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REVIEW ARTICLE

Bladder cancer risk from the perspective of genetic polymorphisms in the carcinogen metabolizing enzymes

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Summary

Urinary bladder cancer is a socially significant healthcare problem. A diverse array of aromatic and heterocyclic amines, derived from the chemical and transport industry, diet, and cigarette smoke are considered carcinogens for the bladder. To exert their carcinogenic effect and to initiate the carcinogenic response, the arylamines require a metabolic activation by the host enzymes to chemically reactive compounds. The aim of this article was to review the latest and basic research developments on the role of the polymorphisms in the carcinogen metabolizing enzymes N-acetyltransferase (NAT), Glutathione S-transferases (GST), and Soluble sulfotransferases (SULT), with emphasis on the susceptibility to urinary bladder cancer. A PubMed search was conducted to identify original and review articles containing information about these polymophic variants in different populations and according to their prevalence in bladder cancer patients.

We noticed that some genotypes were found to be predisposing and some protective for bladder cancer development. The NAT2 slow genotype, together with GSTM1 null genotype facilitated the development of bladder cancer in almost all ethnic groups. The 213His allele of the SULT1A1 gene which is associated with lower enzyme activity and decreased mutagen activation was reported to protect from bladder cancer in almost all studies.

Key words: *bladder, cancer, pharmacogenetic, population, risk*

Introduction

Urinary bladder cancer is a socially significant and costly health care problem [1]. Workplace carcinogens, environmental and lifestyle factors, aging of the world population, as well as the male gender, are deemed to be risk and causative factors for it [2]. A diverse array of aromatic and heterocyclic amines, derived from the chemical and transport industry, diet, and the cigarette smoke are considered carcinogens for the bladder. The occupational exposure to arylamines in particular can raise the risk of bladder cancer as much as 40-100-fold [3]. To exert their carcinogenic effect and to initiate the carcinogenic response, arylamines require a metabolic activation by host enzymes to chemically reactive compounds. These enzymes have variable activity and their uneven distribution in the population may give rise to a genetically determined different individual susceptibility [4-6].

In this article we have reviewed the polymorphisms in the carcinogen metabolizing enzymes NAT, GST, and SULT, with emphasis on the individual and ethnic genetic susceptibility to urinary bladder cancer. We summarised 46 articles using the PubMed, MEDLINE and Google Scholar databases with the following key words: "Bladder cancer", "Genetic polymorphisms", "Carcinogen metabolizing enzymes" and "ethnic" or "population".

Our search was limited to English language and human-subject studies published between

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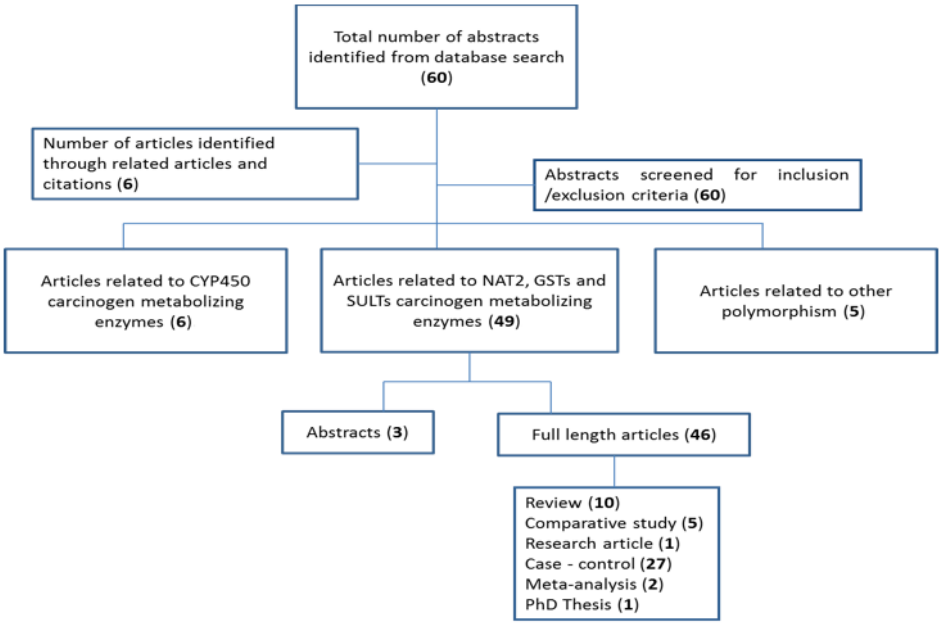

