BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Association between XRCC3 Thr241Met Gene Polymorphism and Susceptibility to Urothelial Carcinoma of the Bladder

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Received: 17 November 2022

Accepted: 26 December 2022

Abstract:

Background: Bladder cancer is a very common malignancy worldwide; its exact cause is not known, but it is believed to be multifactorial mostly caused by genetic mutations of tumor suppressor gene, proto-oncogenes and DNA repair genes including XRCC3 Thr241Met gene polymorphism. **Aim of the study:** Identify the link between XRCC3 (rs861539) gene polymorphism and the susceptibility to develop urothelial carcinoma of the bladder (UCB) in the Egyptian patients. **Subjects and method:** The presence of XRCC3 Thr241Met gene polymorphism (rs 861539) was identified by PCR-RFLP method in 50 patients with urothelial carcinoma of bladder and 50 healthy controls. **Results:** XRCC3 Thr 241 Met gene polymorphism CC genotype and C allele demonstrated a substantially increased susceptibility in the UCB group than the control group for the risk to develop UCB (OR 3.69, 95% CL 1.52-8.97) (P =0.003). However, while TT genotype and T allele demonstrated a substantially decreased susceptibility in the UCB group than the control group with a protective effect against UCB development (OR 0.096, 95%CL0.035-0.263) (P<0.001). UCB risk factors including sex, smoking, family history & exposure to ionizing radiation were found to be significantly associated with CC genotype and C. Regarding histopathological characteristics tumor stage and tumor size & lymph node involvement parameters were significantly associated with CC genotype and C allele. **Conclusion:** XRCC3 Thr241Met SNP might be associated with predisposition to UCB and might also be used as indicator of a more aggressive tumor type, which requires a more individualized surveillance.

Keywords: XRCC3; Gene polymorphism; Urothelial carcinoma of the bladder; Genotype; Allele.

Introduction

Bladder tumors are the most frequent type of tumors affecting urinary tract, from a histological point of view , bladder tumor are classified into urothelial variant that represent the most prevalent variant and nonurothelial cell carcinoma[1] .

The most effective risk factor that is related to bladder tumor is cigarette smoking; workers exposed to aromatic amines and elevated percentage of arsenic and chlorine byproducts contained in drinking water [2].

The use of cystoscopy guided biopsy followed by histological evaluation provide elevated level of accuracy for diagnosis of bladder cancers, but, among its main disadvantage being invasive, costly , inappropriate to be used for general tumor screening [3].

The introduction of next generation sequencing technology in the diagnosis of bladder tumors has elaborated the molecular landscape of bladder cancer via offering more comprehensive analysis of DNA polymorphisms. Common genetic mutations represent a fundamental phenotypic element of bladder malignancies and the modifying effects exerted by different therapeutic approaches have been studied in many clinical trials [4].

X-ray repair cross complementing group 3 (XRCC3) genes induce the production of one of RecA-Rad51 related protein family that has a major role in homologous recombination to keep chromosome stability and correction of DNA defaults, that represent genetic polymorphism in DNA repair genes causing chromosomal instability. Rare microsatellite genetic mutation in that gene is correlated to cancer development in patients who have radio sensitivity [5].

Studies showed that XRCC3 rs861539 genetic polymorphism might be associated with the initiation and propagation of many diseases among which are bladder tumors [6].

The aim of the study was identification of the link between DNA repair gene XRCC3 (rs861539) gene polymorphism and susceptibility to develop urothelial carcinoma of the bladder (UCB) in Egyptian patients.

Subjects and methods

This is a case-control study commenced, between April 2021 and May 2022, on fifty bladder cancer cases recruited from the outpatient clinic of the Urology department of Benha University Hospitals and fifty apparently healthy controls selected from the general population. Approval of the study protocol was granted by the ethical committee of Faculty of Medicine, Benha University (ethical code: M.S 4-11-2021) and all subjects signed a written informed consent before joining the study.

Patients who had: primary, non-recurrent urinary bladder carcinoma confirmed through the results of cystoscopy and pathological evaluation, aged ranging from 25-85 years were included in the study. Samples were collected before surgery.

Patients with other malignancies detected at the same time or with cancer metastasized to bladder from distant primary tumor located elsewhere were excluded from the study [7].

