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RESEARCH ARTICLE

Genetic Association between Xeroderma Pigmentosum Polymorphism Rs2228000 with Staging and Development of Bladder Cancer

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Abstract

Background: Bladder Cancer is the sixth most common malignancy in males worldwide, and the second in Iraq. XPC Repair Gene polymorphism may cause a reduction in DNA repair capacity and influence an individual's susceptibility to bladder cancer and the prognosis of the disease. Objective: To investigate the influence of active tobacco smoking on human DNA repair gene XPC rs2228000 polymorphism in patients with bladder cancer and the impact of XPC polymorphism C>T to the staging and development of the disease. Methods: A total of 62 of histo-pathologically confirmed diagnosed bladder cancer patients, and 38 age-matched healthy controls were involved in the study. All were recruited from February to September 2017 in a case-control study conducted in the Department of Biochemistry at the College of Medicine University of Baghdad. Genotyping of the XPC rs2228000 (C>T) was evaluated using a polymerase chain reaction and by Sanger sequencing method. The odds ratio (OR) and 95% confidence interval (CI) were calculated as a measure of the combined effect of cigarette smoking, and DNA Double-Strand breaks Repair Gene XPC Polymorphism on bladder cancer risk, staging, and development. Result: Heterozygous genotype of the XPC rs2228000 (C>T) showed a significant increase in bladder cancer risk OR (95% CI) = 2.75 (1.0-7.2), p value<0.05. Also, the study found that patients with the polymorphic allele (T genotype) have significantly increased the risk of bladder cancer (OR, 2.7; *p = 0.02). A statistically highly significant increased bladder cancer risk in the smoker with T Allele (OR, 4.3; **p = 0.004). Moreover, T Allele genotypes were also observed to be associated with a significantly increased risk of T1 (OR, 3.9; **p = 0.005). Conclusion: The study suggests that having polymorphic gene genotype of DNA Repair Gene XPC rs2228000 could increase the risk of bladder cancer and also affect the development and staging of the disease while having the genotype could decrease the risk of bladder cancer and increase the survival rate of bladder cancer patients.

Keywords: *Bladder Cancer, XPC, Rs2228000, Polymorphism.*

Introduction

Xeroderma pigmentosum, complementation group C, also known as XPC. One of the most common complementation groups of XP seen in patients is that of XPC [1, 2]. XPC patients exhibit sensitivity to UV radiation and a dramatically increased risk of skin cancer [3].

Also, somatically-acquired mutations in XPC have been associated with the poor prognosis of patients with Non small Cell Lung Carcinoma (NSCLC) [4]. Specific allelic variants of XPC are associated with increased risk of colorectal cancer [5]. Decreased XPC expression has also been shown to correlate with bladder cancer malignancy and its resistance to cisplatin treatment [6]. As mentioned, the XPC protein is required for early DNA damage recognition and has been shown to be the initiator of G-NER [7, 8]. The XPC step is the rate-limiting step in G-NER.

XPC has been shown to exhibit a strong binding affinity for damaged DNA with an affinity for UV-damaged DNA and lesions that cause helical distortions [9-11].

Cells that lack XPC exhibit little or no NER [12, 13]. Studies involving XPC knockout mice showed that these mice are viable and develop normally; however, they exhibit increased sensitivity to UV light and are highly susceptible to skin and lung cancer similar to XPC patients [12, 14]. Urinary bladder cancer is a multifactorial disease, Smoking plus genetic mutation can highly elevate the risk of bladder cancer [15].

Genetic susceptibility to this disease may result from inherited mutations in genes involved in carcinogen metabolism and DNA repair mechanism [16]. Recently polymorphisms in XPC gene have been associated with different cancers including gallbladder cancer, lung cancer and bladder cancer [1, 17, 18]. XPC Ala499Val is a non-synonymous polymorphism is located on chromosome 3 on p24.3 with reference SNP of rs2228000 [19]. This polymorphism change guanine to adenine which changes the amino acid Ala to valine in the position 499 of the XPC protein [20].