Figure 1. Flow chart of paper selection.

1976 and 2014. Figure 1 summarizes the number of studies identified, reasons for exclusion and the profile of the full-length articles included in this review.

Carcinogen metabolizing enzymes

NAT is an enzyme the activity of which leads to detoxification of aromatic amines. It is coded by two genes: *NAT1* and *NAT2* [7]. Each of them has genetic variants which encode for either rapid or slow acetylation. The *NAT 2* enzyme activity is reduced in individuals with two slow-acetylator alleles, which genotype predominates in white population [8,9]. The risk of bladder cancer morbidity in such individuals is higher than in individuals with rapid acetylation [10]. Enzymological and genetic investigations of the *acetyltransferase* gene show that it plays a role in both activation and detoxification of arylamines and their congenials. In the liver, arylamine metabolism includes two alternative pathways: N-acetylation by *NAT2* or N-hydroxylation by CYPIA2. N-acetylation by *NAT2* leads to arylamine deactivation, and formation of non-reactive compounds (Figure 2). N-hydroxylation by CYPIA2 leads to formation of the hydroxylamine. This hydroxylated form is transported to the bladder and metabolized by *NAT1* (highly expressed in bladder epithelium) to a highly reactive species that can form DNA adducts [11]. Alleles with decreased activity in the liver (NAT slow acetylators) as well as alleles with increased activity in the bladder (*NAT1* rapid acetylators) are considered to increase the carcinogenic potential of arylamines [12,13].

GSTs are metabolizing enzymes of phase II that protect normal cells by the detoxification of carcinogens, toxins, drugs, and products of the oxidative stress by glutathione conjugation [14] (Figure 3). The GST enzyme family includes 5 cytosolic isoforms GST-α (GSTA), μ(GSTM), π(GSTP), θ(GSTT), and σ(GSTS). The GSTT1, P1, and M1 isoforms are polymorphic, and particular allelic variants have been suggested to increase or decrease the risk in the development of uroepithelial malignancies [15]. It is thought that upregulation of different classes of various GST in the bladder transitional cell carcinoma (TCC) influences the TCC growth by inhibition of apoptosis and by providing a reduced cellular environment [16].

SULTs are important enzymes in the elimination of various xenobiotics, and the bioactivation of dietary and other bladder carcinogens, such as heterocyclic amines (Figure 2). A functional polymorphism in the *SULT1A1* gene (*SULT1A1** - Arg213His substitution) is deemed related with the susceptibility to a variety of cancers as well as mutagenicity following exposure to arylamines from cigarette smoke and other environmental toxins [17]. Although statistically significant associations were observed between the *SULT1A1** genotype and mammary, pulmonary, esophageal,

Table 1. Investigated odds ratio of cancer risk among people from different ethnicities, according to the NAT, GST and SULTs genotype/phenotype