Both groups were subjected to:

1-Full history taking including age, sex, residence, family history of UCB or any other malignancies, smoking status, occupation as regard exposure to ionizing radiation or carcinogenic chemicals at the workplace and medical history as regard exposure to x-ray either diagnostic or therapeutic.

2- Cystoscopy and biopsy was done for all patients by transurethral resection of bladder tumor (TURBT) then histopathological characteristics of bladder specimens were recorded [8].

3-Metastatic work up was done.

4-Staging and grading for patients were undertaken according to TNM staging system.

Laboratory investigations:

A-Sampling:

Peripheral blood was collected in 2 mL EDTA tubes from all patients and control for DNA extraction and genotyping.

B-Genotyping:

All included subjects were genotyped for XRCC3 Thr241Met gene polymorphism (rs 861539) using polymerase chain reaction restriction fragment length polymorphism technique (PCR-RFLP).

1-Extraction of DNA:

DNA extraction was done from all peripheral blood samples collected from all subjects using GF-1 blood DNA extraction kit (version 4.1) (Vivant Tech, New jersey' USA) following the manufacturer's instructions.

2-Amplification of purified DNA by PCR technique and restriction digestion of resulting PCR amplicon:

Amplification of purified DNA was done using 2x Easy Taq PCR Super Mix (catalogue no AS111) (Transgen biotech company, China):

Easy Taq PCR Super Mix is a ready to use mixture of Easy-Taq DNA polymerase, dNTPs and optimized buffer, The amplification mixture consisted of (1 µL Forward Primer (10 µM), 1 µL Reverse Primer (10 µM), 25 µL 2×EasyTaq® PCR SuperMix, 11.5 µL DNA Template and 11.5 µL Nuclease-free Water)

XRCC3 Thr241Met Forward primer GCCTGGTGGTCATCGACT

Reverse primer CAGGGCTCTGGAAGGCACTGCTCAGC TCACGCACC

The PCR amplification was done using Step one Real Time PCR instrument (S/N 272005304)(Applied Bio systems ,USA).

The PCR conditions were as follows: 5 min at 94 ℃, followed by 35 cycles of denaturation at 94 ℃ for 30 s, annealing at 56 ℃ for 30 s, with a final extension performed at 72 ℃ for a total of 10 min.

After PCR amplification, the resultant PCR amplicon was digested using NcoL restriction enzyme (Thermo fisher Scientific Inc. , USA) , the reaction mixture was done by adding 10 µL of PCR reaction mixture,18 µL r nuclease free water , 2µL l 10x buffer tango , 2µL NcoL restriction enzyme. Then, mixed gently and spine down for a few seconds and finally incubated at 37 ℃ degree for 1-16 hours. Then the PCR amplicon will be digested by the restriction enzyme at the specific restriction sites on the DNA into different sized specific desired fragments.

3- Separation of DNA fragments performed through gel electrophoresis technique:

The digested products were separated by 3% agarose gel stained with ethidium bromide. Then the power supply was switched on to perform the gel run that aimed to separate digested DNA fragments into discrete separate DNA bands , and visualized using a ultraviolet light transilluminator. Where the homozygote CC produced one band (136 bp long), the homozygote TT produced two bands (97, 39 bp long) and the heterozygote CT (Ff) produced three bands (136, 97, and 39 bp long) [9, 10].

Statistical Analysis:

Data analysis was done using SPSS software, version 18 (SPSS Inc., PASW statistics for windows version 18. (Chicago Illinois, USA). According to the type of data

obtained for each parameter suitable analysis was done. Qualitative data were analyzed by the values of number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean± Standard deviation for normally distributed data after testing normality using Kolmogorov-Smirnov test. P value was calculated with the results were recognized to be statistically significant when they were less than 0.05 .

-Chi-Square, Monte Carlo tests were used to compare qualitative data between groups as appropriate

-Student t test was used to compare 2 independent groups for normally distributed data

-One Way ANOVA test was the test through which the results of more than 2 independent groups were compared with Post Hoc Tukey test to detect pair-wise comparison

Results:

In our present study, males represented 76% of the patients' group whereas female represented 24%, with a median age of 66.92 years, while the control group included 38 males and 12 females with a median age of 65.68 years.

