Research Article

*CYP3A4*1B* and *CYP3A5*3* Single Nucleotide Polymorphisms in Iranian Bladder Cancer Patients

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Abstract

The environmental procarcinogen which are responsible for carcinogenesis, to form the proximate carcinogen, they require metabolic activation by drug metabolizing enzymes. The *CYP3A* subfamily enzymes play an important role in elimination of drugs. The substrates for *CYP3A4* enzyme are drugs and endogenous substances. Therefore, allelic changes in the coding regions of *CYP3A4*, increases the risk of developing cancers. *CYP3A5* is expressed polymorphically in human liver, but consistently in lung, colon, and kidney.The purpose of this study was to analysis the frequency of alteration in *CYP3A4* and *CYP3A5* genes and to determine the role of their polymorphisms in bladder cancer patients. For this reason, 113 patients with bladder cancer and same number of healthy people as control were collected from Hashemi Nezhad Hospital, Tehran, Iran. DNA was extracted and investigated by PCR-RFLP method. Data analysis was performed using SPSS software (version 19). The results indicated that there was no significant association between *CYP3A4*1B* gene polymorphism and bladder cancer risk (OR=1.83, 95% CI=0.97-3.46, P=0.062). Also no association was found with individuals carrying the *3 genotype of *CYP3A5* gene with bladder cancer in this study among studied population (OR=1. 28; 95% CI=0.68-2.41, P=0.42). No association was found between genotypes and grade and stage of disease with bladder cancer.

Key words: Bladder cancer; *CYP3A4* and *CYP3A5* gene polymorphisms; Iranian population

Introduction

Bladder cancer is one of the commonly diagnosed cancers in the world. It is the fifth most common neoplasm in western society with ~54,400 new cases in the United States per year (1). It has been estimated that in 2008, almost 386,300 new bladder cancer cases were diagnosed and that 150,200 patients succumbed to the disease (2). Urothelial cancer (transitional cell carcinoma) is the predominant histological subtype in Europe, where it accounts for 90% of all bladder cancers and three times more common in men than women (2). Carcinoma of bladder occours in old ages and it is said that 80% of the patients are in the age of 50-79 year, and incidence of this disease increases in the seventh decade of life (3). After TUR (Transurethral Resection) of superficial bladder cancer, patients are monitored by cystoscopy at regular intervals because the recurrence rate of superficial bladder cancer is up to 70% (4). Among the patients with bladder cancer, 50% of them will relapse due to metastatic disease (5,6). Patients with high grade disease require timely treatment (7,8). Tumorigenesis of bladder is a complex, multistep and multifactorial event, in which different somatic mutations, toxic carcinogenic chemicals, and inflammatory agents are implied to play a role in its ethiogenesis (9). Most of the chemicals carcinogens need to be activated before they interact with other molecules to cause

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cancer (10). Enzymes which metabolize cancer producing component can change the risk of them to initiate cancer (11). Microsomal CYPs metabolize both endogenous and exogenous substrates. The conversion of xenobiotics to more hydrophilic forms by the CYP mono-oxygenase system is particularly important in protecting the body from small molecular weight foreign compounds. Cytochrome P-450 genes incode for phase I drug metabolism enzymes which play important roles in carcinogenesis of many chemicals. Theses enzymes activate many anticancer prodrugs and also inactivate many anticancer drugs (12). The metabolism of procarcinogen to be converted to nontoxic compounds is a very complex process and starts with producing genotoxic products from xenobiotics chemicals. In the human liver and intestine, *CYP3A* is present mostly in the form of *CYP3A*4 and *CYP3A5*, which are involved in the oxidation, peroxidation, and reduction of almost 50% of drugs (13). A single nucleotide polymorphism (SNP) in these genes is probably responsible for individual differences in transcriptional and translational levels, enzyme properties, and ultimately in enzyme inactivation (14). Therefore, the polymorphisms in phase I enzymes are followed by accumulation of intracellular genotoxic components (15). The *CYP3A4* and *CYP3A5* genes are located closed to one another on chromosome 7q22.1, and are expressed in the breast, prostate and small intestine, but it is highly expressed is in the human liver (16). The most common variant in *CYP3A4*, is *CYP3A4*1B*, in the 5'UTR of 392A>G transition (17). In *CYP3A5* gene also, a SNP rs776746 (6986A>G; A allele = *CYP3A5*1* and G allele = *CYP3A5*3*) in intron 3, creates an alternative splice site in the pre-mRNA, causes the production of aberrant mRNA with a premature stop codon (18,19). This SNP leads to polymorphic expression of *CYP3A5*. *CYP3A5*3* homozygotes lack *CYP3A5* expression, but individuals with at least one *CYP3A5*1* wild type allele express *CYP3A5* (19). In people with at least one *CYP3A5*1* wild type allele, results in 2- to 3-fold higher total *CYP3A* activity in vitro (20, 21). Therefore, polymorphic expression of *CYP3A5* may account for some of the individual variation in clearance of *CYP3A* substrates.

