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basis for the (S)-mephenytoin 4'-hydroxylase polymorphism in human populations. Poor metabolizers (PMs) of CYP2C19 represent approximately 3−5% of Caucasians, a similar percentage of African-Americans and 18−23% of Asians [43]. Kaisary *et al.* [44] reported an association between bladder cancer and CYP2C19 phenotype by using measurement of S-mephenytoin hydroxylation. CYP2C19 phenotype was not associated with increased risk of bladder cancer, but a weak association was found between non-aggressive bladder cancer and high CYP2C19 activity. The most common variant allele, *CYP2C19*2A*, has an aberrant splice site in exon 5 [45]. There is one report about a negative association between *CYP2C19*2A* polymorphism and bladder cancer risk [20]. Despite the wide range of substrate specificity and abundance in the liver, the CYP2C enzymes do not seem to have a significant role in carcinogen metabolism. The possibility should not, however, be ruled out.

5. *CYP2D6*

CYP2D6 is expressed in the liver, gut and brain neurons [46]. CYP2D6 metabolizes several important clinically used drugs [47], but there is little evidence of it having a role in carcinogen activation. CYP2D6 is suspected to be involved in the activation of tobacco-specific nitrosamines, such as 4-(metylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [48]. With debrisoquine as a substrate, a high inter-individual variability in CYP2D6 activity has been observed *in vivo*. Inter-individual differences in the metabolic capacity of the CYP2D6 may be expected to be a key factor in susceptibility to developing urothelial cancer where environmental chemicals are implicated. A genetic polymorphism at CYP2D6 debrisoquine hydroxylase gene locus affects 5−10% of the Caucasian population and < 1% of the Chinese or Japanese population, and is responsible for the compromised metabolism (poor metabolizer phenotype). There are some reports that investigated the association between CYP2D6 phenotype and urothelial cancer (Table 1). Three papers reported that there was no difference in the distribution of oxidative polymorphism of debrisoquine [24, 49, 50]. Kaisary *et al.* [44] detected a higher oxidative rate of debrisoquine in patients with aggressive urothelioma than in those with a less undifferentiated disease. Benitez *et al.* [51] reported that the distribution of frequencies of metabolic ratio values tend to have lower values in the patients ($P<0.05$), and patients with a high occupational risk for urothelioma had lower metabolic ratio values ($P=0.03$).

The *CYP2D6* gene is located on chromosome 22q13.1. A number of alleles have now been characterized at the *CYP2D6* locus. Inactivating mutations at the *CYP2D6* gene are *CYP2D6*3* (deletion of A2549 in exon 5), *CYP2D6*4* (G1864A at splicing site), *CYP2D6*5* (complete deletion of the wild-type allele *CYP2D6*1*), *CYP2D6*6A* (deletion of T1707 in exon 3) and *CYP2D6*11, *12, *13, *14, *15, *16.* The *CYP2D6*3*, *CYP2D6*4* and *CYP2D6*5* alleles account for the majority (greater than 90%) of the poor metabolizer phenotype [52]. The phenotype-genotype concordance, which predicts the metabolic phenotype by genetic analysis, was found to be between 93.4% and 100% [53]. Three reports showed a negative association between CYP2D6 genetic polymorphism and urothelial cancer [20, 54, 55], but one reported that a significant increase in the proportion of poor metabolizers or heterozygotes was seen in

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urothelial cancer patients [56]. Chinegwundoh *et al.* [57] found that there was a trend for those heterozygous at the *CYP2D6* locus and with a history of smoking to develop more aggressive diseases, but this trend did not reach statistical significance.

Among control groups, the frequency of the CYP2D6 poor metabolizers has been assumed in some ethnic groups (Table 1). The frequency of the CYP2D6 poor metabolizers are 0.5－1.2% in Asian populations and 2.1－6.1% in European populations. The meta-analysis of two studies in Asian populations (151 cases, 287 controls) and six studies in European populations (1057 cases, 1875 controls) was conducted [20, 24, 49－51, 54, 56, 57]. The summary odds ratio(OR) for the CYP2D6 poor metabolizers was 1.91 (95%Confidence interval(CI)=0.28－13.30) in Asians and 1.06 (95%CI=0.76－1.49) in Europeans. To reveal these associations relating to tobacco smoking, future research is needed.