First author [Ref]	*Population*	*Cases*	*Controls*	*Cancer risk - OR (95%CI)*	*Enzyme genotype/phenotype*
Hayes [24]	Chinese	38	43	Bladder cancer 0,3 (0,0-2,2)	NAT2 slow acetylator - low benzidine exposure
				0,7 (0,1-4,5)	NAT2 slow acetylator - medium benzidine exposure
				0,6 (0,1-3,5)	NAT2 slow acetylator - high benzidine exposure
Song [25]	Chinese	208	212	Bladder cancer 2,42 (1,47–3,99)	NAT2 slow acetylator
				1,64 (1,11–2,42)	GSTM1 null
				1,72 (1,00–2,95)	GSTM1/GSTT1 - double null
Kim [26]	Korean	113	221	Bladder cancer 1,81 (1,12-2,93)	GSTM1 null
				0,85 (0,54-1,35)	GSTT1 null
				6,79 (0,67- 68.82)	NAT2 slow acetylator among smokers
Lee [27]	Korean	232	165	Bladder cancer 1,6 (1,0–2,4)	GSTM1 null
				1,3 (0,9–2,0)	GSTT1 null
				2,2 (1,2–4,3)	GSTM1 null/GSTT1 null
Sobti [28]	Indian	100	76	Bladder cancer 1,00 (0,46 – 2,16)	CYP2D6 heterozygous
				2,90 (0,76–11,10)	CYP2D6 heterozygous and GSTT1 null
				2,53 (1,17–5,46)	GSTT1 null
Katoh [29]	Japanese	145	145	Bladder cancer 1,71 (1,05–2,79)	GSTM1 null
				2,62 (1,36–5,05)	GSTM1 null and GSTT1-positive
				1,25 (0,62–2,51)	GSTM1 null and GSTT1 null
Katoh [30]	Japanese	83	122	Oral cancer 1,93 (1,05-3,58)	GSTP1G genotype (GSTP A/G or GSTP G/G)
		47	122	Lung cancer 1,18 (0,52-2,58)	GSTP1G
		140	122	Gastric 1,56 (0,9-2,73)	GSTP1G
		103	122	Colon 1,58 (:0,88-2,87)	GSTP1G
		106	122	Urothelial 1,47 (0,78-2,80)	GSTP1G
Tsukino [32]	Japanese	325	325	Bladder cancer 1,37 (1,01-1,87)	GSTM1 null
				3,09 (1,69-5,63)	NAT2 slow
				1,48 (1,01-2,15), in relation of smoking	GSTM1 null
				4,28 (1,96-9,36), in relation of smoking	NAT2 slow acetylator
Ozava [18]	Japanese	166	214	Bladder cancer 2,45 (1,04-5,98)	SULT1A1*1 ((213)Arg) and NAT2 slow acetylator
				2,07 (0,48–9,84)	SULT1A1*2 ((213)His) and NAT2 slow acetylator
Hung [33]	Caucasian - Italian	201	214	Bladder cancer 0,67 (0,45–1,03)	SULT1A1 ((213)His)
Wu [22]	Taiwanese	187	308	Esophageal cancer 3,53 (2,12-5,87)	SULT1A1 ((213)His)
Roupret [34]	Caucasian - French	268	268	Urothelial cell carcinomas 2.18 (1,28-3,69)	SULT1A1*2