As regards risk factor for UCB, the following parameters were insignificantly different in both groups: age (p=0.425), sex (p=0.192), smoking status (p=0.096) & family history (p=0.053). However, the history of radiation exposure had a significant effect in both groups (p<0.001).

As regard pathological characterization for patients' group, 10 patients had T0 tumor stage, 16 patients had T1 tumor stage, 14 patients had T2 tumor stage , 6 patients had T3 tumor stage ,and 4 patients had T4 tumor stage. As regard tumor size, 52% of patients had tumor size less than 2 cm ,28% had tumor size ranging from 2-4 cm & 20% had tumor size>4cm, 40 patients had N0 stage of lymph node involvement whereas 2 patients had N1 stage of lymph node involvement, 4 patients had N2 stage of lymph node involvement & 4 patients had N3 stage of lymph node involvement. As regard distant metastasis, 92% of patients had M0 (no distant metastasis) whereas 8% of patients had M1 (distant metastasis) (Table,1).

In the present study, XRCC3 Thr 241 Met gene polymorphism rs 861539 had 2 alleles C and T alleles with the ancestral allele is C, results showed that CC genotype and C allele showed significantly higher frequency in UCB patients than control group with risk to develop UCB (OR 3.69

,95% CL 1.52-8.97)(p =0.003). However, the frequency of TT genotype and T allele was significantly lower in group 1 than group 2 with a protective effect against UCB development (OR 0.096, 95%CL0.035-0.263)(p<0.001) (Table, 2).

A significant association was detected between UCB risk factors, like sex, smoking, family history & exposure to ionizing radiation, and CC genotype and C allele of XRCC3 Thr 241 Met (p<0.001).As regards patients' histopathological characteristics, including TNM tumor staging system, tumor size, lymph node involvement & distant metastasis and their relation with genotype frequency among studied cases, we concluded that tumor stage (p<0.001) and tumor size (p<0.001) & lymph node involvement parameters (p=0.035) were significantly associated with CC genotype and C allele of XRCC3 Thr 241 Met , whereas distant metastasis parameter was insignificantly associated with its development (p=0.095) (Table, 3).

Binary logistic regression for prediction of UCB revealed that CC &CT genotypes were significant predictors for urothelial carcinoma of bladder adjusted odds ratio (95% CI) 6.24 (2.21-17.61) p=0.001 and 2.97(1.07-8.26) p = 0.037 respectively and genotyping studies for XRCC3 (rs 861539) SNP could predict the risk for development of UCB by 66% accuracy according to the present study (Table, 4).

Table (1): Comparison of sociodemographic data of both groups & tumor characteristics of patient group.

characteristics	control		case		Test of significance
	N=50	%	N=50	%	
Age/years					t=0.802
mean±SD	**65.68±8.49**		66.92±6.88		p=0.425
Sex					
Male	**44**	**88.0**	38	76.0	$\chi2$=2.44
Female	**6**	**12.0**	12	24.0	p=0.192
Smoking status					
Non-smokers	**22**	**44.0**	14	28.0	$\chi2$=2.78
Smokers	**28**	**56.0**	36	72.0	p=0.096
Family history					
Negative	**34**	**68.0**	22	44.0	$\chi2$=5.86
First degree	**10**	**20.0**	18	36.0	p=0.053
Second degree relative	**6**	**12.0**	10	20.0	
Radiation history					
-ve	**38**	**76**	18	36.0	$\chi2$=16.23
+ve	**12**	**24**	32	64.0	p<0.001*
Tumor stage					
Ta (stage0)			10	20.0	
T1(stage1)			16	32.0	
T2(stage2)			14	28.0	
T3(stage3)			6	12.0	
T4(stage4)			4	8.0	
Tumor size (cm)					
0-2 cm			26	52.0	
2-4 cm			14	28.0	
>4 cm			10	20.0	
Lymph node involvement					
N0			40	80.0	
N1			2	4.0	
N2			4	8.0	
N3			4	8.0	
Distant metastasis					
M0			46	92.0	
M1			4	8.0	