6. *CYP2E1*

CYP2E1 is an ethanol inducible enzyme, known to be involved in the metabolic activation of several organic compounds with low molecular weight, including *N*-nitrosamines found in tobacco smoke. The CYP2E1 is expressed at high levels in the liver and at lower levels in several extra-hepatic tissues. Wide inter-individual variation in the expression of the *CYP2E1* gene has been reported in humans, which is possibly attributable to gene-environment interaction. Significant inter-ethnic differences exist in *CYP2E1* polymorphism, but there is no clear evidence that any of these polymorphisms are related to altered function *in vivo*. All polymorphisms reported in the literature are located in the non-coding regions of *CYP2E1*, while the coding regions of *CYP2E1* seem to be well conserved among different ethnic groups and species [58]. Restricton fragment length polymorphisms (RFLPs) have been detected for TaqI (intron 7; *CYP2E1*1B*)[58], RsaI (intron 5)[60], DraI (intron 6; *CYP2E1*6*) [59]. Interestingly, PstI and RsaI RFLPs identify two further variant sequences in the 5' untranslated region (*CYP2E1*5A* and *CYP2E1*5B*), and, furthermore, the RsaI RFLP has been associated with the alteration in the transcriptional activation of the gene. There are some reports that investigated the association between *CYP2E1* polymorphisms and urothelial cancer risk, but none of them reported significant associations (Table 1) [20, 42, 55, 61, 62].

GSTs polymorphism

The GSTs are a family of enzymes, which catalyze the conjugation of a wide variety of xenobiotics, including environmental carcinogens, with glutathione. Although the vast majority of GST conjugates represents detoxification products, several instances exist where GST activity does not result in the detoxification, but rather activation. In humans, there are four main classes of α (glutathione S-transferase-α), μ (glutathione S-transferase-μ), π (glutathione S-transferase-π), θ (glutathione S-transferase-θ), each of which contains 1 or more of the homodimeric or heterodimeric isoforms, glutathione S-transferase-α 1-1 (GSTA1-1), GSTA1-2 and so forth [63, 64]. Genetic polymorphisms have been reported for *GSTM1*, *GSTT1* and *GSTP1*, resulting in either decreased or altered enzyme activity. Because

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of their detoxification role, these polymorphisms may play an important role in urothelial cancer susceptibility.

1. *GSTM1*

Five μ class genes (M1－M5) situated in tandem on chromosome 1p13 have been identified. *GSTM1* is expressed in human liver, stomach, brain and other tissues, while GSTM2－M5 subunits have been detected in extrahepatic tissues. *GSTM1* enzyme has received considerable attention in relation to urothelial cancer because of its role in the detoxification of benzo[a]pyrene and other polycyclic aromatic hydrocarbons found in tobacco smoke. Three polymorphisms of the *GSTM1* gene, namely *GSTM1*0*, *GSTM1*A* and *GSTM1*B*, have been identified. *GSTM1*0* is a deleted allele, and the homozygotes allele (*GSTM1* null genotype) express no *GSTM1* protein [65]. *GSTM1*A* and *GSTM1*B* differ by only a single base in exon 7, however, there is no evidence of a functional difference between *GSTM1*A* and *GSTM1*B*, and the two are typically categorized together as a single functional phenotype. Most studies of *GSTM1* polymorphism and cancer have compared the homozygous deletion genotype with the genotypes containing at least one functional allele. The genotype with the homozygous deletion of the *GSTM1* gene is called "*GSTM1*-null", whereas the genotype having at least one copy of the gene is called "*GSTM1*-positive". *GSTM1* null genotype was shown to occur in approximately 50% of the population of various ethnic origins among controls (Table 2).

Many studies investigated the association between *GSTM1* polymorphism and urothelial cancer (Table 2) [20, 21, 55, 66－88]. Most studies recognized an increased risk associated with a lack of *GSTM1* activity. Recently, two meta-analyses of published studies have been reported [89, 90]. Johns *et al.* [89] reported that a meta-analysis of 15 case-control studies had been carried out using a random effects model, and the OR for risk of bladder cancer risk associated with *GSTM1* deficiency was 1.53 (95%CI=1.28－1.84). Engel *et al.* [90] performed meta- and pooled analyses of published and unpublished, case-control, genotype-based studies that examined associations between *GSTM1* polymorphism and bladder cancer (17 studies, 2149 cases, 3646 controls). They excluded studies conducted in populations with a high prevalence of exposure to known bladder cancer risk factors other than tobacco smoke. Using a random effects model in the meta-analysis, they obtained a summary OR of 1.44 (95%CI= 1.23－1.68) for *GSTM1* null status with all studies included. Studies conducted in Asia generated a summary OR of 1.73 (95% CI=1.66－1.81); in Europe, a summary OR of 1.39 (95% CI= 1.09－1.77); and in the USA, a summary OR of 1.44 (95% CI=1.38－1.50). Pooled analyses using original data sets from 10 studies (1496 cases, 1444 controls) and adjusted for age, sex and race produced similar results. There was no evidence of multiplicative interaction between the *GSTM1* null genotype and ever smoking in relation to bladder cancer, although there was a suggestion of addictive interaction (addictive interaction=0.45, 95%CI=0.03－ 0.93).