Zhang has shown that polymorphisms of the XPC gene can alter the DNA repair capacity and modulate the susceptibility to many cancers [21]. The Ala499Val (C/T) in exon nine of the XPC gene and has been recently recognized in several tumors including urinary bladder cancer [20]. However, other study finds that there is no association between the rs2228000 polymorphism and bladder cancer and more studies are needed [22].

Marital and Methods

Patient and Control Sample

A Case-control study conducted at the Chemistry and Biochemistry Department University of Baghdad/college of medicine, this case-control study was carried out on 100 subjects during the period from February 2017 to September 2017. All patients were recruited from Gazi Al-Harery Hospital for Specialized Surgery/ Baghdad/ Iraq. Out of these 100 subjects, 62 subjects (47 males, 15 females) with urinary bladder cancer and 38 cancer-free subjects (28 males, 10 female).

The participants in this study were age and sex match. All patients were first diagnosed with bladder tumor and investigated by a urologist and underwent cystoscopy examination for transurethral resection of bladder tumor (TURB) or undergo cystoscopy with biopsy of bladder lesion for histopathological examination. The main exclusion criteria were as follows: individual with a history of urinary tract infection, bladder stone, a patient with previous cancer, with cancer metastasized to bladder from another origin and those with previous chemotherapy or radiotherapy.

Control subjects were cancer-free and had no history of tumors, and were recruited from the patient's companion. Subjects who smoked once a day for more than six months were defined as ever smokers. After taking authorization agreement from the subjects a Five mL Whole Blood samples were obtained into sterile EDTA tubes and stored at -4°C for genomic DNA extraction.

DNA Extraction and Genotyping

Genomic DNA was extracted from whole blood samples using the Promega DNA extraction kit, USA, which were collected in 5ml tubes containing ethylenediaminetetraacetic acid (K3EDTA) from bladder cancer cases and free-cancer controls. Extracted DNA was stored at −80°C for further SNP genotyping.XPC rs2228000 C/T Fragments amplified using polymerase chain reaction (PCR).

Primers for the genotyping of XPC rs2228000 C/T gene Fragments was newly designed by the author using multiple primer design software by NCBI and Sigma Aldrich. Primer sequences were 5′-AAAGGCTGGGTCCAAGAGTG -3′ (forward) and 5′-ACCCACTTTTCCTCCTGCTC -3′ (reverse) were used to amplify the target fragment containing the XPC rs2228000 polymorphism. The fragments of the XPC rs2228000 polymorphism were amplified in 25 mL of reaction mixture containing 2 µl of genomic DNA template, 0.75 µl of each primer, 9 µl H2O, 12.5 µl of PCR master mix (Promega, Madison, WI, USA) which contain 0.1 Mm of each dNTP, 1 ¥ PCR buffer, 10 MM Tris-HCl, 50 mM KCl and 0.1%Triton X-100), 1.5 mm MgCl2, and 1.0 unit of Taq polymerase.

The PCR amplification program was as follows: one cycle for 4-min as denaturation step at 95°C; 30 cycles of 95°C for 50 sec, 60°C for 50 sec, and 72°C for 50 sec; and a final extension at 72°C for 10 min. The PCR product was 981 bp and was checked on a 1% agarose gel as shown in Figure 1.

Furthermore, PCR product for all samples was sent to South Korea for the direct sequencing using by the Sanger sequencing method (Macrogen, South Korea). Sequencing results are received by email then analyzed using the genious software. Figure (2) show the analyzing process of the XPC rs2228000 gene sequences on genius software.