Continued on next page

Wang [20]	North Americans - caucasian origin	463	485	Lung cancer 1,41 (1,04 – 1,91)	SULT1A1*2
Rouissi [35]	Tunisian	125	125	Bladder cancer risk 526 (2,08 – 13,57) (among smokers)	GSTM1 wild
				8,25 (3,20-21,76)	GSTM1 null
				6,64 (2,25-20,31)	GSTT1 wild
				6 (1,44-27,01)	NAT2 rapid
				12,12 (3,06-52,4)	NAT2 intermediate
				12 (3,08-51,08)	NAT2 slow
				1,11 (0,78-1,60)	NAT1
Okkles [38]	Caucasian – Danish	254	242	1.35; (1,02 - 1.80)	NAT2 slow genotype
				1,17 (0,82-1,66)	GSTM1
				1.51; 0.89-2.55)	*NAT2* slow */GSTM1null*
Bell [39]	Caucasian Black	213 16	199 12	1,7 (1,1-2,5)	GSTMl null
Gu [42]	Caucasian	507	513	0,95 (0,72– 1,25)	NAT1*10 (homo- and heterozygous)
				1,31 (1,01–1,70)	NAT2 slow acetylator
Filiadis [43]	Caucasian - Greece	89	147	3,73 (1,52-9,13)	*NAT2* slow acetylators - 341C/341C homozygotes
				12,46 (2,36-65,89)	*NAT2* slow acetylators -. 341C/857A compound heterozygotes
Matic [44]	Caucasian Serbia	201	122	1,34 (0,82–2,20)	GSTA1 AB+BB, low GST activity
				1,23 (0,77–1,99)	GSTM1 null
				1,00 (0,59–1,70)	GSTT1 null
				3,48 (1,60–7,54)	GSTA1 AB+BB, adjusted to smoking
				3,62 (1,60–8,10)	GSTM1 null, adjusted to smoking
				2,77 (1,30–5,80)	GSTT1 null, adjusted to smoking
Taylor [45]	Whites Blacks	215 15	191 12	2,8 (1,8-4,4);	NATI*I0
Yuan [47]	North Americans	731	740	1,48 (1,19-1,83)	GSTM1 null
				2,03 (1,12-3,69)	NAT2 slow acetylator
				0,42 (0,23-0,78) women	SULT1A1*2
Zheng [49]	Caucasians, Hispanics African– Americans	351 19 14	353 18 15	0,84 0,60-1,19) men	SULT1A1*2

and urothelial cancer [18,19], there are altogether few studies on the *SULT1A1* and the results are inconsistent [18,20-22].

Polymorphic enzyme variants related to the bladder cancer susceptibility in different ethnic groups (Table 1)

The incidence of bladder cancer varies in different ethnic groups. It is highest in Southern Europe and lowest in Western Africa [23]. This could be due to the different environmental factors, as well as to different genetic predisposition in these population groups.

Asia

Many studies on the Chinese, Japanese, Korean, and Indian populations have been published. In 1993, Hayes et al. investigated the Chinese

