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Short Communication

Polymorphisms of DNA repair genes are risk factors for prostate cancer

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ABSTRACT

DNA repair gene alterations have been shown to cause a reduction in DNA repair capacity. We hypothesised that DNA repair gene polymorphisms may be risk factors for prostate cancer (PC). To test this hypothesis, DNA samples from 165 cases of prostate cancer and healthy controls were analyzed by PCR-RFLP to determine the genotypic frequency of three DNA repair genes (*XRCC1*, *XPC* and *XRCC7*). We found that the frequency of 939Gln variant at *XPC Lys939Gln* was significantly lower in PC cases (OR = 0.39, P = 0.016). Haplotype analysis of *XRCC1 Arg194Trp (C/T)* and *Arg399Gln (G/A)* revealed that the frequency of the T–A haplotype was significantly higher in PC patients. This is the first report on the studies of XPC and XRCC1 *Arg194Trp* polymorphisms in PC, and our present data suggest that *XPC Lys939Gln* and the T–A haplotype of *XRCC1 Arg194Trp* and *Arg399Gln* may be risk factors for PC in Japanese.

1. Introduction

Prostate cancer (PC) is one of the most common malignancies in men in the United States.[1] The aetiology of prostate cancer is largely unknown. Although several risk factors have been shown, ethnicity, family history and age have been associated with the increased risk.[2] In addition, diet has been linked to prostate cancer risk and prevention.[3]

Human DNA repair mechanisms protect the genome from DNA damage caused by endogenous and environmental agents. Genetic polymorphisms of DNA repair genes have been reported to lead to amino acid substitution in various cancers. Base excision repair (BER) is the repair mechanism for small lesions such as single-strand breaks, non-bulky adducts, oxidative damage, alkylation, or methylation. The *hOGG1* gene, which is in this category, encodes a DNA glycosylase/AP lyase. It suppresses the mutagenic effects of 8-hydroxyguanine by catalysing its removal from reactive oxygen species (ROS). In this regard, Xu *et al.*[4] found two sequence variants of this gene and showed an association between these polymorphisms and prostate cancer risk.[4] The X-ray cross-complementing group 1 (XRCC1) is also one of the enzymes participating in the BER pathway and acts as a scaffolding intermediate by interacting with Ligase III, DNA polymerase-β and poly (ADP-ribose) polymerase.[5] Shen *et al.* described two polymorphisms in XRCC1 (*Arg194Trp*

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and *Arg399Gln*), which are non-conservative amino acid changes.[6] The polymorphism of the *XRCC1* codon 399 was shown to be correlated with DNA repair activity[7] and associated with susceptibility to various cancers.[7]

Recently, we reported an association between the polymorphism of *XRCC1 Arg399Gln* and the risk of renal cell carcinoma.[8] Van Gils *et al.*[9] investigated the *XRCC1* codon 399 polymorphism in prostate cancer. They found no discernible difference between PC cases and controls for the *XRCC1* codon 399 variants, but found a remarkable risk for the combination of low dietary intake of vitamin E and the *XRCC1* codon 399 *Gln/Gln* genotypes.[9] Although Ribicki *et al.*[10] and Ritchey *et al.*[11] also investigated the *XRCC1* codon 399 polymorphism in prostate cancer, a significant association was found only in the latter study. To our knowledge, there have been no studies of the XRCC1 Arg194Trp polymorphism in prostate cancer.

Among DNA repair systems, the nucleotide-excision repair (NER) pathway repairs bulky DNA adducts and includes xeroderma pigmentosum group D (*XPD*) and xeroderma pigmentosum group C (*XPC*) repair genes. The *XPD* gene encodes a DNA helicase, its product being one of the integral members of the transcription factor TFIIH.[12] The XPC protein, involved in the NER pathway, binds to HR23B to form the XPC-HR23B complex and is thought to be an early damage detector and initiatior of NER.[13] The XPC codon 939 polymorphism (A–C transition, exon 15) results in a Lys to Gln alteration, which has been found to be associated with increased risk of bladder and lung cancer.[14,15] Among non-homologous end joining double-strand break repair genes, the *XRCC7* gene encodes the catalytic polypeptide of DNA-activated protein kinase: Wang *et al.*[16] found that the *XRCC7* gene polymorphism was associated with glioma. No studies have examined the risk of the polymorphisms of this group of DNA repair genes, including *XRCC1 Arg194Trp*, *XPC Lys939Gln*, and *XRCC7* in prostate cancer.