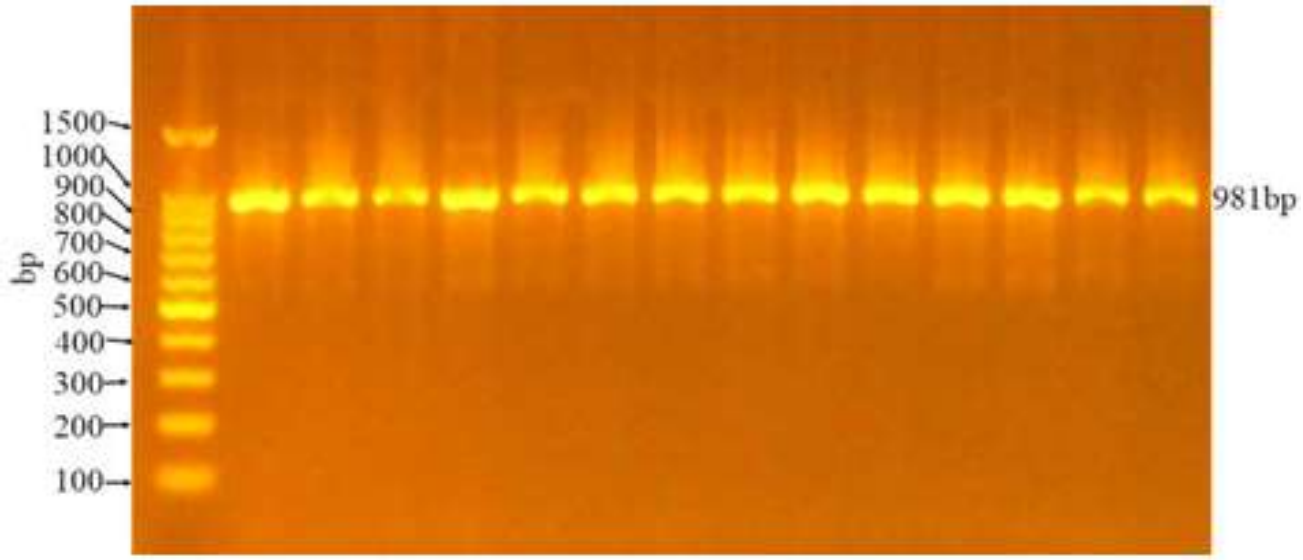

Figure1. An electrophoretic graph of the PCR product of the XPC rs2228000 C/T Gene polymorphism using Promega master mix on 1% agarose, 70V, and for 2 hour (7 µl of DNA loaded in each well)

