. In all of these tests, *P* values of less than 0.05 were considered statistically significant.

**Table 1** General characteristics of the controls and CRC patients

| | Cases | Controls | *P* |
|---|---|---|---|
| n (male/female) | 121 (78/43) | 197 (131/66) | 0.8 |
| Age (SD) | 64.3 (11.2) | 65.5 (17.3) | 0.45 |
| Smoking status (smoker/never) | 60/61 | 123/74 | 0.03 |

## Results

The general characteristics of the cases and the controls appear in Table 1. For the total of 318 samples, the mean (SD) ages of cases and controls were 64.3 (11.2) and 65.5 (17.3), respectively. The mean ages of the cases and controls did not differ significantly. Likewise, the gender distributions of cases and controls were not statistically significant. The percentages of males were 64.5% of the cases and 66.5% of the controls. However, there were significantly more smokers among the controls (62.4%) than among the cases (49.6%).

Table 2 and Additional file 1: Table S1 illustrates the frequencies of *PER3* rs2640908. The proportions of *PER3* genotypes were not contradicted by the Hardy-Weinberg equilibrium ($P = 0.8$). The T/T genotype was significantly less common in the CRC cases than in the controls (adjusted ORs: 0.32 (95% CI: 0.15–0.63)). When comparing to the C/C genotype, the T/T genotype could be protective concerning carcinogenesis of CRC.

We analysed the distributions of the *PER3* stratified by smoking and gender (Tables 3 and 4) ( Additional file 1: Table S2 and S3). The T/T genotype of *PER3* was significantly less common in the cases than in the controls, regardless of smoking status. In addition, among males only, the T/T genotype was significantly more common in controls compared to cases (adjusted ORs: 0.23 (95% CI: 0.09–0.59)).

## Discussion

*CLOCK*, *NPAS2* and *BMAL1* proteins are basic helix-loop-helix PAS-domain-containing transcription factors that activate transcription of the *PER* and *Cry* genes. After the *PER* protein reaches a certain concentration, *PER* and *Cry* translocate to the nucleus and interact with the CLOCK-BMAL1 complex. This mechanism inhibits their own transcription to form a negative feedback loop [11, 31]. Therefore, the circadian system influences the cell cycle by means of gene expression and post-translational mechanisms [15]. Moreover, circadian genes affect cell proliferation and apoptosis by controlling tumour suppressor genes and cell cycle genes. This mechanism is based on auto-regulatory transcription and a translation feedback loop, in both of which *PER* genes take a central position.

The results of the present study indicate a significant negative association between the T allele of *PER3* rs2640908 and colorectal cancer carcinogenesis. This enables us to designate the T/T genotype as a possible key inhibitory factor in colorectal cancer in males. However, we do not find the same relationship in females, nor do we find any significant interaction between *PER3* and smoking status.

The correlation between the genotype T/T in *PER3* rs2640908 and lower risk of certain cancers has been reported in previous research [28, 29]. The T allele of the *PER3* gene has been shown to reduce the risk of death in hepatocellular carcinoma and gastric cancers [20, 28, 29].

The *PER* gene is an essential circadian clock gene that organises the processes of proliferation [32], metabolism, differentiation [23], and apoptosis [21] in the cell cycle. Therefore, *PER3* dysfunction causes disruption of cell check-points and an inability to spot malignant cells with DNA damage [33]. Furthermore, the *PER3* mRNA level has been reported to be lower in colon cancer tissue than in normal tissue [23]; the expression of *PER3* is associated with tumour location, cell differentiation, tumour stage, and response to therapy [23, 34]. The prognosis of cancer patients with high *PER3* expression is better than the prognosis of those with low *PER3* expression [28], and low expression of *PER3* is associated with reduced survival rates [25]. Knockout *PER3* mice have an increased probability of developing breast cancer induced by the introduction of a carcinogenic agent [25, 35].