Biochemical information suggest that these enzymes are involved in carcinogenesis. Most of the epidemiological studies have already been performed with one of these enzymes. The power of both genes polymorphisms has not yet been studied so far. In other way, CYP3A4 and CYP3A5 play a relevant biological role on different tissues, no studies have addressed whether polymorphism of these enzymes are related to bladder cancer risk or not. Therefore, we conducted a study to examine CYP3A4 and CYP3A5 enzymes on urinary bladder cancer in Iranian population. Since activation and detoxification of carcinogens are mainly influenced by the activity of detoxification enzymes, therefore, we performed this study to investigate whether polymorphisms of *CYP3A4* and *CYP3A5* genes modify the urinary bladder cancer risk in this study on Iranian population.

Materials and Methods

Subjects and DNA extraction

This case-control study was consist of 113 bladder cancer patients which were admitted to the Hashemi Nezhad Hospital, Tehran, Iran and equal number of healthy individual with no history of cancer. Informed consent was obtained from patients and control subjects.

Genomic DNA of all cases and controls was extracted from tissues and blood, using proteinase K digestion followed by phenol/chloroform extraction at pH 7.4 (22). Phenol/chloroform/isoamyl was added to the tissue and the mixture vortex for 10 secs. It was then centrifuged at 8000rpm for 5 mins at room temperature and aspirate out the top layer. The aqueous layer was then transferd into sterile 1.5-ml microcentrifuge tube and 100% Ethanol and 0.1 volume 3M sodium acetate pH 5.0 was add. Then centrifuged at maximum speed for 10 mins at room temperature, gently the supernatant was aspirated out. 150 µl of 70% Ethanol was added. The pellet was dried in air.

PCR-RFLP

forward primer was CATCAGTTAGTAGACAGATGA and the reverse primer was GGTCCAAACAGGGAAGAAATA. The reverse primer was designed to make a Ssp I restriction site where the 6789A allele is incorporated. PCR amplifications were performed in a total volume of 25 µl, comprising 2.5 µl of PCR buffer, 40 pmol/l of each primer, 0.2 mmol/l of each dNTP, 1.5U Taq DNA polymerase (Sinaclon), and 100ng of genomic DNA as a template. Amplification conditions included of denaturation at 95°C, annealing at 61°C for *CYP3A4**1B or 54°C for *CYP3A5*3* and extension at 72°C each for 1 min. The PCR products were digested with PstI (*CYP3A4*1B*) and SspI (*CYP3A5*3*) in reaction mixtures with a total volume of 20 µl for 1 h at 37 °C, after which they were separated by 3% agarose

gel electrophoresis. TAE (40 mM Tris-acetate, 1 mM EDTA) was add to the agarose-containing flask and heated until the agarose was completely dissolved. Ethidium bromide (EtBr) in a concentration of 0.5 µg/ml was added. Loading dye was mixed with DNA samples, then DNA was run on the gel electrophoresis. Measuring the intensity of absorbance of the DNA solution at wavelengths 260 nm and 280 nm was used as a measure of DNA purity by spectrophotometer. All pure sample of DNA which had a ratio of 1.8 at 260/280 were chosen for further experiments. The data were analyzed using the computer software SPSS for windows (version 19). The odds ratio (OR) and its 95% confidence interval (CI) was estimated by unconditional logistic regression as a measure of the associations between genotypes and bladder cancer.