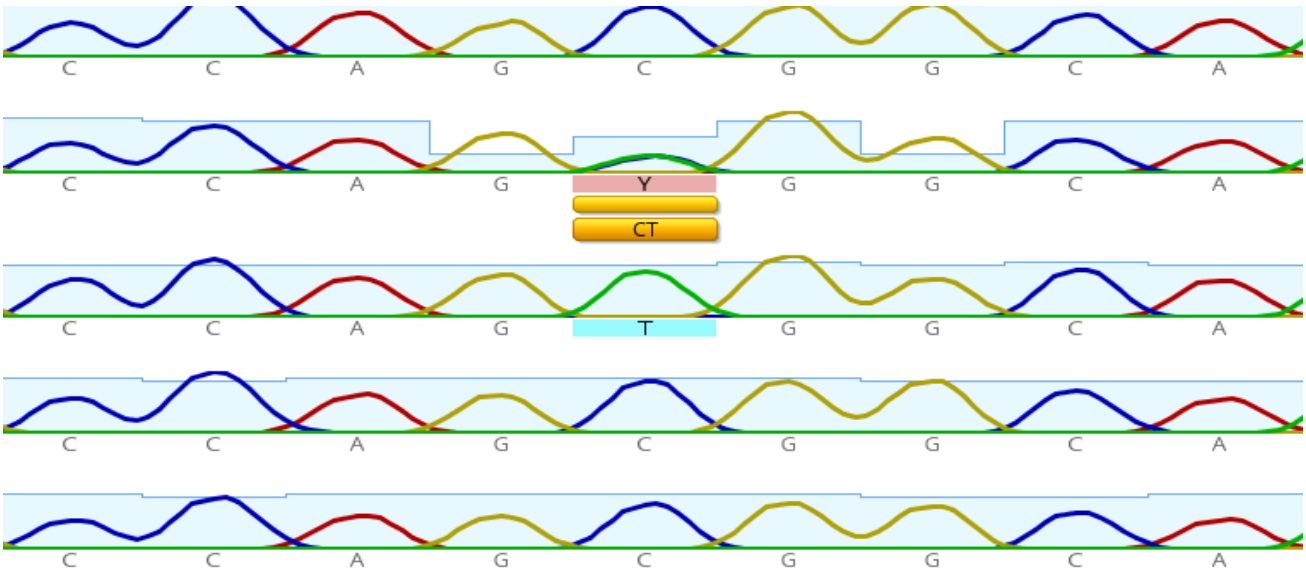

Figure 2: Sequencing analysis by genious software for the XPC rs2228000 C/T polymorphism after sequencing by Sanger sequencing, automated DNA sequence, by Macrogen Corporation – Korea. This figure show different types of the XPC rs2228000 C/T polymorphism each sequencing line represent different individual sample three Sequencing line showed

- **CC genotype as one blue band (wild type)**
- **CT genotype as blue and green band (heterozygous)**
- **TT genotype as one blue green band (homopolymeric)**

Statistical Analysis

The data of the study were stored in a Microsoft Excel spreadsheet and analyzed on the computer using the SPSS software 16 and Microsoft excel program (2016). Numeric variables were expressed as mean ± SD. Student t-test was applied for comparison of mean between two groups. Chi-square test used to compare frequency. Chi-square test was performed to evaluate differences in frequency distributions of demographic characteristics, certain variables, and each genotype and allele of the XPC rs2228000 polymorphisms between the bladder cancer cases and free- cancer controls. Moreover, we determine if the cases and control samples were demonstrated Hardy–Weinberg equilibrium. Multivariate logistic regression and unconditional univariate and analyses were carried out to calculate ORs and 95% CI and to obtain the association of bladder

cancer risk with the genetic polymorphisms of XPC rs2228000 and for the joint effects of cigarette smoking and staging of the bladder cancer.

Results

Characteristic of the Subjects

Total of 100 individual was analyzed in the study in the present study. The control groups consisted of 38 healthy individuals, while the patients were 62. Demographic characteristics of the studied groups are summarized in Table 1 and Table 2. Patients and control was sex, age, weight, height, and BMI matched. Mean ± SD was calculated for the two group (patients and control). A mean age (± SD) for bladder cancer was 63.6±8.3 years and mean age (± SD) 63±6.5 years for healthy controls. There was no statically different association between bladder cancer patients and control p-value > 0.05.

Table 1: Basic characteristics of study groups

Categories	Cases n=68 (mean ± SD)	Control n=38 (mean ± SD)	*p*
Age	63.6±8.3	63±6.5	0.38
weight	80.5±10.3	82.4±11.2	0.09
Height	170.7±9.5	167.9±6.9	0.07
BMI	27.8±4.2	29.3±3.9	0.06

Male was more frequent to have bladder cancer than female (75% of individuals were male) Table 2. The highest number and percentage of patients with bladder cancer were found to be at the age of>60 years which is showed in (table 2). Smoker individual showed a high risk of bladder cancer comparing to non-smoker group OR (95% CI) 2.51 (1.09-5.79) *p=0.03. Bladder cancer Patients were grouped according to the stage of cancer to 3 group (Ta, T1, T2). In this study T1 was the highest frequent stage among the three stages showed in the Table (2).