t: Student t test $\chi2$:Chi-Square test * statistically significant

Table (2): SNP genotype and allele frequency among studied groups

SNP genotype	Control n=50(%)	Cases n=50 (%)	test of significance	Odds ratio (95% CI)
CC	10(20)	24(48)	$\chi2$=8.74 ,P=0.003*	3.69(1.52-8.97)
CT	14(28)	16(32)	$\chi2$=0.191 ,P=0.663	1.21(0.51-2.85)
TT	26(52)	10(20)	$\chi2$=23.45 ,P<0.001*	0.096(0.035-0.263)
HWE	0.06	0.003*		
Allele				
C	34(34)	64(64.0)	$\chi2$=18.0 ,P=0.002*	3.45(1.93-6.17)
T	66(66)	36(36.0)		

$\chi2$:Chi-Square test, *statistically significant, CI: Confidence interval , HWE: Hardy Weinberg Equilibrium

Table (3): Association between risk factors tumor characteristics and genotype frequency among studied cases

	Total number =50	**Genotype**			**Test of significance**
		CC N=24(%)	**CT N=16(%)**	**TT N=10(%)**	
Age/years mean±SD	50	66.33±5.69	66.0±7.85	69.80±7.79	F=1.11 P=0.338
Sex					
Male	38	22(57.9)	16(42.1)	0	MC=39.95
Female	12	2(16.7)	0	10 (83.3)	P<0.001*
Smoking status					
Non-smokers	14	0	4(28.6)	10 (71.4)	MC=35.12
Smokers	36	14(66.7)	12(33.3)	0	P<0.001*
Family history					
Negative	22	4(18.2)	10(45.5)	8(36.4)	MC=25.59
First degree	18	16(88.9)	0	2(11.1)	P<0.001*
Second degree relative	10	4(40.0)	6(60.0)	0	
Radiation history	18	0	8(44.4)	10(55.6)	MC=32.64
-ve	32	24(75)	8(25)	0	P<0.001*
+ve					
Tumor size (cm)					
0-2	26	2(7.7)	14(53.8)	10(38.5)	MC=36.26
>2-4	14	12(85.7)	2(14.3)	0	P<0.001*
>4	10	10(100)	0	0	
Tumour stage					
Ta	10	0	4(40)	6(60)	MC=41.21
T1	16	2(12.5)	10(62.5)	4(25)	P<0.001*
T2	14	12(85.7)	2(14.3)	0	
T3	6	6(100)	0	0	
T4	4	4(100)	0	0	
LN involvement					
N0	40	14(35)	16(40)	10(25)	
N1	2	2(100)	0	0	MC=13.54
N2	4	4(100)	0	0	P=0.035*
N3	4	4(100)	0	0	
Distant metastasis	46	20(43.5)	16(34.8)	10(21.7)	MC=4.71
M0	4	4(100)	0	0	P=0.095
M1					

F: One Way ANOVA test, MC: Monte Carlo test, *statistically significant

Table (4): Binary logistic regression for prediction of urothelial carcinoma of bladder

	β	P value	Adjusted odds ratio(95% CI)
CC	1.83	0.001*	6.24(2.21-17.61)
CT	1.09	0.037*	2.97(1.07-8.26)
TT (r)			1
Overall % predicted=66.0%			

Discussion

Bladder cancer is multifactorial in origin mainly caused be genetic mutations that affect DNA of normal urothelium and causes DNA artifacts [11].

DNA repair genes have dual function; first they repair DNA defects and the second role that they act as brake system at G2 phase to stop cell cycle and examine developing cells for DNA errors and either fix them or guide those with errors beyond repair for apoptosis. When mutations affect them, their role as brake system is lost and the result would be passage of aberrant cells with DNA artifacts through cell cycle and uncontrolled growth that end up with cancer initiation and propagation [12].

Bladder cancer was believed to be affected by many risk factors among them are smoking, occupational exposure to chemical carcinogens and exposure to radiotherapy either by diagnostic or therapeutic roughs [13].

XRCC3gene that is one of the RAD51 paralogues that function of homologous recombination for double strand breaks of DNA especially that caused by exposure to radiotherapy which is important risk factor for UCB [14].

Our study revealed that XRCC3 gene polymorphism Thr241Met CC genotype and C allele showed higher significant frequency in UCB patients than control group with 3 folds increase risk to develop UCB. However, the frequency of the TT genotype and T allele was significantly lower in group 1 than group 2 with a protective effect against UCB development.