Results

We determined the allelic frequency of the *CYP3A*4*1B and *CYP3A*5*3 in a group of 113 Iranian subjects by PCR-RFLP assays. Samples with CYP3A4 genotype gave 229, 122, and 33bp bands, whereas samples with *CYP3A*4*1B genotype presented 199, 122, 33 and 30bp bands (Fig. 1) Samples with *CYP3A5*1 genotype gave 148, 125, and 20bp bands, whereas samples with *CYP3A5*3 genotype showed 168 and 125bp bands (Fig. 2).

The variable and genotyping data are shown in tables 1 and 2 respectively. *CYP3A*4*1B allele frequencies were 17.7% for patients and 28.3% for control group. Of these 113 patients, there were twenty three carriers of the *CYP3A5*1 allele and ninety *CYP3A5*3 genotype. The frequency of the CYP3A4*1B and CYP3A5*3 variant allele in the population had ORs of 1.83 (95% CI=0.97-3.46, P=0.62) and 1.28 (95% CI=0.68-2.41, P=0.42), respectively. Our findings indicating that *CYP3A*4*1B is very rare alleles in the studied population and also an approximate 79.6% of the Iranian population in this study carrying *CYP3A5*3 genotype may appear fail to express CYP3A5 protein.

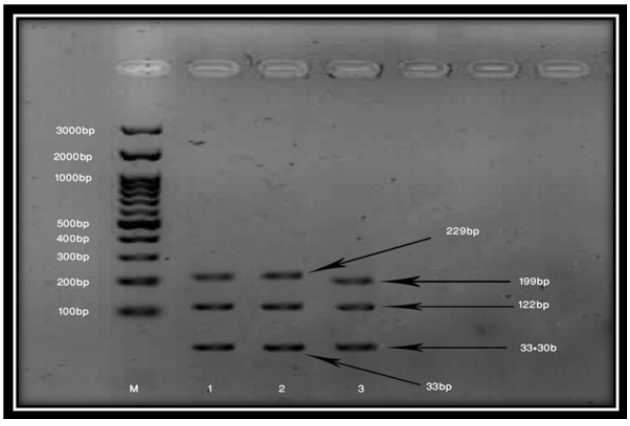

Figure 1: RFLP analysis of *CYP3A4* gene, M (Marker, 100bp), 1-2 line: wild type (229,122,33bp) and line 3: mutant (199,122,33,30bp).

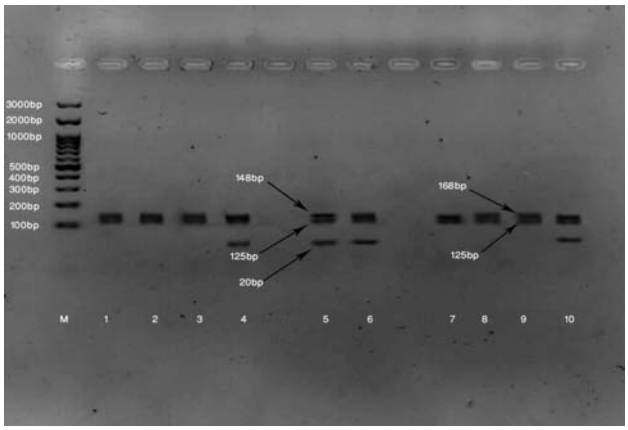

Figure 2: RFLP analysis of *CYP3A5* gene, M (Marker, 100bp), 1-3 and 7-9 lines: wild type (148,125,20bp) and line 10: mutant (168,122, 20bp).