The biological function of *PER3* rs2640908 has not yet been clearly explained. Functional prediction of *PER3* rs2640908 has indicated that this SNP is located in the exonic splicing enhancer (ESE) region (http:// snpinfo.niehs.nih.gov/snpfunc.htm). SNP of *PER3* in the ESE region can affect mRNA splicing and may disrupt the binding of serine/arginine-rich (SR) proteins, reducing the efficiency of exon definition and potentially leading to the use of an alternative splice site. This, in turn, may cause alterations in translation initiation sites and translation efficiencies [36]. Based on these reports, we

**Table 2** Association between PER3 genotype and CRC

| Genotype | Case | Control | OR(95%CI) | *P* | Adjusted OR(95%CI)[a] | *P* |
|---|---|---|---|---|---|---|
| C/C | 36 | 38 | Ref | | Ref | |
| C/T | 65 | 100 | 0.69 (0.39–1.19) | 0.18 | 0.67 (0.38–1.18) | 0.17 |
| T/T | 20 | 59 | 0.36 (0.18–0.71) | 0.003 | 0.32 (0.15–0.63) | 0.001 |

[a] Adjusted by gender, age and smoking status

**Table 3** Association between PER3 genotype and CRC when stratified by smoking status

| Never smoker | Case | Control | ORs(95%CI) | *P* | Adjusted ORs(95%CI)[a] | *P* |
|---|---|---|---|---|---|---|
| C/C | 18 | 11 | Ref | | Ref | |
| C/T | 29 | 36 | 0.49 (0.2–1.21) | 0.28 | 0.48 (0.19–1.18) | 0.11 |
| T/T | 14 | 27 | 0.32 (0.12–0.85) | 0.02 | 0.31 (0.11–0.84) | 0.02 |
| Smoker | | | | | | |
| C/C | 18 | 27 | Ref | | Ref | |
| C/T | 36 | 64 | 0.84 (0.41–1.74) | 0.65 | 0.85 (0.42–1.78) | 0.67 |
| T/T | 6 | 32 | 0.28 (0.1–0.81) | 0.02 | 0.28 (0.09–0.77) | 0.02 |

[a] Adjusted by gender and age

hypothesized that *PER3* rs2640908 lowers risk among CRC patients by controlling *PER3* transcription factors, thus regulating cell proliferation, cell cycles and apoptosis. Our result showing that *PER3* rs2640908 indeed affected CRC needs to be validated with further experimental study in the future.

With regard to the relation between *PER3* polymorphism and colorectal cancer, we found no difference in this study between smokers and people who have never smoked. This result might suggest that there is no interaction between smoking and *PER3* polymorphism. There is no interaction between smoking and *PER3* polymorphism with respect to carcinogenesis in, for example, colorectal cancer. This result contradicts the findings of another study concerning the association between smoking and other circadian cycles [37].

In Japan, in comparison with the rest of the world, the rate of deaths from cancer is low although the smoking rate is relatively high. This phenomenon is called the "Japanese smoking paradox" [38, 39]. Probable explanations of this paradox include: lower levels of cancer-causing ingredients in Japanese cigarettes, genetic factors that result in Japanese men being more resistant to the development of smoking-related cancers, lower alcohol consumption and lower fat intake by Japanese males, and higher efficiency of filters in Japanese cigarettes [40]. The healthy diet of the Japanese population, the good quality of food and nutrient consumption levels in Japan may also decrease the risk of cancer even among smokers [40]. Despite our study's indication that there is no difference between the smoker and nonsmoker groups in terms of the association between *PER3* polymorphism and colorectal cancer, this result should not be interpreted as indicating that tobacco is safer or less harmful for people than is generally believed, especially for Japanese [39].

We find a significant relationship between the polymorphism of *PER3* rs2640908 and colorectal cancer risk in males, but not in females. Androgens control cellular growth and differentiation in some of the hormone-dependent organs as well as in colorectal tissue [41]. In addition, the androgen receptor is a ligand-dependent transcription factor involved in controlling cellular proliferation and differentiation [41]. A study using rats and mice also showed that colonic adenoma developed with testosterone [42]. The depletion of male hormones by orchidectomy reduces the probability of the development of colonic adenoma. On the other hand, the administration of dihydrotestosterone increases development of colonic adenoma. In female mice, depletion of female hormones by ovariectomy does not influence the development of colonic adenoma [42]. However, some reports have indicated that androgen receptors influence the circadian cycle [42–45]. Disruption of circadian rhythm correlates with pathogenic conditions, including cancer [15, 44]. Our results concerning a link between *PER3* polymorphism and colorectal cancer risk among males might relate to the effects of androgens on cellular proliferation and differentiation in colorectal cancer cells.

