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Scientific Research

Detection of Polymorphisms of DNA Repair Genes (XRCC1 and XPC) in Prostate Cancer*

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ABSTRACT

Prostate cancer is a common disease with a multifactorial and complex etiology. It is the most common male malignancy and the second leading cause of death in many countries. The widespread use of PSA testing has increased the detection of this cancer at earlier stages, although this diagnostic method has proved to be insufficient to identify the disease. DNA in most cells is regularly damaged by endogenous and exogenous mutagens. At least four main partially overlapping damage repair pathways operate in mammals. Common polymorphisms in DNA repair genes may alter protein function and an individual's capacity to repair damaged DNA; deficits in repair capacity may lead to genetic instability and carcinogenesis. In the present study, we investigated the genotypic distribution of XRCC1 and XPC polymorphisms and its association with prostate cancer risk, pathological staging and Gleason's scoring. The present study was conducted in the departments of Clinical Pathology, Pathology, and Urology Faculty of Medicine, Alexandria University-Egypt. A total number of 50 patients with pathologically confirmed prostate cancer and 50 age-matched control subjects were enrolled in this study. The diagnosis was made on the basis of histopathological findings, following radical prostatectomy or transurethral resection of the prostate (TURP). Genomic DNA was extracted from peripheral blood using QIAamp blood DNA isolation kits. PCR followed by enzymatic digestion of the PCR products for (XRCC1, XPC) was used for the genotyping of these polymorphisms. Statistical analyses were performed using SPSS statistics version 20. The genotype frequencies of the studied polymorphisms in all the samples (n = 100), PC patients (n = 50) and healthy controls (n = 50) were consistent with the Hardy-Weinberg equilibrium distribution (p-value > 0.05). There was no statistical difference in the genotypes of the XRCC1 Arg399Gln and XPC Lys939Gln between cases and controls. The "Gln" allele frequency of XPC Lys939Gln as well as the "Gln" allele frequency of XRCC1 Arg399Gln tended to be lower in controls than in PC patients. Yet, these decreases were not statistically significant. We also examined the combined effect of XPC and XRCC1 and we found a decreased PC risk when XPC 939 Lys/Lys + Lys/Gln and XRCC1 399 Arg/Arg + Arg/Gln are combined (OR = 0.370, 95% CI = 0.142 - 0.962).

Keywords: Prostate Cancer; Polymorphisms; PCR; XRCC1; XPC

1. Introduction

Prostate cancer is a common disease with a multifactorial and complex etiology. It is the most common male malignancy and the second leading cause of death in many countries [1]. Several risk factors such as ethnicity, family history, and age have been shown to be associated with the increased prostate cancer risk [2].

The widespread use of PSA testing has increased the detection of this cancer at earlier stages, although this diagnostic method has proved to be insufficient to identify the disease [3].

Pathological staging and Gleason scores for grading are the most important prognostic factors but they have

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been shown to imperfectly discriminate patients at risk for progression [3]. Therefore, research has been directed toward identifying molecular markers that can predict prostate cancer predisposition and progression.

DNA in most cells is regularly damaged by endogenous and exogenous mutagens. Unrepaired damage can lead to effects, triggering cell-cycle arrest or cell death, or long term effects in the form of irreversible mutations contributing to oncogenesis [4].

At least four main partially overlapping damage repair pathways operate in mammals, namely, nucleotide-excision repair (NER), base-excision repair (BER), homologous recombination and end joining [4].

Common polymorphisms in DNA repair genes may alter protein function and an individual's capacity to repair damaged DNA; deficits in repair capacity may lead to genetic instability and carcinogenesis [5]. There is emerging evidence that polymorphic genes may modulate effects of endogenous androgens or environmental toxicans on prostate cancer risk [6].

The xeroderma pigmentosum complementation group C (XPC) protein plays a key role in NER pathway. The functional DNA-binding domains of XPC interact with HR23B to form a complex that recognizes and binds to the sites of DNA damage. Deficiency in XPC has been involved in tumorigenesis [7].

The X-ray cross complementing group 1 (XRCC1) is one of the enzymes participating in the BER pathway and acts as a scaffolding intermediate by interacting with ligase III, DNA polymerase-B and poly (ADP-ribose) polymerase [8].

In the present study, we investigated the genotypic distribution of XRCC1 and XPC polymorphisms and its association with prostate cancer risk, pathological staging and Gleason's scoring.