We hypothesised that the polymorphisms of DNA repair genes could be risk factors for prostate cancer (PC). To test this hypothesis, we examined whether the *XRCC1* (*Arg194Trp*, *Arg399Gln*), *XPC Lys939Gln* and *XRCC1G6721T* polymorphisms are risk factors for PC through analysis for SNPs of various DNA repair genes in normal and prostate cancer samples. Since smoking has been proven to be a risk factor for PC,[2] we also investigated the relationship between polymorphisms of DNA repair genes and smoking status in PC cases.

2. Materials and methods

2.1. Samples

A total of 165 patients with pathologically confirmed prostate cancer (PC), and 165 age-matched control individuals were enrolled in this study. The mean ages of the patient and control groups were 68 ± 5 and 67 ± 15 years, respectively.

Genomic DNA was obtained from the peripheral blood of healthy controls and patients. All of the patients tested were diagnosed with prostate cancer on the basis of histopathological findings from radical prostatectomy at Shimane University Hospital (Izumo Japan). They were classified according to the WHO criteria and staged according to the tumour-node-metastasis (TNM) classification and the Gleason grading system. Healthy controls consisted of volunteers with no apparent abnormal findings upon medical examination at Shimane University Hospital. The smoking status were investigated through interviews with doctors or nurses. The current smokers were defined as those who smoked within 12 months of tumour development. The former smokers were those who had quit smoking more than 12 months before tumour development. None of these patients had received androgen deprivation therapy before radical prostatectomy. The participation rates were 99% and 80% for the patients and controls, respectively.

There were no significant differences between patients and control groups with regard to family history of cancer and body mass index.

2.2. PCR-RFLP genotyping

Each PCR was carried out in a total volume of 20 μl consisting of 0.3 μl of a 10 μM solution of each primer, 1.5 mM $MgCl_2$, 0.8 mM dNTP, 0.5 U RedTaq DNA polymerase (Sigma, St. Louis, MO), 1 μl of genomic DNA (80 ng/μl) and 15.6 μl H_2O using a PTC 200 Thermal Cycler (MJ Research). Primer sets and annealing temperatures used for the PCR-RFLP assay are shown in Table 2.[8,15,16] The PCR program had an initial denaturation step of 7 min at 94 °C followed by 35 cycles of 30 s at 94 °C, 45 s of annealing at 57–62 °C based on the primers and 45 s at 72 °C.

For *XRCC1 Arg194Trp*, nested PCR was done (Table 2).

For RFLP analysis, PCR products were digested with *Pvu*II, *Msp*I, *Pvu*II and *Pvu*II (New England Biolabs, Beverly, MA) for *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln*, *XPC Lys939Gln* and *XRCC7 G6721T*, respectively, by the manufacturer's protocols. The PCR products were separated by electrophoresis in a 2.0% agarose gel, and subsequently stained with ethidium bromide (Fig. 1).

Table 1 – Characteristics of PC patients and controls

	Cases (n = 165)	Controls (n = 165)
Age (means ± S.D.)[a]	68 ± 5	67 ± 15
pT		
1	0 (0%)	
2	108 (65%)	
3	53 (32%)	
4	4 (2%)	
Gleason sum		
<7	82 (50%)	
7	54 (32%)	
>7	29 (18%)	
Preoperative serum		
<4	24 (15%)	
4–10	75 (45%)	
>10	66 (40%)	
Smoking status		
Current smokers	43 (26%)	
Former smokers	29 (18%)	
Never smokers	93 (56%)	

a Cases *versus* controls, P = 0.20.