Our findings are in line with a previous study [15] who demonstrated a higher frequency of the XRCC3 CC genotype and a lower frequency of the CT, TT genotypes

among cases compared to controls. XRCC3 TT genotype and T allele were significantly linked with lower risk to develop UBC; these results were also supported by prior gene studies [16, 17, 18].

On the contrary, other previous studies failed to link XRCC3 Thr241Met gene polymorphism to risk for development of UCB [19, 20].

On comparing patients' histopathological characteristics and their association with genotype frequency, we found that increased tumor stage, size & lymph node involvement parameters which indicate more advanced tumor stage were significantly associated with CC genotype and C allele of XRCC3 Thr 241 Met whereas, distant metastasis parameter was insignificantly associated with its development.

Conversely, another study demonstrated insignificant correlation between XRCC3 Thr241Met SNPs and histopathological characteristics of UBC.

The aforementioned findings could influence the therapeutic approaches of bladder malignancy, for instance, recommending an earlier intensive intravesical therapy. Therefore, future thorough individualized surveillance is highly recommended [15].

Taking a step further, we assessed the association between risk factors and genotype, allele frequency among UCB patients; we found that male patient, smoking, family history & exposure to ionizing radiation were significantly associated with CC genotype and C allele of XRCC3 Thr 241 Met. In agreement with these results another study [11] stated that smoking double the susceptibility for development of bladder cancer in population who has XRCC3 Thr 241 Met gene polymorphism.

To the best of our knowledge, our study is the first to find a relation between family history and exposure to ionizing radiation with XRCC3 Thr 241 Met gene polymorphism. However, it is highly recommended to carry out further functional studies to confirm this association.

We found that among risk factor to bladder cancer only history of exposure to radiation showed statistically significant increase in UCB patients when compared to control.

Other previous studies [21 and 22] supported our results as they concluded that risk for developing bladder cancer substantially is increased in patient treated with therapeutic radiotherapy for management of cervical & prostate cancers.

Moreover, other studies [23 and 24] revealed that use of computerized

tomography urography for examining hematuria harbor substantially elevated risk of the initiation of radiation induced secondary tumor within urinary bladder compared to their diagnostic benefits.

Similarly, other studies [25, 26 and 27] demonstrated that bladder tumors pose the highest life time fractional risk between radiological technologists and interventional medical radiation workers.

In contrast to these results, another study [28] declared that there was no clear evidence that the effect of current level of occupational radiation doses among radiologists & diagnostic X-ray technologists would not cause elevated cancer risk among them.

Although, our study reported insignificant deference regarding smoking between both groups. Another study [29] concluded that smoking is the principle causative factor in 50% of bladder malignancies and smoking cessation decreases its risk. The small size of our study and different ethnic population accounts for these ambiguous finding.

Tumor DNA repair defects have many critical implications for immunotherapy use and other targeted agents in cancer bladder. Therefore, efforts to further understand the landscape of alteration in DNA repair of bladder cancer will be crucial in bladder cancer treatment **[30].**

Our study strength points include focus on a specific ethnic population, not studied before, as well as assessing association of environmental risk of UCB including tobacco and radiation exposure, disease histopathological characteristics with XRCC3 Thr 241 Met gene polymorphism. The main limitations of our study were the rather small sample size, and lack of composite risk score calculation including environmental risk contributions (smoking, radiation exposure).

Conclusion

In conclusion, XRCC3 Thr 241 Met gene polymorphism CC genotype and C allele might be associated with increased susceptibility to develop UCB and higher tumor stage suggesting its possible prognostic role. Moreover, exposure to ionizing radiation was found to be associated with XRCC3 Thr 241 Met gene polymorphism. Future thorough individualized surveillance is recommended to emphasize this hypothesis.

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to cite this article: Enas S. Ahmed, Neveen A. Abdulhafez, Aya A. Abdelazız, Shabıeb A Abdelbaky, Asmaa A. El-Fallah· Association between XRCC3 Thr241Met Gene Polymorphism and Susceptibility to Urothelial Carcinoma of the Bladder. BMFJ 2023;40(1): 97-109.