2. Subjects and Methods

The present study was conducted in the departments of Clinical Pathology, Pathology, and Urology Faculty of Medicine, Alexandria University-Egypt. A total number of 50 patients with pathologically confirmed prostate cancer and 50 age-matched control subjects were enrolled in this study. The diagnosis was made on the basis of histopathological findings, following radical prostatectomy or transurethral resection of the prostate (TURP). The cases were classified according to the WHO criteria, and staged according to the tumor-node-metastasis (TNM) classification and the Gleason grading system. The range of age of the included patients and controls was 40 - 80 years. Controls were apparently healthy subjects on medical examination. Informed consent was obtained from all subjects included in this study according to the Ethical Committee for Human Research in Alexandria Main University Hospital. Samples (peripheral blood and prostatic tissue biopsy) were collected from Urology Department; Faculty of Medicine, Alexandria University over 1 year between 2010 and 2011.

PCR-RFLP genotyping

Genomic DNA was extracted from peripheral blood using QIAamp blood DNA isolation kits (Qiagen, Crawley, United Kingdom) according to the manufacturer's protocol.

2.1. Polymerase Chain Reaction (PCR)-Restriction Fragment Length Polymorphism (RFLP) Analysis

PCR followed by enzymatic digestion of the PCR products for (XRCC1, XPC) was used for the genotyping of these polymorphisms. Amplification reactions were performed in a total volume 50 µl containing 50 - 100 ng DNA and 20 pmol each primer. 2X PCR master mix (Fermentas Life Science) was used. It is composed of: dNTPs (dATP, dCTP, dGTP, and dTTP) 0.4mM of each, MgCl2 (4 mM) and 0.05 units/ml of Taq polymerase in reaction buffer. Samples were amplified by DNA thermal cycler (Techne Cambridge LTD) for XRCC1 Arg399Gln, and XPC Lys939Gln. 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˚C - 62˚C based on the primers and 45 s at 72˚C.

2.2. XRCC1 Arg399Gln Polymorphism

The XRCC1 Arg399Gln polymorphism was amplified in a 616-bp fragment by using the following primers:

xrcc1-399F (5'-TTGTGCTTTCTCTGTGTCCA-3') and xrcc1-399R (5'-TCCTCCAGCCTTTACTGATA-3'). The PCR product was digested with Fast Digest MspI (Fermentas, life scince). The recognition site for the MspI restriction endonuclease is present only in the Arg (WT) allele; hence, digestion of the Arg allele results in products of 376 bp and 240 bp, whereas the Gln allele remains undigested.

2.3. XPC Lys939Gln Polymorphism

The XPC Lys939Gln polymorphism was amplified in a 281-bpfragment by using the following primers:

xpc-939F (5'-ACCAGCTCTCAAGCAGAAGC-3') and xpc-939R (5'-CTGCCTCAGTTTGCCTTCTC-3'). The PCR product was digested with Fast Digest PvuII (Fermentas, life scince). The wild (WT/AA) allele remains undigested, hence Lys digestion (AA) gives 280 bp and variant digestion (Gln/CC) gives 150 and 131 bp fragments .

Fast Digest enzymes (Fermentas, Life science) are advanced line of restriction enzymes for rapid DNA digestion in 5 - 15 minutes supplied with 10× Fast Digest buffer 1 µl of Fast Digest enzyme is formulated to digest

up to 0.2 μg of PCR product in 5 minutes.

Each restriction digestion reaction (30 μl) involved the following components at room temperature in the following order: 17 μl water nuclease free, 2 μl 10× Fast Digest buffer, 10 μl PCR product and1 μl Fast Digest enzyme. Then the components were mixed up gently and spun down and then incubated at 37˚C for 5 - 10 min.

The digested products were resolved on 3% agarosre gel, stained with ethidium bromide and analyzed under UV light.

2.4. Statistical Methodology

Statistical analyses were performed suing SPSS® Statistics version 20 (IBM Corp., New York, USA). Association between categorical variables was tested using Chi-square test (X2). When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Firsher's Exact test(FEP). Odds ratio (OR) and the corresponding 95% confidence interval (CI) were computed to quantify the risk associated with gene polymorphism. Significance test results are quoted as two-tailed probabilities and judged at the 5% level.

3. Results

1. Clinico-pathological criteria of the patients:

The present study included 50 patients diagnosed with prostatic cancer and 50 age-matched controls.

Table 1 shows that the mean age of the patients was 65.4 ± 8.7. The average Gleason sum was 6.8 ± 1.6, their serum PSA was greatly variable ranging from 4 to 297 ng/ml with a median value of 48. Most of the 50 PC patients were of grade T2 & T3 (n = 40, 80%), had no nodal metastasis (N0) (32, 64%). Nearly half of them were classified as stage II (52%).