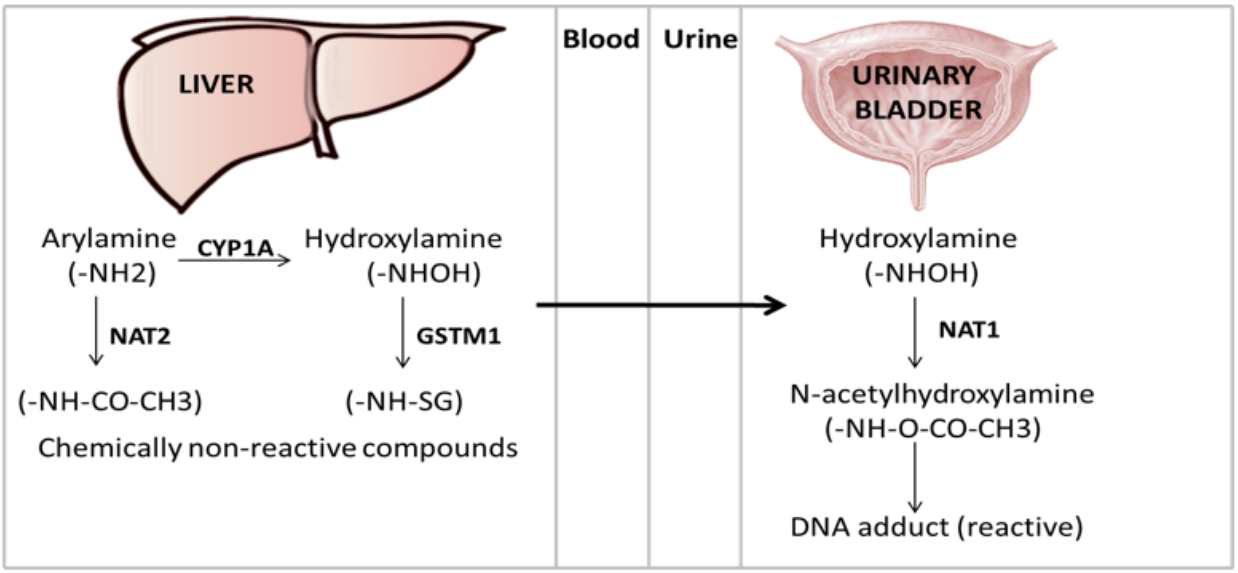

Figure 2. Simplified scheme of arylamine metabolism pathway. Arylamines are N-acetylated by NAT2 in the liver, transforming them to relatively nonreactive. Alternatively, they may be N-hydroxylated by CYPIA2, transported to the bladder, and undergo O-acetylation by NATI, to form a highly reactive species.

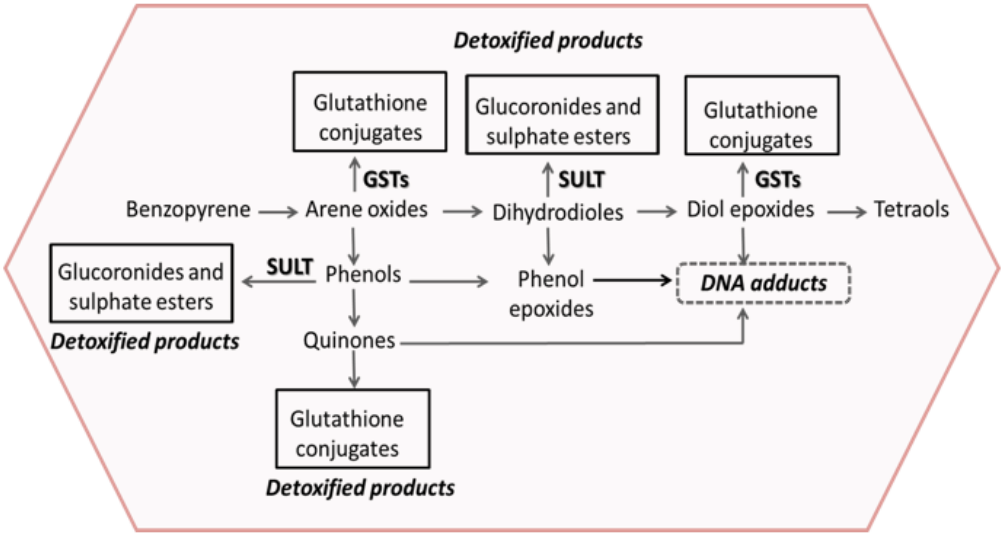

Figure 3. Simplified scheme of action of the enzymes glutathione S-transferases (GSTs) and soluble sulfotransferases (SULTs) in the detoxification of polycyclic aromatic hydrocarbons (PAH).

population occupationally exposed to benzidine and found no increase in the bladder cancer risk for the slow N-acetylation phenotype or for slow N-acetylation-associated double mutations in *NAT2* [24]. No interaction between this genotype and benzidine exposure was observed. This can be explained with the fact that benzidine is a much better substrate for *NAT1* than *NAT2* [24]. However, increased risk and a higher grade of differentiation of bladder cancer were associated with the *NAT2* slow-acetylator genotype, *GSTM1* null and *GSTM1/GSTT1* - double null alleles [25].

Moreover, among the studied P450 variants, the carriers of at least one *CYP2A6*4* allele showed a lower risk of bladder cancer development than the non-carriers. *CYP2A13* was not associated with an increased risk or unfavorable tumor characteristics [25]. In a similar study in Korean population, an increased risk for bladder cancer was found among the patients with a history of tuberculosis and bronchial asthma, carriers of a combination of rapid acetylator genotypes and either *GSTM1* null or *GSTT1* null genotypes [26] (the smoking history turned out to be insignificant). Similarly to the Chinese population, *GSTM1* null genotype was found to be a significant risk factor for bladder cancer, whereas *GSTT1* and slow acetylator genotypes were insignificant. In 2000, Kim et al. could not find any association between *GSTM1*, *GSTT1*, slow acetylator genotypes, and bladder cancer risk among smokers [26]. However in the following study performed in South Korea, a strong association was found between *GSTM1* null genotype and bladder cancer risk [27]. Another study from India indicated a 3-fold increase in the risk of developing bladder cancer in the presence of *GSTT1* null and one copy of the variant *CYP2D6* allele, while there was no association between the heterozygous genotype of the *CYP2D6* gene with risk of bladder cancer. Subjects with the *GSTM1* null genotype had a slightly significant association with the bladder cancer risk which increased to 2,5-fold in the presence of the *GSTT1* null genotype [28].