Table 2 – Primers and restriction enzymes used for the detection of XRCC1, XPC, and XRCC7 polymorphisms

Gene	Primer sequences	Product size	Restriction enzyme	References
XRCC1 Arg194Trp	(First) 5′-GCCCCGTCCCAGGTA-3′ 5′-AGCCCCAAGACCCTTTCACT-3′ (Second) 5′-ATGAGAGCGCCAACTCTCTG-3′ 5′-CTACCCTCCTCCCTCAGACC-3′	490 bp 175 bp	*PvuII*	This study
XRCC1 Arg399Gln	5′-TCTCCCTTGGTCTCCAACCT-3′ 5′-AGTAGTCTGCTGGCTCTGG-3′	402 bp	*MspI*	[8]
XPC Lys939Gln	5′-ACCAGCTCTCAAGCAGAAGC-3′ 5′-CTGCCTCAGTTTGCCTTCTC-3′	281 bp	*PvuII*	[15]
XRCC7 G6721T	5′-CGGCTGCCAACGTTCTTTCC-3′ 5′-TGCCCTTAGTGGTTCCCTGG-3′	368 bp	*PvuII*	[16]

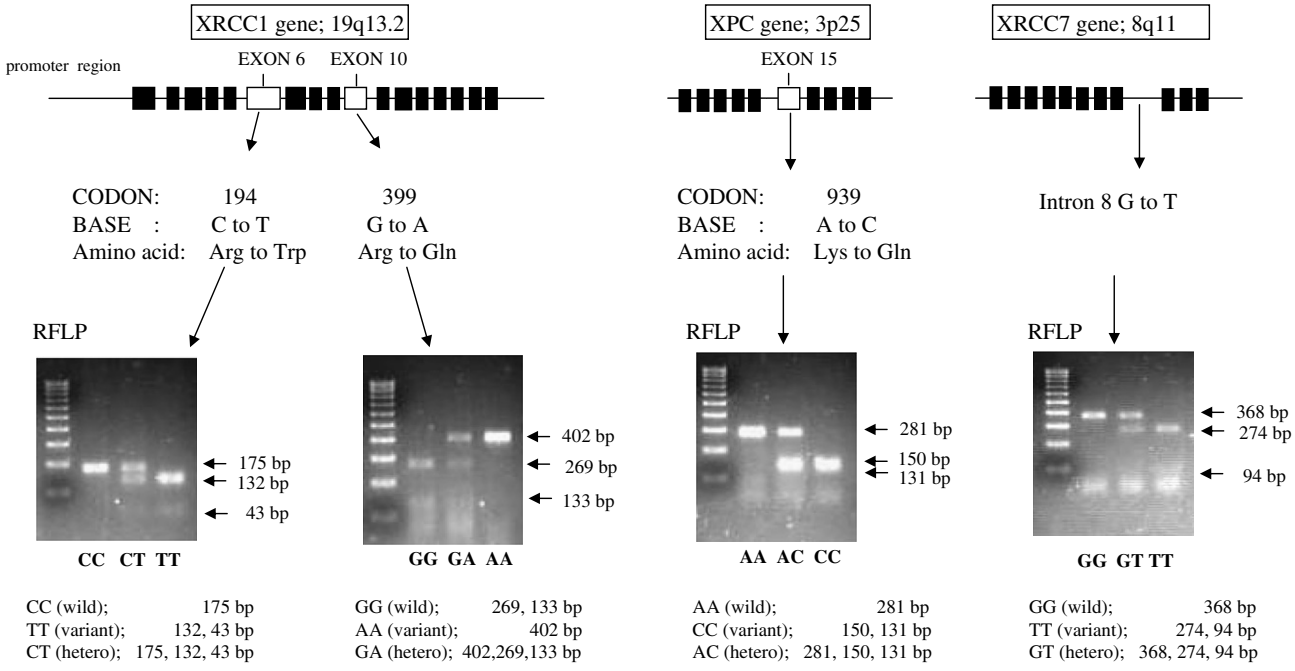

Fig. 1 – Schematic representation of the *XRCC1*, *XPC* and *XRCC7* gene structure and gel displaying of RFLP.