2. *GSTT1*

To our knowledge, there are 14 reports investigating the associations between *GSTT1*

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polymorphism and urothelial cancer (Table 2) [20, 21, 75－81, 83－85, 87, 88]. Among control groups, the frequency of the null genotype has been assumed in some ethnic groups. The frequency of null genotype is highest among Asian populations (46－52%) (Table 2). Among European populations, the frequency was measured to range from 11 to 22% (Table 2).

We reviewed 12 case-control studies that investigated associations between *GSTT1* polymorphisms and urothelial cancer (Table 2) [20, 75－80, 83－85, 87, 88]. Ten case-control studies reported no associations between *GSTT1* null genotype and urothelial cancer risks [20, 75, 77, 79, 80, 83－85, 87, 88]. However, two of those reported that the risk of bladder cancer with *GSTT1* null genotype was significantly higher among non-smokers [20, 75]. Two studies reported significant associations between *GSTT1* null genotype and urothelial cancer risk [76, 78]. Furthermore, individuals with the null genotype for both *GSTM1* and *GSTT1* were at a significantly higher risk for developing bladder cancer than individuals with both genes present.

A meta-analysis of three studies in Asian populations (489 cases, 530 controls) and seven studies in European populations (1034 cases, 1094 controls) was conducted (20, 75, 77, 79, 80, 81, 83－85, 88). The summary OR for the *GSTT1* null type was 1.06 (95%CI=0.83－1.35) in Asians and 0.82 (95%CI=0.65－1.03) in Europeans. These results suggested that *GSTT1* null type might be a reduced risk for urothelial cancer in Europeans, but not in Asians.

3. *GSTP1*

There are five case-control studies that investigated the association between *GSTP1* polymorphisms and urothelial cancer [83, 85, 87, 91, 92]. Three of these [83, 87, 91] reported that *GSTP1*a/b or b/b genotypes might be associated with an increase in bladder cancer risk among British, Italian and Turkish populations. Furthermore, the risk for *GSTP1*a/b or b/b genotypes with bladder cancer was elevated in individuals with the combination of cigarette smoking and *GSTM1* null genotype [87]. Two papers reported that no significant increase in the frequency of the *GSTP1*b allele was found in tumor patients among Japanese and Germans [85, 92].

NATs polymorphism

Although N-hydroxy arylamines can react with DNA at acidic urinary pH, further activation by NAT1 in the urothelial has been suggested as a final activation step leading to DNA adducts, mutations and neoplasia [93]. This metabolic pathway led the hypothesis that the NAT2 slow activity type and NAT1 high activity type were risk factors for urothelial cancer among smoking groups. A number of reports supported this hypothesis, but some did not support it.

1. *NAT1*

A significant association between urothelial cancer and smokers possessing the *NAT1*10* allele was reported in two studies [94, 95], but not in two others (Table 3) [96, 97]. In the two former studies, the association was highest among smokers who possessed both *NAT1*10*

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Table 2. Previous reports of association between GSTs polymorphisms and urothelial cancer