The opposite was reported in Japanese patients, where urothelial cancer risk was increased due to the *GSTM1* null genotype, especially among smokers. The individuals with a combination of *GSTM1* null genotype and *GSTT1* positive genotype had a 2-fold risk compared with the *GSTT1* null genotype [29].

Another GST variant - *GSTP1* - is involved in the inactivation of cigarette smoke carcinogens. Sequence variation in the gene may alter the bladder cancer susceptibility. The study of the *GSTP1* AG polymorphism (which reduces the catalytic activity of the GSTP1 enzyme) in Japanese patients with different types of smoking-related cancers, showed no difference between smoking patients and controled individuals for the frequency of the *GSTP1* AG polymorphism for any cancer [30]. In 2007, Kellen et al. investigated the association between *GSTP1* Ile105Val and bladder cancer risk. *GSTP1* Ile105Val appeared to be associated with a modest increase in the risk of bladder cancer and the association turned to be the strongest in Asian countries [31] .

Unlike the previous described studies, Tsukino et al. (2004) showed that the *GSTM1* null and *NAT2* intermediate or slow genotype are associated with increased risk of urothelial cancer in relation to smoking amount [32]. In this case – control study in Japanese population, the frequencies of *GSTM1* null and *NAT2* slow genotypes were found to be significantly higher in the cases compared to controls [32].

In 2002, Ozawa et al. performed combined analyses of different alleles of carcinogenic aromatic amine-activating phase II enzymes [18]. The highest risk for urothelial cancer was shown for the combination of *SULT1A1* and *NAT2* slow genotypes. Additionally, the wild-type *SULT1A1* ((213) Arg) alleles were slightly overrepresented in both smoking and nonsmoking urothelial cancer patients compared to *SULT1A1*2* ((213) His) allele, which is in agreement with the study of Hung et al. [33]. However *SULT1A1* ((213) His) allele was associated with statistically significantly increased risks of esophageal cancer in Taiwan, lung cancer in USA , and upper urinary tract urothelial cell carcinomas in French patients [20,22,34].

Africa

In the Tunisian population it was found that *NAT2* slow acetylator individuals carrying wild-type *GSTT1* or *GSTM1* null genotypes had a higher risk for bladder cancer. This effect increased for smokers, harboring slow or an intermediate *NAT2*, wild-type *GSTT1*, and *GSTM1* null genotypes, compared to non-smokers carrying rapid *NAT2*, wild-type *GSTM1* and *GSTT1* null genotypes. Among the *NAT2* slow acetylator genotype, the *NAT2*5/*7* diplotype was reported to have a highest risk for bladder cancer development [35].

Europe

NAT2 enzyme activity is reduced in about 50% of Europeans, and in 1982 Cartwright et al. suggested that acetylator status could be used to identify susceptible individuals in potentially hazardous occupations [36].

This finding was comfirmed by Risch et al. in 1995 who reported an excess of slow acetylators in bladder cancer patients with a history of smoking or occupational exposure to aromatic amines [37].