To confirm the genotype ascribed by PCR–RFLP, the PCR products were subjected to direct sequencing using an ABI PRISM 377 DNA sequencer (Applied Biosystems, Inc., Foster City, CA).

2.3. *Statistical analysis*

Hardy–Weinberg equilibrium and haplotype frequency were evaluated using SNPAlyze version 2.2 (DYNACOM Co. Ltd., Tokyo, Japan). The χ^2 test was used to compare the genotype frequency between patients and controls. The odds ratio (ORs) was obtained by unconditional logistic regression analysis and adjusted for age as a continuous variable. All statistical analyses were performed using StatView (version 5; SAS Institute Inc., NC). A *p*-value of less than 0.05 was regarded as statistically significant.

3. Results

3.1. *Characteristics of PC patients and controls*

Table 1 shows the mean age, pT, Gleason sum, preoperative serum PSA and smoking status of individual PC patients. Two-tailed Student's *t* tests were used to compare the distributions of age between patients and control subjects. There was no significant difference of mean age between cases and controls (Table 1). In the 165 prostate cancer cases, 102 (65%) organ confined and 82 (50%) were had a Gleason sum (GS) of less than 7.

3.2. *Hardy–Weinberg equilibrium*

The genotype frequencies of the four polymorphisms in total samples ($n = 330$), PC patients ($n = 165$) and healthy controls

($n = 165$) were consistent with the Hardy–Weinberg equilibrium distribution (p-value > 0.05).

3.3. *XRCC1 Arg194Trp, XRCC1 Arg399Gln, XPC Lys939Gln and XRCC7 G6721T polymorphisms and PC*

Table 3 shows the genotype distribution of the *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln*, *XPC Lys939Gln* and *XRCC7 G6721T* polymorphisms between the PC cases and healthy controls. A significant decrease in the Gln/Gln genotype of *XPC Lys939Gln* was observed in patients compared to controls (OR = 0.39, 95%CI 0.18–0.87, $p = 0.016$) (Table 3). There was no statistical difference in the genotypes of the *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln* and *XRCC7 G6721T* polymorphisms between cases and controls. The frequencies of the variant alleles between cases and controls were as follows: *XPC Lys939Gln* (0.30, 0.35), *XRCC1 Arg194Trp* (0.35, 0.30), *Arg399Gln* (0.28, 0.27) and *XRCC7 G6721T* (0.69, 0.72) (Table 4). The Gln allele frequency of *XPC Lys939Gln* tended to be lower in PC patients (Table 4).

We also examined the combined effect of XPC and other genes, and found increased PC risk when the *XPC 939 Lys/Lys + Lys/Gln* and *XRCC1 194 Arg/Trp + Trp/Trp* are combined (OR = 1.80, 95%CI = 1.16–2.78) (Table 5).

3.4. *Haplotype analysis*

The distributions of haplotypes of XRCC1 codon 194 (C/T) and codon 399 (G/A) polymorphisms were compared between PC patients and controls. When the frequency of T–A haplotype of codon 194 (C/T) and codon 399 (T/A) was compared with that of other haplotypes (C–A + C–G + T–G) between PC

Table 3 – Distribution of four DNA repair gene polymorphisms in PC patients and controls