Table 1: Distribution of allelic and genotypes frequencies among patients and controls

Genotype	Patients (%)	Controls (%)	OR (95% CI)	P-value
CYP3A4*1A	(82.3) 93	(71.7) 81	1.00	
CYP3A4*1B	(17.7) 20	(28.3) 32	1.83 (0.97-3.46)	0.062
CYP3A5*1	(20.3) 23	(24.7) 28	1.00	
CYP3A5*3	(79.6) 90	(75.2) 85	0.77 (0.41-1.45)	0.42

OR, odds ratio; CI, Confidence Interval; the P< 0.05 was considered statistically significant.

The age of the subjects ranged from 30 to 71 years (mean ± SD, 48.22 ± 9.7 years), and in control group ranged from 30-85 years (mean ± SD, 64.39 ± 10.4 years). Most of the patients were among male while among control group maximum number was female. Most of the patients 55 (48.6%) were in stage II and 67 (59.3%) of patients were pathologically well differentiated. No association was found between *CYP3A*4 and *CYP3A5* genes polymorphisms with regard to gender, age at diagnosis, tumor site or stage and grade.

Discussion

*CYP3A4*1B* results from an A to G transition in the 59 promoter region (18) and its frequency was found to be low in Iranian population (17.7%). Our finding is in agreement with other published results reporting in White (3.6%) and Hispanics populations (11.0%) (18, 22), absent in the Chinese and Japanese

Table 2: Distribution of variables among patients and controls

Variable	(%) Patients	(%) Controls
Number	113	113
Age (years)		
Mean range	30-71	30-85
Mean (±SD)	9.7 ± 48.22	10.4 ± 64.39
Sex		
Male	(85.8) 97	(45.1)51
Female	(14.1) 16	(54.8) 62
Clinical stages		
I	(31.8%) 36	
II	(48.6%) 55	
III	(19.4%) 22	
Pathological grades		
Well differentiated	(59.3%) 67	
Moderate differentiated	(0.9%) 1	
Poor differentiated	(39.8%) 45	

(18, 22) and much higher in Blacks (23, 24), 53% among African Americans, but 9% in Caucasians, and 0% in the Chinese, Malay and Indian populations, (23, 25), indicating that this is very rare allele in the Asian population. Therefore, no association was found between this gene polymorphism and bladder cancer among studied Iranian population. Rebbeck have shown that the patients with prostate cancer are more likely to have the *CYP3A4*1B* allele than normal groups and this has been reported in other studies as well (18). In a case-control study of Australian, Caucasian women also, *CYP3A4*1B* was not associated with breast cancer (OR= 0.86, 95% CI; 0.54-1.33) and ovarian cancer (OR = 1.51, 95% CI; 0.80-2.89) (26, 27). Paris et al. evaluated the frequency of *CYP3A4*1B* genotype in 174 African-American prostate cancer patients and 116 healthy controls and found the OR for *CYP3A4*1B* carriers was not significant (OR = 1.1, 95% CI; 0.6-2.1). While a study of *CYP3A*4*1B genotyping which was conducted on 84 Scottish, Caucasian men; all had a diagnosis of benign prostatic hyperplasia and had been recruited prospectively with respect to a prostate cancer diagnosis (28). In this group, inheritance of *CYP3A4*1B* was associated with the sixfold increase in risk (relative risk=6.3, 95 % CI: 2.3, 17.3) of developing prostate cancer in a period of 6–15 years. Consistent with these results, those for comparison of frequency of *CYP3A4*1B* between cases and controls showed no any associations (OR=0.9, 95% CI: 0.6-1.4 for Caucasians and OR = 1.0, 95 % CI: 0.4-2.5 for African Americans). However, when stratified by aggressively, results showed that *CYP3A4*1B* was an important risk factor for more aggressive prostate cancer in Caucasians (OR=1.9, 95 % CI: 1.0-3.6) but not for African Americans (OR=0.5, 95 % CI: 0.2-1.4) (29). In another study of a group of US girls (n = 137; 57 Hispanic, 39 African American, and 41 Caucasian) early-onset menarche, a factor for breast cancer risk, was associated with inheritance of the *CYP3A*4*1B allele (OR = 3.21, 95 % CI: 1.62-6.89) (30). In black American men, no association was observed between the rs2740574 A or G alleles, or other SNP alleles in *CYP3A*4, and the probability of developing prostate cancer (31). Overall, the data from the five prostate cancer studies described did not show a direct role of *CYP3A*4*1B in carcinogenesis of prostate (18, 25, 32, 33). There was no significant difference between Scottish Caucasian and Saudi populations with respect to the frequency of the *CYP3A4* G variant allele (P=0.16). The *CYP3A4*1B* variant was found to be common in Ghanaian population but rare in Saudi and Scottish Caucasian populations (13). The *CYP3A4*1B* variant has been found to be the major allelic variant among African origin people, but other studies did not report this variant in Chinese, Taiwanese, or Japanese (32, 34).