Table 2: Frequency distributions of selected variables between the bladder cancer cases and cancer-free controls

		Cases (n = 62)		Controls (n = 38)			
Variables		Count	N%	Count	N%	OR (95% CI)	*p*†
Sex	Female	15	24.2%	10	26.3%	1.00	-
	Male	47	75.8%	28	73.7%	1.11 (0.44-2.82)	0.81
Age group (years)	>60	39	62.9%	26	68.4%	1.00	-
	<=60	23	37.1%	12	31.6%	1.2 (0.54-3.00)	0.57
Smoking status	Never-Smoker	19	30.6%	20	52.6%	1.00	-
	Ever-Smoker	43	69.4%	18	47.4%	2.51 (1.09-5.79)	0.03*
Cancer Stage	Ta	17	27.4%	-	-	-	-
	T1	26	41.9%	-	-	-	-
	T2	19	30.6%	-	-	-	-

Genotypes and Allele Frequencies for XPC rs2228000

XPC rs2228000 polymorphism distribution and allele frequencies in the cases and bladder cancer groups and the results of Hardy– Weinberg equilibrium are shown in table 3 . The polymorphic allele frequency of the XPC rs2228000 in bladder cancer patients was higher than in control (0.22, 0.09) respectively. The polymorphic TT genotype in the bladder cancer group was 3.2% of total bladder cancer patients, whereas no TT genotype was observed in the control group. However, both bladder cancer and control group was in Hardy– Weinberg equilibrium p-value >0.05 for the XPC rs2228000 polymorphism.

Table 3: Genotypes and Allele frequency of XPC rs2228000 among bladder cancer and control.

XPC rs2228000	Genotype, n (%)			Allele frequency		(HWE)
	CC	CT	TT	p	q	*p-value*
Bladder Cancer	37 (59.7)	23 (37.1)	2 (3.2)	0.78	0.22	0.48
Control	31 (81.6)	7 (18.4)	0 (0)	0.91	0.09	0.53

Comparison of XPC rs2228000 Polymorphism

Odds ratios were calculated by taking the homozygous wild type (CC) as reference genotype and comparing the rest genotypes

with it (heterozygous CT genotype, homozygous polymorphic genotype TT genotype, and CT+TT) as shown in Table 4. Heterozygous genotype showed a significant increase in bladder cancer risk OR (95% CI) = 2.75 (1.0-7.2), *p value<0.05. However, no significant association was seen in the Study subjects who carried the TT genotype p=0.36. Similar statically significant bladder cancer risk increase was observed in (CT+TT) when compared with the wild genotype as reference OR (95% CI) = 2.9 (1.14-7.8) *p=0.02. Polymorphic T allele of the XPC rs2228000 polymorphism showed a significant increase in bladder cancer risk when compared with the wildtype allele C genotype, OR (95% CI) = 2.7 (1.13-6.65), *p=0.02.

Table 4: Distribution/genotyping of XPC rs2228000 polymorphism in 68 Bladder Cancer patients and 38 cancer-free controls

	Cases (n = 68)		Controls (n = 38)			
XPC rs2228000	Count	N %	Count	N %	OR (95% CI)	p
CC	37	59.7%	31	81.6%	1.00	-
CT	23	37.1%	7	18.4%	2.75 (1.0-7.2)	0.04*
TT	2	3.2%	0	0.0%	4.2 (0.19-90.7)	0.36
CT+TT	25	40.3%	7	18.4%	2.9 (1.14-7.8)	0.02*
C	97	78.25%	69	90.8%	1.00	-
T	27	21.75%	7	9.2%	2.7 (1.13-6.65)	0.02*

Association of XPC rs2228000 Polymorphism with Smoking Status

The combined effect of XPC rs2228000 polymorphism and cigarette smoking was measure by the wildtype allele genotype in never-smoker individual as reference genotype. Polymorphic allele T genotype of the XPC rs2228000 individual showed non-significant association bladder cancer risk among in non-smoker individual OR (95% CI) = 5.9 (0.65-53.14), p=0.11. For smoker individual, Both T and C allele showed a significant increase in bladder cancer risk p-value was (**p=0.004). However, the Odd ratio of the T allele was about double that of C allele (2.5, 4.5).