Lower et al. in 1979 examined the possible correlations between N-acetyltransferase pheno-

type and urinary bladder cancer risk in rural and urban populations. Urban urinary bladder cancer patients from Denmark displayed a 13% excess of individuals with the slow acetylator phenotype when compared to a control group [10]. In rural population from Sweden, where bladder cancer incidence is lower than in urban, no difference in slow acetylator distribution was observed between bladder cancer and control populations. The latter was thought to be due to relative lack of involvement of arylamines in the etiology of rural bladder cancer. In 1997, Okkles et al. reported that *NAT1* and *NAT2* allele frequencies were not significantly different between the cases and controls in a Danish population [38]. An association between the *NAT2* slow genotype and bladder cancer risk existed only among smokers. In this group a higher frequency of the mutant NAT2 allele and a corresponding lower frequency of the wild-type *NAT2* allele was shown among the cases compared with the controls [38]. Although about 50% of Caucasians have deletion of the two copies of the gene coding for *GSTM1* (*GSTM1* 0/0 genotype) and have been shown to be at higher risk of bladder cancer, Okkles et al. (1997) found no association of the *NAT1* and *GSTM1* genotypes with bladder cancer risk among smokers [38-40]. Furthermore, they thought that combinations of the *NAT2* and *GSTM1* genotypes were not risk factors of bladder cancer, and normal *NAT1*/fast *NAT2* seems to be a protective genotype combination cornpared with all other *NAT1*/*NAT2* genotype combinations.

One of the *NAT1* allele variants - *NAT1*10* - is thought to be a rapid acetylator allele associated with an increase in the N-acetyltransferase activity in bladder, colon, liver, and erythrocytes, and an increase of carcinogen-DNA binding adduct in the urinary bladder. *NAT1*10* allele is responsible for the higher levels of metabolic activation of N-hydroxy-aromatic amines in human urinary bladder cytosol and human uroepithelial cells [41]. However, in the study of Gu et al. (2005) with 507 Caucasian bladder cancer patients and 513 age-, gender-, and ethnicity-matched healthy controls, no significant association between *NAT1*10* allele and bladder cancer risk was found [42]. According to the *NAT2* slow acetylator genotypes their results confirmed the studies of Cartwright et al. (1982), Risch et al. (1995) and Okkles et al. (1997) that these genotypes are risk factors for bladder cancer, particularly in smokers and older individuals [36-38]. Heavy smokers with *NAT2* slow acetylator genotypes showed an over 6-fold increase in bladder cancer risk compared to smokers with *NAT2* rapid acetylator genotypes [42].

In a case-control study that included 89 TCC Greek patients and 147 controls, a higher frequency of slow acetylator genotypes was found in the patient group. Among them, 341C/341C homozygotes and 341C/857A compound heterozygotes had the most excessive risk for bladder cancer. The 341C/341C homozygotes were reported to have a higher risk for more aggressive disease [43]. In another Mediterranean region (Spain) Garsia-Closas et al. (2005) showed that the *GSTM1* null genotype increased the overall risk of bladder cancer, and the *NAT2* slow-acetylator genotype increased the risk, particularly among cigarette smokers [8]. These polymorphisms could account for up to 31% of bladder cancers because of their high prevalence, although the relative risks were modest.

In 2013, Matic et al. found no significant difference in the distributions of *GSTM1*, *GSTT1*, *GSTA1*, and *GSTP1* gene variants between patients and controls in their hospital-based case-control study [44]. Significant association with bladder cancer risk was found for lower activity *GSTA1* AB/BB and *GSTM* null genotype in smokers compared to *GSTA1* AA and *GSTM1* active non-smokers.

Hung et al. in their study showed that 213His allele of the *SULT1A1* gene was associated with lower enzyme activity and decreased mutagen activation, that might result in a protective effect on bladder carcinogenesis [33]. However, the results based on a male population of Northern Italy, showed that the *213His* allele of the *SULT1A1* gene was associated with a moderately reduced risk of bladder cancer [33]. Opposite results were reported for the SULT1A1 ((213)His) allele in a population of French Caucasian patients, where it was associated with statistically significantly increased risks of upper urinary tract urothelial cell carcinomas [34].