2. Hardy-Weinberg equilibrium:

The genotype frequencies of the studied polymorphisms in all the samples (n = 100); PC patients (n = 50) and healthy controls (n = 50) were consistent with the Hardy-Weinberg equilibrium distribution (p-value > 0.05).

3. XRCC1 Arg399Gln and XPC Lys939Gln polymorphisms:

Table 2 shows the genotype distribution of the XRCC1 Arg399Gln and XPC Lys939Gln polymorphisms between the PC cases and controls. There was no statistical difference in the genotypes of the XRCC1 Arg399Gln and XPC Lys939Gln between cases and controls.

The frequencies of the variant alleles between cases and controls were as follows: XPC Lys939Gln (0.43, 0.37) and XRCC1 Arg399Gln (0.29, 0.23) (**Table 3**) (**Figures 1** and **2**).

The "Gln" allele frequency of XPC Lys939Gln as well as the "Gln" allele frequency of XRCC1 Arg399Gln tended to be lower in controls than in PC patients. Yet, these decreases were not statistically significant.

Table 1. Characteristics of PC patients.

	Cases (N = 50) n (%)	
Age		
M ± SD	65.4 ± 8.7	
(Min.-Max)	(52 - 82)	
PSA (ng/ml)		
Mdn	48	
(Min.-Max)	(4 - 297)	
Gleason sum		
M ± SD	6.8 ± 1.6	
(Min.-Max)	(4 - 10)	
T		
T1	6	12.0
T2	20	40.0
T3	20	40.0
T4	4	8.0
N		
N0	32	64.0
N1	13	26.0
Nx	5	10.0
M		
M0	19	38.0
M1	4	8.0
Mx	27	54.0
Stage		
II	26	52.0
III	13	26.0
IV	11	22.0

We also examined the combined effect of XPC and XRCC1 and we found a decreased PC risk when XPC 939 Lys/Lys + Lys/Gln and XRCC1 399 Arg/Arg + Arg/Gln are combined (OR= 0.370, 95% CI=0.142-0.962) (**Table 4**).

4. Relation of the XPC polymorphism with clinical parameters in PC patients:

Table 5 shows the relation of XPC polymorphisms with clinic-pathological parameters including age of onset, Gleason score, and the stage of the tumor in PC patients.

The frequency of Gln/Gln genotype of the XPC tended

Table 2. Distribution of two DNA repair gene polymorphisms in PC patients and controls.

Genotype		Case (n = 50) n (%)		Control (n = 50) n (%)		OR (95%)	Test of association
							X^2 (p-value)
XRCC1	Gln/Gln	8	(16.0)	3	(6.0)	0.335 (0.083 - 1.346)	2.554 (0.110)
	Arg/Arg + Arg /Gln	42	(84.0)	47	(94.0)		
	Arg/Arg	29	(58.0)	30	(60.0)	1.086 (0.489 - 2.411)	0.041 (0.839)
	Gln/Gln + Arg /Gln	21	(42.0)	20	(40.0)		
XPC	Gln/Gln	9	(18.0)	5	(10.0)	0.506 (0.157 - 1.635)	1.329 (0.249)
	Lys/Lys + Lys/Gln	41	(82.0)	45	(90.0)		
	Lys/Lys	16	(32.0)	18	(36.0)	1.195 (0.522 - 2.737)	0.178 (0.673)
	Gln/Gln + Lys/Gln	34	(68.0)	32	(64.0)		

Table 3. Comparison of the allele frequency of XPC Lys939Gln and XRCC1 Arg399Gln between PC patients and healthy controls.

Genotype		Case (Alleles no. = 100) n (%)		Control (Alleles no. = 100) n (%)		OR (95%)	Test of association
							X^2 (p-value)
XRCC1	**Arg**	71	(71)	77	(77)	1.367 (0.725 - 2.581)	0.936 (0.333)
	Gln	29	(29)	23	(23)		
XPC	**Lys**	57	(57)	63	(63)	1.284 (0.729 - 2.265)	0.750 (0.386)
	Gln	43	(43)	37	(37)		

Table 4. Comparison of the combined effect of XPC and XRCC between PC patients and healthy control.

Genotype		Case (n = 50) n (%)	Control (n = 50) n (%)	OR (95%)	Test of association
XPC	**XRCC1**				X^2 (p-value)
Lys/Lys + Lys/Gln	**Arg/Arg + Arg/Gln**	33 (66.0)	42 (84.0)	0.370 (0.142 - 0.962)	4.320 (0.038)
Lys/Lys + Lys/Gln	**Gln/Gln**	8 (16.0)	3 (6.0)	2.984 (0.743 - 11.988)	2.554 (0.110)
Gln/Gln	**Arg/Arg + Arg/Gln**	5 (10.0)	9 (18.0)	0.506 (0.157 - 1.635)	1.329 (0.249)
Gln/Gln	**Gln/Gln**	0 0.0	0 0.0	--	--

Table 5. Association of the XPC Lys939Gln polymorphism with clinical parameters in prostate cancer patients.