**Table 4** Association between PER3 genotype and CRC when stratified by sex

| Male | Case | Control | ORs(95%CI) | *P* | Adjusted ORs(95%CI)[a] | *P* |
|---|---|---|---|---|---|---|
| C/C | 24 | 27 | Ref | | Ref | |
| C/T | 45 | 67 | 0.76 (0.39–1.47) | 0.41 | 0.76 (0.39–1.51) | 0.44 |
| T/T | 9 | 37 | 0.27 (0.11–0.68) | 0.005 | 0.23 (0.09–0.59) | 0.003 |
| Female | | | | | | |
| C/C | 12 | 11 | Ref | | Ref | |
| C/T | 20 | 33 | 0.56 (0.21–1.49) | 0.24 | 0.53 (0.19–1.44) | 0.22 |
| T/T | 11 | 22 | 0.46 (0.15–1.37) | 0.16 | 0.43 (0.14–1.28) | 0.13 |

[a] Adjusted by age and smoking status

This study includes some limitations: firstly, the proportions of smokers differed between the cases and the control group. Both proportions were higher than Japan's current smoking rate, which is approximately 30%. The reason for the relatively high rate of smokers in this study is that the smoker group included ex-smokers. However, the smoking rate in the control group was higher than the rate among the cases. The smoking rate, therefore, could not have influenced our results. Secondly, the sample size might not have been large enough to evaluate the association of *PER3* rs2640908 to CRC carcinogenesis of *PER3*. However, to the best of our knowledge, this study is the first to report a correlation between *PER3* single nucleotide polymorphisms (SNPs) and colorectal cancer in the Japanese population; this study could thus become a basic reference for future research. Thirdly, the fact that the control sample consisted of hospital patients with non-cancerous diseases means that healthy people were not sampled. This might have affected the results. Fourthly, we recognize that some information that could affect the results was missing, such as tumour location, stage of cancer, and other risk factors that could influence colorectal cancer such as diet, body mass index (BMI), alcohol consumption, and physical activity.

## Conclusions

A significant association was found between the T allele of *PER3* polymorphism (rs2640908) and reduction of colorectal cancer risk, especially in males. Smoking behaviour did not influence this association. Therefore, the conclusion of the current study remains limited and need further validation.

## Additional file

**Additional file 1: Table S1.** Multivariate analysis of factors associated with CRC. **Table S2.** Multivariate analysis of factors associated with CRC stratified by smoking status. **Table S3.** Multivariate analysis of factors associated with CRC stratified by sex. (DOCX 17 kb)

### Abbreviations

BMAL1: Brain and muscle Arnt-like protein 1; BMI: Body mass index; BsrFI: restriction enzyme; CLOCK: Circadian locomotor output cycles kaput; CRC: Colorectal cancer; Cry1: Cryptochrome 1; Cry2: Cryptochrome 2; DNA: Deoxyribonucleic acid; mRNA: messenger ribonucleic acid; NF-kB: Nuclear factor – kappa beta; NPAS2: Neuronal PAS domain protein 2; PCR: Polymerase chain protein; PCR-RFLP: Polymerase chain protein—restriction fragment length polymorphism; PER: Period gene; PER1: Period 1; PER2: Period 2; PER3: Period 3; SCN: Suprachiasmatic nucleus; SIRT1: Sirtuin type 1; SNPs: Single-nucleotide polymorphisms; TLRs: Toll-like receptors; UOEH: University of Occupational and Environmental Health Hospital; WCRF/AICR: World Cancer Research Fund/ American Institute for Cancer Research; WHO: World Health Organization; $x^2$ test: Pearson's chi-square test

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### Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

### Authors' contribution

Ho designed the experiment, carried out the molecular genetic studies, performed statistical analysis and wrote the manuscript; TH and NK designed the genetic analysis, and participated in the sequence alignment. YK interpreted and reviewed the experiment design, revised the proposal and guided the statistical analysis and critically reviewed the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The Ethical Committee of University of Miyazaki Faculty of Medicine approved this study procedure on December 7, 2005 (Approval Number: 239). All patients recruited gave written consent to participate in the study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

## Publisher's Note



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