North America

The role of N-acetylation polymorphisms in smoking-associated bladder cancer was evaluated by Taylor et al. in 1998 [45]. They found no association between the studied *NAT2* genotypes (*NAT2*4*, *NAT2*5*, *NAT2*6*, *NAT2*7*, *NAT2*14*) and bladder cancer risk whether the genotypes were considered alone or in combination with smoking. They demonstrated increased bladder cancer risk for individuals carrying the *NAT1*10* allele among smokers. The highest risk was observed

for patients homozygous for the *NAT1*10* allele. The authors also showed that bladder cancer risk from smoking exposure is particularly high in those who inherit *NAT2* slow alleles in combination with one or two copies of the *NAT1*10* allele. In 2004, Castelao et al. reported that *NAT1*-rapid, *NAT2*-rapid, and *CYP1A2*-rapid genotype/phenotype influence the protective effect of carotenoids on bladder cancer in non-Asians of Los Angeles, California [46]. Later, Yuan et al. (2008) found no associations between bladder cancer risk and *NAT1* genotype or *CYP1A2* phenotype, but reported a strong association for *GSTM1* and *NAT2* slow acetylation among individuals with known high exposures to carcinogenic arylamines [47].

Bell et al. (1993) and Muscat et al. (2008) investigated the racial differences in *GSTM1*, *P4501A2* (*CYP1A2*) and *NAT2* genotype frequency in black and whites [39,48]. Bell et al. [39] found that the *GSTM1* 0/0 genotype occurred less frequently among blacks (35%) than among whites (49%). Muscat et al. calculated that the putative combined low risk phenotype (slow *CYP1A2*/rapid *NAT2*) was more common in blacks than in whites (25 vs 15%) [48]. No significant racial differences were observed in slow and rapid CYP1A2 phenotypes, and in the combined slow NAT2/rapid CYP1A2 phenotype.

In the Zheng et al. study (2003) of the Soluble sulfotransferase *SULT1A1* gene (213His allele) a statistically significant reduced risk of bladder cancer was observed only in women but not in men with the mutant allele [49]. There was also a reduced bladder cancer risk in never smokers with the mutant allele, but not in former or current smokers.

Conclusion

There is a large amount of data generated from numerous studies with various designs. In each study an assorted enzyme set, isoenzymes or allelic variants were used.

The most prevalent genetic variant for Asians which increases the bladder cancer risk is the *GSTM1* null genotype. There is no consensus on the effect of the *NAT2* slow acetylator genotype. The protective polymorphic variant for bladder cancer development was found to be *CYP2A6*4* allele.

In the Tunisian population, genetic variants facilitating the development of bladder cancer are slow *NAT2*, wild-type *GSTT1* and *GSTM1* null genotypes. The protective genotypes are rapid *NAT2*, wild-type *GSTM1* and *GSTT1* null genotypes.

For for North Americans and Europeans *NAT2* slow acetylator and *GSTM1* 0/0 genotypes are risk factors for bladder cancer and normal *NAT1* / fast *NAT2* seems to be a protective genotype combination. The lower frequencies of the *GSTM1* 0/0 and slow *NAT2* genotypes in blacks than in whites, and a higher frequencies of low risk phenotype (slow CYP1A2 / rapid NAT2) in blacks, may be offered as an explanation for the observed lower incidence of bladder cancer in Afroamericans.

The 213His allele of the *SULT1A1* gene - associated with lower enzyme activity and decreased mutagen activation - is reported to protect from bladder cancer in almost all studies.

All the described genetic variants are only predisposing factors for bladder cancer development. A combination with a high exposure to carcinogenic, such as arylamines, smoking and hazardous occupational exposures is needed to trigger the malignant neoplastic process. That is why we suggest that genotyping for relevant risk polymorphic variants, and regular screening of susceptible individuals working in conditions of well defined carcinogenic exposures might help reduce the incidence, severity and mortality of bladder cancer.

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