Table 5: Impact of Smoking on XPC rs2228000 Allele polymorphism in cases and controls

Smoking status	Genotype	Count	n %	Count	n %	OR (95% CI)	p
non-smoker	G	33	86.8%	39	97.5%	1.00	-
	T	5	13.2%	1	2.5%	5.9 (0.65-53.14)	0.11
smoker	G	64	74.4%	30	83.3%	2.5 (1.3-4.7)	0.004**
	T	22	25.6%	6	16.7%	4.3 (1.48-33.25)	0.004**

Association XPC rs2228000 genotypes with bladder cancer stage

Patients were stratified into three Categories according to the stage of bladder cancer (low stage Ta, medium T1, higher stage T2). The odds ratio was measured by comparing the three-stage genotypes with the control genotypes study as shown in table 6. The XPC rs2228000 CT+TT genotype showed a highly significant increase for Ta and T1 (OR=3.93, *p=0.03; OR=3.7, *p=0.02) respectively, whereas there was no significant association for the CT+TT genotype and T2 p=0.81. T allele of the XPC rs2228000 showed a statically significant increased risk of bladder cancer for the T1 stage (**p=0.005). However, no significant association was observed in T allele when compared with the wildtype C genotype of the XPC rs2228000 for the T2 and Ta (p>0.05).

Table 6: Association of XPC rs2228000 polymorphism with tumor stage categories

	Control N (%)	Bladder Cancer Stage N (%)			(a-b)			(a-c)			(a-d)		
XPC rs2228000	(a)	Ta(b)	T1(c)	T2+(d)	OR	95 % CI	P	OR	95 % CI	p	OR	95 % CI	p
CC	31 (81.6)	9 (52.9)	13 (50.0)	15 (78.9)	1.00								
CT+TT	7 (18.4)	8 (47.1)	11 (42.3)	4 (21.1)	3.93	1.12-13.8	0.03*	3.7	1.18-11.8	0.02*	1.18	0.29-4.6	0.81
C	69 (90.8)	26 (76.5)	37 (71.2)	34 (89.5)	1.00								
T	7 (9.2)	8 (23.5)	15 (28.8)	4 (10.5)	3.0	0.9-9.2	0.05	3.9	1.49-10.6	0.005**	1.15	0.31-4.2	0.82

Discussion

The XPC gene is responsible for the encoding of a protein which involved in the DNA nucleotide excision repair (NER) by recognizing DNA damage and is involved in the repairing of bulky DNA adducts formed by carcinogenic metabolites and oxidative DNA damage, which known bladder cancer risk factors [23].

The association between XPC polymorphisms and bladder cancer susceptibility has been studied extensively, but the results have been inconsistent [24]. A potential rationale behind these gene-cancer risk associations is that these genetic variants may result in alterations in phenotypes [25].

In this study, the genotypes and Allele frequencies of XPC rs2228000 polymorphism and the risk of bladder cancer has been investigated. Both individuals (bladder cancer and control) were in Hardy– Weinberg equilibrium which made them suitable for this genetic study. The q allele frequency of the XPC rs2228000 was 0.22 which higher in the bladder cancer group when compared to the q allele carrying by the cancer-free control group which is equal to 0.09. A previous study showed that the XPC rs2228000 polymorphic q allele is higher in the bladder cancer group and equal to 0.34 among Chinese population [26].

Furthermore, the nearest q allele frequency for XPC rs2228000 polymorphisms was among Europe population which is equal to 0.26 in bladder cancer patient [27]. This result is supported by the finding of the XPC rs2228000 q allele elevation among bladder cancer Patient. Also, Comparison of XPC rs2228000 genotyping and increasing of bladder cancer risk was made. In the present study, it has been found that heterozygous genotype of XPC rs2228000 polymorphism had a significant increase in bladder cancer risk while no significant was found in the homo-polymorphic genotype but OR was high and equal to 4.2.