In contrast to CYP3A4, the CYP3A5 protein isoform is known to be expressed in only a small percentage of Caucasian individuals and this has been linked to a common transition in intron 3 of the *CYP3A5* gene (*CYP3A5*3*), which introduces a frameshift during translation and results in a truncated, nonfunctional protein (19, 20). Individuals carrying at least one *CYP3A5*1* allele express *CYP3A5* whereas subjects homozygotes for *CYP3A5*3* allele do not express *CYP3A5* protein (35). The allelic frequency of *CYP3A5**3 in the studied population (79.6%) was similar to the Chinese (77.8%), Japanese (76.8%) (P=0.86) (36), but significantly lower than Dutch Caucasians (91.7%) (P=0.006), and higher than African Americans (47.5%) (P=0.001) (37). In another case-control study on Iranian population was found that 99% of Iranian were carrier of GG genotype compared with about 70% of the Chinese and Japanese and 19% of the Caucasian population (38). No positive association between *CYP3A5*3* genotype and bladder cancer risk was found as observed among the studied population. As no statistically significant association in the allele frequencies were observed for liver, stomach and colorectal cancer patients (39). While, in a combined ethnic groups study, the genetic

association of rs776746 in white men, was indicating an increased probability of developing prostate cancer with the A allele of *CYP3A5* gene (31). The *CYP3A5*3* genotype was also positively associated with prostate cancer when data from African Americans and Caucasians were combined (OR = 2.9, 95% CI: 1.4, 6.2) (29) In another case-control study, Garsa, et al., found a dramatic interethnic variation as in Europeans, the *CYP3A5**3 variant was the predominant allele (94%), but this allele had a much lower frequency in the Africans (12%). Similarly, other study among three ethnic groups, indicated that there were marked interethnic variations in the frequencies of alleles and genotypes for the *CYP3A5**3 polymorphism among African Americans, Dutch Caucasians, and Chinese populations (17). The *CYP3A5**3 variant allele and homozygote were more frequent in Dutch Caucasians than in Chinese and much less common in African Americans (35). The frequency of *CYP3A5**3 allele in patients with therapy-related acute myeloid leukemia and myeloidsplastic syndrome was in 279 children with acute lymphoblastic leukemia, and no association of *CYP3A5**3 allele and increased risk to develop acute myeloid leukemia was observed (40). Consistent with the currently observed genotype frequency of 79.6% among Iranian population, Lee et al, (41) found that 70% to 90% of Caucasian subjects were homozygous variant for *CYP3A5**3 and thus were deficient in functionally active CYP3A5.

These results indicated that the *CYP3A5**3 frequency shows dramatic interethnic allelic variation among different populations.

Taking together the findings reported in the present study, it can be concluded that common polymorphisms of CYP3A4 and CYP3A5 enzymes with functional relevance are not significant factors in urinary bladder carcinogenesis in Iranian population. This was the first attempt to study *CYP3A* gene polymorphisms in Iranian bladder cancer patients. Larger population studies are required for a more accurate understanding of *CYP3A*4-*CYP3A*5 haplotypes.

Interethnic variation highlights the need to be analysed clinically relevant SNPs and haplotypes in a different ethnic groups. An understanding of the genetic variation that exists in various populations will aid in tailoring health care to different populations.

Conclusion

The results of our study indicate that the polymorphisms of *CYP3A*4 and *CYP3A*5 genes cannot be used as toxicological susceptibility markers in bladder cancer.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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