Genotype		Lys/Lys + Lys/Gln **(n = 41)**		Lys/Lys **(n = 9)**		OR (95%)	Test of association
Age	<70	22	(54)	6	(67)	0.579 (0.127 - 2.636)	FEP = 0.713
	≥70	19	(46)	3	(33)		
PSA (ng/ml)	<50	21	(51)	7	(78)	0.300 (0.056 - 1.620)	FEP = 0.266
	≥50	20	(49)	2	(22)		
Gleason	<7	19	(46)	5	(56)	0.691 (0.162 - 2.948)	FEP = 0.721
	≥7	22	(54)	4	(44)		
Stage	II	22	(54)	4	(44)	1.447 (0.339 - 6.177)	FEP = 0.721
	III/IV	19	(46)	5	(56)		

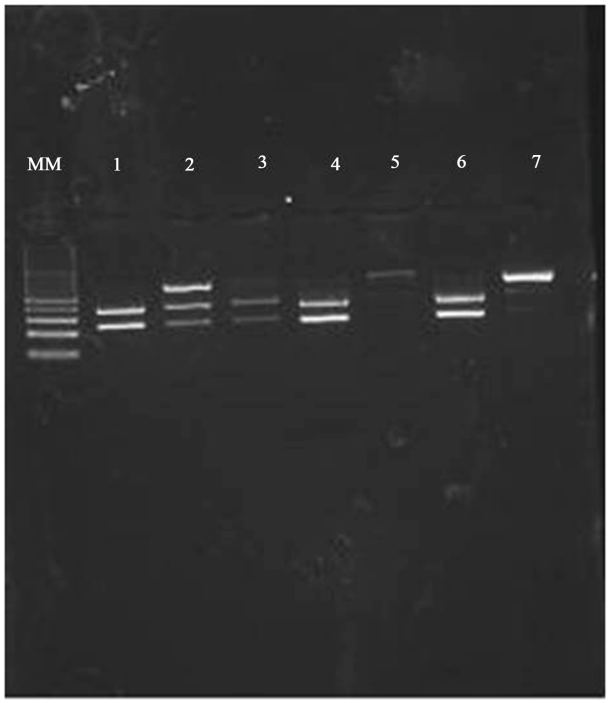

Figure 1. Agarose gel electrophoresis of the digested product of PvuII restriction endonuclease of XPC in 7 cases and controls. Lane MMshows a 50 bp molecular weight marker. Lanes 1, 3, 4 and 6 (131 bp, 150 bp) variant CC genotype. Lane 2 shows (281 bp, 150 bp and 130 bp)heterozygous mutated AC genotype, lanes 5 and 7 show (281 bp) wild type AA genotype.

Figure 2. Agarose gel electrophoresis of the digested product of MspI restriction endonuclease of the XRCC1 in 4 subjects. Lane MM shows a 50 bpmolecular weight marker, Lanes 1 and 3 show wild type GG (269 bp, 133 bp), lane 2 shows heterozygous GA (402 bp, 269 bp and 133 bp), lane 4 shows variant AA (402 bp).

to be lower in older age (≥70) group than in younger age group (<70) (OR = 0.579, 95%CI = 0.127 - 2.636) as well as in patients with higher PSA (≥50) than in patients with lower PSA (<50) (OR = 0.300, 95%CI = 0.056 - 1.620). Yet, these associations were not statistically significant.

5. Relation of the XRCC1 polymorphism with clinical parameters in PC patients:

The associations between XRCC1 polymorphisms with clinico-pathological parameters were shown in **Table 6**. None of these associations were statistically significant. However, the frequency of Gln/Glnwas considerably higher in patients with high Gleason sum (≥7) than in patients with low Gleason sum (<7).

4. Discussion

Prostate Cancer is the most frequently diagnosed malignancy and a common leading cause of cancer death among males worldwide [1,9].

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 [4].

The *XPC* gene, located on chromosome 3p25, contains 16 exons and 15 introns and encodes a 940 amino acid protein [10]. Several polymorphic variants in the *XPC* gene have been identified and *XPC* Lys939Gln is one of the three most common SNPs.