However, highly significant was found in (CT+TT) genotype when compared to the wild-type genotype. Small group number of the TT genotype could be the reason why the polymorphic individual did not show a significant association. Furthermore, the T allele of XPC rs2228000 polymorphism showed a highly significant association in increasing bladder cancer risk when compared to the wild-type C allele. In contrast, Single nucleotide polymorphism analysis revealed a strong association XPC rs2228000 polymorphism with increasing bladder cancer risk, supporting the previous findings on the various ethnic populations [28, 29]. Also, Previous a meta-analysis study observed a significant correlation of XPC rs2228000 with bladder cancer risk in Europeans, Indians, and Chines but not in Americans population [27].

Still, a few studies have reported that Ala499Val substitution is not related to UBC risk [26, 30]. However, XPC rs2228000 polymorphism has appeared to be a substantial risk factor for cancer as evidenced by some recent studies on various cancers [22].

Recently, Ala499Val (rs2228000) in exon 8 polymorphism in intron 9, have been associated with an increased risk of many human malignancies such as ovarian, colorectal cancer, cataract, pargets disease and lung cancer [19, 31-33]. XPC rs2228000 change alanine to valine in the location of 499, hints valine has an isopropyl group where alanine has a methyl group, this amino acid changing could affect the structural and functional of the XPC protein and may reduce its activity.

Cigarette smoking is a well-ascertained risk factor for bladder cancer [34, 35]. As shown in, it has been found that cigarette smoking was associated with overall bladder cancer risk OR=2.51. Similarly, a recent study showed that cigarette smoking was associated with overall bladder cancer risk (OR, 2.48) [26]. However, there is wide variability in individual responses to cigarette smoking. For example, heavy smoking is considered a high-risk factor for bladder cancer, but only a small percentage of heavy smokers develop this disease.

This suggests that some people may be hyper-susceptible and that this is potentially associated with genetic factors. Recent molecular biological studies demonstrated that the risk of bladder cancer due to cigarette smoking is precisely linked to genetic markers that were detected using microarray analysis or the single-nucleotide polymorphism (SNP) method [15, 36, 37].

In the present study, smoker individual, carrying the polymorphic T allele showed a highly significant increase in bladder cancer risk OR was (4.3).

Also, the C allele showed lower significant risk in smoker individual OR=2.5. This finding proves that cumulative of a genetic and occupational factor could highly increase bladder cancer risk more than only an occupational factor.

The mechanisms underlying the noted gene-environment synergy persist to be elucidated. One could hypothesize of the XPC rs2228000 gene affect the damage recognition of smoking-induced DNA bulky adducts, in turn leading to more unrepaired DNA damage and higher genomics mutagenesis. Using logistic regression, it has been found a statistically significant increasing trend of bladder cancer risk in (CT+TT) genotype of the XPC rs2228000 polymorphism for both of Ta and T1 (OR=3.93, p=0.03; OR=3.7, p=0.02) respectively.

However, no significant association for the CT+TT genotype and the higher stage T2.Also, the same significant association was found when comparing the polymorphic allele T with the wild-type C allele genotype for the T1 (p=0.005) and slightly significant with the Ta (p=0.05). However, no significant association was found with the T2 Stage of the bladder cancer. Urinary bladder cancer has been well-documented that the malignancy and progression are associated with multiple gene defects or mutations [38-40]. In summary, the current study observed that the XPC rs2228000 polymorphism independently increased the susceptibility of bladder cancer.

More importantly, the combined influences of smoking and mutant gene enhance the formation of bladder cancer tumor. Also, it has been found that the rate of developing and prognosis of the disease is profoundly affected by the mutation of the XPC rs2228000 gene which made the genetic marker powerful in the diagnosis and monitoring Bladder cancer tumors. Cohort-study and further structural-functional analysis are needed to evaluate the biological mechanism of this polymorphism XPC rs2228000 and the bladder cancer risk.

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