Gene	Genotype	Cases ($n = 165$) (%)	Controls ($n = 165$) (%)	Crude			Adjusted for age		
				OR	95%CI	p-Value	OR	95%CI	p-Value
XPC									
Lys939Gln	Lys/Lys	77 (47)	72 (44)						
	Lys/Gln	78 (47)	70 (42)						
	Gln/Gln	10 (6)	23 (14)	0.39	0.18–0.87	0.016	0.38	0.17–0.86	0.015
	Lys/Lys + Lys/Gln	155 (94)	142 (86)	2.51	1.15–5.46	0.017	2.50	1.14–5.45	0.016
XRCC1									
Arg194Trp	Arg/Arg	70 (42)	85 (52)						
	Arg/Trp	74 (48)	62 (38)						
	Trp/Trp	21 (13)	18 (10)	1.19	0.61–2.31	0.60	1.20	0.62–2.32	0.61
	Arg/Trp + Trp/Trp	95 (58)	80 (48)	1.44	0.93–2.22	0.09	1.45	0.94–2.23	0.10
Arg399Gln	Arg/Arg	87 (53)	86 (52)						
	Arg/Gln	63 (38)	69 (42)						
	Gln/Gln	15 (9)	10 (6)	2.03	0.71–5.82	0.18	2.02	0.72–5.83	0.19
	Arg/Gln + Gln/Gln	78 (47)	79 (48)	0.98	0.63–1.50	0.95	0.98	0.63–1.50	0.95
XRCC7									
G6721T	G/G	12 (7)	12 (7)						
	G/T	79 (48)	67 (41)						
	T/T	74 (45)	86 (52)	0.74	0.48–1.15	0.18	0.76	0.49–1.18	0.19
	G/T + T/T	153 (93)	153 (93)	1.00	0.44–1.15	0.99	1.02	0.45–1.17	1.00

Table 4 – Comparison of the allele frequency of four DNA repair gene between PC patients and healthy controls

Gene, allele	Cases ($n = 330$[a]) n (%)	Controls ($n = 330$[a]) n (%)	OR (95%CI)
XPC Lys939Gln			
Lys allele	232 (70)	214 (65)	1.28 (0.93–1.78)
Gln allele	98 (30)	116 (35)	
XRCC1 Arg194Trp			
Arg allele	214 (65)	232 (70)	
Trp allele	116 (35)	98 (30)	1.28 (0.93–1.78)
XRCC1 Arg399Gln			
Arg allele	237 (72)	241 (73)	
Gln allele	93 (28)	89 (27)	1.06 (0.76–1.50)
XRCC7 G6721T			
G allele	103 (31)	91 (28)	
T allele	227 (69)	239 (72)	0.84 (0.60–1.17)

a n refers to allele number.

Table 5 – Prostate cancer risk for combined effect of XPC 939 , XRCC1 and XRCC7

Combined genotypes		Number of cases (%)	Number of controls (%)	OR (95% CI)	*p*-Value
XPC 939 Gln/Gln	*XRCC1 194 Arg/Arg*	6 (4)	11 (7)	1.0 (referent)	
XPC 939 Gln/Gln	*XRCC1 194 Arg/ Trp + Trp/Trp*	4 (2)	12 (7)	0.32 (0.10–1.00)	0.043
XPC 939 Lys/Lys + Lys/Gln	*XRCC1 194 Arg/Arg*	64 (39)	75 (45)	0.86 (0.56–1.33)	0.50
XPC 939 Lys/Lys + Lys/Gln	*XRCC1 194 Arg/ Trp + Trp/Trp*	91 (55)	67 (41)	1.80 (1.16–2.78)	0.008
XPC 939 Gln/Gln	*XRCC1 399 Arg//Gln + Arg/Arg*	6 (4)	12 (7)	1.0 (referent)	
XPC 939 Gln/Gln	*XRCC1 399 Gln/Gln*	4 (2)	11 (7)	0.35 (0.11–1.11)	0.06
XPC 939 Lys/Lys + Lys/Gln	*XRCC1 399 Arg/Gln + Arg/Arg*	72 (44)	67 (41)	1.13 (0.73–1.75)	0.57
XPC 939 Lys/Lys + Lys/Gln	*XRCC1 399 Gln/Gln*	83 (50)	75 (45)	1.21 (0.98–1.87)	0.37
XPC 939 Gln/Gln	*XRCC7 TT*	5 (3)	15 (9)	1.0 (referent)	
XPC 939 Gln/Gln	*XRCC7 GG + GT*	5 (3)	8 (5)	0.61 (0.20–1.92)	0.39
XPC 939 Lys/Lys + Lys/Gln	*XRCC7 TT*	69 (42)	71 (43)	0.95 (0.61–1.47)	0.82
XPC 939 Lys/Lys + Lys/Gln	*XRCC7 GG + GT*	86 (52)	71 (43)	1.44 (0.93–2.22)	0.09