It is located in the coding sequence of the *XPC* gene. The nucleotide change from A to C leads to an amino acid change from lysine to glutamine in the coding sequence of the *XPC* gene and has been reported to lead to reduced repair capacity. This genetic variation has also been reported to result in reduced specificity of this gene in recognition and repair of the DNA damage as well as in protein expression, thus allowing more somatic DNA mutations or alterations to occur [11,12].

XPC polymorphism was reported to be associated with the risk of many cancers, such as head and neck [13], lung [14], breast [15] and bladder [16].

XRCC1 is located on chromosome 19q13.2. The protein encoded by this gene is involved in the efficient repair of DNA single-strand breaks formed by exposure to ionizing radiation and alkylating agents. This protein interacts with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase to participate in the base excision repair pathway [17].

To our knowledge this is the first study to evaluate the risk of the XPC Lys939Gln and XRCC Arg399Gln polymorphisms with prostate cancer in a sample of Egyptian population.

Our results showed that no statistical difference in the genotype of XPC Lys939Gln between cases and controls.

Table 6. Association of the XRCC1 Arg399Gln polymorphism with clinical parameters in prostate cancer patients.

Genotype		Arg/Arg + Arg/Gln (n = 42)		Gln/Gln (n = 8)		OR (95%)	Test of association
Age	<70	24	(57)	4	(50)	1.333 (0.293 - 6.064)	FEP = 0.718
	≥70	18	(43)	4	(50)		
PSA (ng/ml)	<50	24	(57)	4	(50)	1.333 (0.293 - 6.064)	FEP = 0.718
	≥50	18	(43)	4	(50)		
Gleason	<7	23	(55)	1	(12)	8.474 (0.956 - 75.082)	FEP = 0.050
	≥7	19	(45)	7	(88)		
Stage	II	22	(52)	4	(50)	1.100 (0.242 - 4.991)	FEP = 1.000
	III/IV	20	(48)	4	(50)		

This is in contrast to the report that demonstrated that prostate cancer patients with at least one variant allele at XPC Lys939Gln had a slightly reduced risk of prostate cancer and a slightly reduced risk when both variants were present.

In the present study, we did not find a significant association between the genotype of the XRCC1 Arg399Gln and prostatic cancer cases or controls. Our findings are in agreement with the previously reported non-significant lower risk associated with this genotype in three different studies in the U.S. population [18-20]. However, two other studies found higher prostatic cancer risk for the carriers of this allele [21,22].

A case-control study in China of 5 DNA repair markers found a positive association between PC risk and the XRCC1 399Gln/Gln genotype [18]. A significantly increased risk of PC was observed in white men with the XRCC1 399Gln allele (OR 1.6; 95% CI 1.1 - 2.4). This study has found that white men with the following combined genotypes XRCC1 (399Arg/Gln_Gln/Gln)/APE1 (51Gln/Gln) (OR: 4.0; 95% CI: 1.3 - 12.5) and XRCC1 (399Arg/Gln_Gln/Gln)/APE1(148Asp/Asp) (OR: 2.9; 95% CI: 1.4 - 6.1) genotypes have higher risk for PC [9]. However, another study reported reduced PC risk for men who carry 1 or 2 copies of the variant alleles at the XRCC1 codons 194 and 399 compared with those who were homozygous for the common allele (OR: 0.8; 95% CI: 0.4 - 1.8 and OR_0.8; 95% CI, 0.5 - 1.3), respectively [19].

We also examined the combined effect of XPC Lys939Gln and XRCC1 Arg399Gln on prostate cancer risk, and the resultant ORs for XPC Lys939Gln (Lys/Lys + Lys/Gln) + XRCC1 Arg399Gln (Arg/Arg + Arg/Gln) were 0.370. We found a decreased prostatic cancer risk when the previous genotypes were combined. In a study conducted by Hirata *et al.* [23], the results showed that an additional effect was not observed in the combined analysis compared to XPC Lys939Gln (Lys/Lys + Lys/Gln). This was considered to be due to the increased frequencies of the XPC Lys allele.

5. Conclusion

In conclusion, our results suggested that there is no association between XPC Lys939Gln, XRCC1 Arg399Gln and PC risk. Although the combined effect of XPC Lys/Lys + Lys/Gln and XRCC1 Arg/Arg + Arg/Gln decreased PC risk, it didn't reach a statistically significant level. To our knowledge, this is the first report on the studies of XPC Lys939Gln and XRCC1 Arg399Gln polymorphisms in a sample of Egyptian prostatic cancer patients. Further studies with a larger sample size and other DNA repair polymorphisms that may play a role in the pathogenesis of PC and the inclusion of other environmental factors as smoking are necessary to confirm these findings.

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