Table 6 – Comparison of haplotypes derived from the genotypes of *XRCC1Arg194Trp* (C/T) and *Arg399Gln* (G/A) with risk of prostate cancer

Haplotype	Case[a] (n[b] = 330) (%).	Control[a] (n = 330) (%)	*p*-Value
C–G	165 (50.0)	145 (43.8)	0.118
T–G	72 (21.9)	96 (29.2)	0.0032
C–A	49 (14.9)	87 (26.5)	0.0003
T–A	44 (13.2)	2 (0.5)	<0.0001

a Values are *n* (%).
b *n* refers to allele number.

patients and healthy controls, it was significantly higher in patients ($p < 0.0001$) (Table 6).

3.5. *Relation of the XPC polymorphism with clinical parameters in PC patients*

Table 7 shows the relation of *XPC Lys939Gln* polymorphisms with clinicopathological parameters including age at onset, Gleason sum, pT and smoking status in PC patients. Although there was no statistically significant association of the *XPC Lys939Gln* genotypes with these parameters, the frequency of Lys/Lys genotype of the *XPC Lys939Gln* tended to be higher in higher Gleason sum (GS) groups (GS $\geqslant$ 7) than in lower groups (GS < 7) (OR = 1.4, 95%CI = 0.74–2.54). We found no association between smoking status and the XPC polymorphism (Table 7). Although the smoker's data for controls were not available, the percentage of smokers in the patient group tested was not different from that of the entire Japanese population (44 *versus* 49%).[17]

4. Discussion

Among prostate cancer risk for XRCC1 gene polymorphism, the results of codon 399 genotype frequencies are not consistent.[9–11] There are no reports concerning the *XRCC1 Arg194Trp* polymorphism in prostate cancer. We demonstrated that the frequency of the *Arg/Trp + Trp/Trp* genotype of *XRCC1 Arg194Trp* tended to increase in PC patients compared to controls (OR = 1.44, 95%CI = 0.93–2.22, *p*-value = 0.09). Moreover, we examined the haplotype of XRCC1 codon 194 and codon 399 in prostate cancer. Interestingly, the frequency of T–A haplotype was significantly increased in PC patients ($p < 0.0001$). It seems that the decreased tendency of the C–A

Table 7 – Association of the XPC Lys939Gln polymorphism with clinical parameters in prostate cancer patients

Cases (n = 165)	*XPC Lys 939Gln*		OR (95% CI)	*p*-Value
	Lys/Lys	Lys/Gln + Gln/Gln		
Age at onset				
<71 years (n = 77)	42 (55)	51 (45)		
>71 years (n = 88)	35 (40)	37 (60)	1.14 (0.62–2.12)	0.65
Gleason sum				
<7 (n = 82)	35 (43)	47 (57)		
>7 (n = 83)	42 (51)	41 (49)	1.4 (0.74–2.54)	0.30
pT				
T1,T2 (n = 108)	51 (47)	57 (53)		
T3,T4 (n = 57)	26 (46)	31 (54)	0.9 (0.49–1.78)	0.84
Smoking status				
Non-smoker (n = 93)	43 (46)	50 (54)		
Smoker (n = 72)	34 (47)	38 (53)	1.0 (0.56–1.92)	0.89

or T–G haplotype in patients was attenuated by the presence of the C or G allele, respectively. In this regard, Matullo *et al.*[18] reported on the bladder cancer haplotype of XRCC1 in Caucasians, although it is difficult to compare their data with ours, since the frequency of the codon194 variant in Caucasian is much lower than that of Japanese.

Recent studies have shown that XRCC1 polymorphism is associated with risk for various cancers because the allele frequencies of XRCC1 are different in Asians than in Caucasians.[19] Our control data for codon 194 and codon 399 are consistent with Asian reports (Table 4).[19] The effect of the *XRCC1 Arg194Trp* polymorphism is different according to cancer type, namely, the 194Arg allele has been thought to be a risk factor in gastric cancer, while 194Trp allele has been reported to be associated with lung cancer and squamous cell carcinoma of the head and neck (SCCHN).[20]

The XPC gene product contributes to the global genome repair (GGR) pathway, is a member of the NER pathway and is tightly associated with one of the two human homologues of *Saccharomyces cerevisiae* RAD23 protein (HR23B).[13] The XPC-HR23B complex has a structure-specific affinity for certain defined lesions, including UV-induced photoproducts, the acetylaminofluorence adduct (AAF) and artificial cholesterol moieties. There are six core NER factors (XPC-HR23B, TFIIH, XPA, RPA, XPG, and ERCC1-XPF). Among these factors, only the XPC-HR23B complex can bind damaged DNA, changing the DNA conformation around the lesion.[13,14] In this regard, Van Hoffen *et al.*[21] showed that the basic steps of NER are as follows: (1) recognition of a DNA lesion, (2) single strand incision at both sides of the lesion, (3) excision of the lesion-containing the single stranded DNA fragment, (4) DNA repair synthesis to replace the excised nucleotides, and (5) ligation of the remaining single strand nick. Prior studies have shown that the XPC-HR23B complex is the DNA damage detector and initiator of the GGR reaction.[13,14] Mice with deletion of the XPC gene have been reported to develop lung cancer.[22]

This is the first report demonstrating the risk of the XPC exon 15 (*Lys939Gln*) polymorphism with PC. Prostate cancer patients with at least one variant alleles at XPC K939Q had a slightly reduced risk of PC OR = 0.88, 95%CI 0.57–1.37) and a significantly reduced risk when both variant alleles were present (OR = 0.39, 95%CI 0.18–0.87, $p = 0.016$). Recently, studies have also shown that the XPC Lys939Gln polymorphism is associated with a decreased risk of lung cancer and endometrial cancer.[23,24] Our results are in agreement with these reports.

We also examined the combined effect of XPC *Lys939Gln*, XRCC1 and XRCC7 on PC risk, and the resultant ORs for XPC *Lys939Gln* (Lys/Lys + Lys/Gln) + XRCC1 *Arg194Trp* (Arg/Trp + Trp/Trp) were 1.80 (Table 5). An additional effect was not observed in the combined analysis compared to XPC *Lys939Gln* (Lys/Lys + Lys/Gln) (Table 3). This was considered to be due to the increased frequencies of the XPC Lys allele (Table 4).

Although the effects of XPC Lys939Gln and XRCC1 Arg194Trp on DNA repair capacity are unknown, there have been several recent studies on this topic. Vodicka *et al.* reported that the *in vitro* irradiation-specific DNA repair rate tended to be lower in individuals with the Gln/Gln genotype of the XPC Lys939Gln polymorphism compared with those with the Lys/Lys genotype.[25] Cornetta *et al.* demonstrated that XPC heterozygous subjects (Lys/Gln) had decreased residual DNA damage 60 min after irradiation compared with wild-type and homozygous genotypes.[26] With regard to XRCC1 Arg194Trp, it was shown that irradiation-specific DNA repair rates decreased with increasing number of variant alleles in XRCC1 Arg399Gln in combination with variant alleles for two other XRCC1 polymorphisms, Arg194Trp and Arg280His.[27] Taylor *et al.* showed that wild-type and variant alleles had the same repair activity in the single-strand repair break in XRCC1 deficient EM9 cells *in vitro* transfection experiment.[28] This is the first report on the association of *XPC* codon 939 and *XRCC1* codon 194 polymorphisms in PC. These results suggest that the XPC *Lys939Gln* polymorphism may be a risk factor for PC and XRCC1 codon 194 polymorphism may pose a slight risk for prostate cancer in Japanese. Further studies with a larger sample size are necessary to confirm this finding.

Conflict of interest statement

None declared.

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