Genotype	Author, year of publication (reference number)	Population	Number of cases[1]	Number of controls	Analysis methods	Frequencies of variant genotype cases/controls(%)	Crude OR or results OR (95%CI)
GSTM1 deletion polymorphism	Zhong *et al*, 1993(66)	British	97	225	Southern blotting	40/42	0.9 (0.6−1.5)
	Daly *et al*, 1993(67)	British	53	52	PCR	85/60	3.8 (1.5−9.5)
	Lafuente *et al*, 1993(68)	Spanish	75	75	ELISA	67/45	2.4 (1.2−4.7)
	Bell *et al*, 1993(69)	American	229	211	PCR	60/47	1.7 (1.2−2.5)
	Lin *et al*, 1994(70)	American	114	1104	PCR	57/49	1.4 (0.9−2.0)
	Brockmoller *et al*, 1994(71)	German	296	400	ELISA, PCR	59/51	1.4 (1.0−1.9)
	Rothman *et al*, 1996(72)	Chinese	38	43	PCR	61/61	1.0 (0.4−2.5)
	Lafuente *et al*, 1996(73)	Egyptian	80	70	ELISA	59/51	1.3 (0.7−2.6)
	Brockmoller *et al*, 1996(20)	German	374	373	PCR	58/52	1.3 (1.0−1.8)
	Okkels *et al*, 1996(74)	Danish	234	202	PCR	57/50	1.3 (0.9−2.0)
	Kempkes *et al*, 1996(75)	German	113	170	PCR	68/54	1.8 (1.1−3.0)
	Anwar *et al*, 1996(55)	Egypitan	22	21	PCR	86/48	7.0 (1.7−28.8)
	Abdel-Rahman *et al*, 1998 (76)	Egyptian	37	34	PCR	70/44	3.0 (1.1−7.9)
	Bringuier *et al*, 1998(21)	Australian	62[2]	0	PCR	39/*[3]	No association between p53 mutation and GSTM1 polymorphism among cancer cases
	Katoh *et al*, 1998(77)	Japanese	145[4]	145	PCR	57/45	1.6 (1.0−2.5)
	Salagovic *et al*, 1999(78)	Slovakian	76	248	PCR	53/50	1.1 (0.7−1.9)
	Georgiou *et al*, 2000(79)	Greek	89	147	PCR	63/38	2.8 (1.6−4.7)
	Kim *et al*, 2000(80)	Korean	112	220	PCR	70/56	1.8 (1.1−2.9)
	Martone *et al*, 2000(81)	Italian	45	0	PCR	56/*[3]	No association between p53 mutation and GSTM1 polymorphism among cancer cases
	Mungan *et al*, 2000(82)	Dutch	61	61	PCR	62/43	2.1 (1.1−4.3)
	Peluso *et al*, 2000(83)	Italian	130	54	PCR	47/54	0.8 (0.4−1.4)
	Schnakenberg *et al*, 2000 (84)	German	157	223	PCR	59/58	1.1 (0.7−1.6)
	Steinhoff *et al*, 2000(85)	German	135	127	PCR	59/45	1.8 (1.1−2.9)
	Aktas *et al*, 2001(86)	Turkish	103	202	PCR	54/35	2.2 (1.4−3.6)
	Toruner *et al*, 2001(87)	Turkish	121	121	PCR	62/45	2.0 (1.2−3.3)
	Lee *et al*, 2002(88)	Korean	232	165	PCR	64/52	1.6 (1.1−2.5)

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Table 2. Previous reports of association between GSTs polymorphisms and urothelial cancer(continued)

Genotype	Author, year of publication (reference number)	Population	Number of cases[1]	Number of controls	Analysis methods	Frequencies of variant genotype cases/controls(%)	Crude OR or results OR (95%CI)
GSTT1 deletion polymorphism	Kempkes *et al*, 1996(75)	German	113	170	PCR	18/18	1.0 (0.5−1.8)
	Brockmoller *et al*, 1996(20)	German	374	373	PCR	18/21	0.8 (0.6−1.2)
	Katoh *et al*, 1998(77)	Japanese	145[4]	145	PCR	41/48	0.8 (0.5−1.2)
	Abdel-Rahman *et al*, 1998 (76)	Egyptian	37	34	PCR	46/15	4.9 (1.6−14.9)
	Bringuier *et al*, 1998(21)	Australian	82[2]	0	PCR	5/*[3]	No association between p53 mutation and GSTT1 polymorphism among cancer cases
	Salagovic *et al*, 1999(78)	Slovakian	76	248	PCR	28/17	1.9 (1.0−3.4)
	Georgiou *et al*, 2000(79)	Greek	89	147	PCR	6/11	0.5 (0.2−1.4)
	Kim *et al*, 2000(80)	Korean	112	220	PCR	42/46	0.9 (0.5−1.3)
	Martone *et al*, 2000(81)	Italian	44	0	PCR	9/*[3]	No association between p53 mutation and GSTT1 polymorphism among cancer cases
	Peluso *et al*, 2000(83)	Italian	122	54	PCR	11/11	1.0 (0.4−2.9)
	Schnakenberg *et al*, 2000 (84)	German	157	223	PCR	18/22	0.8 (0.5−1.3)
	Steinhoff *et al*, 2000(85)	German	135	127	PCR	15/13	1.1 (0.6−2.3)
	Toruner *et al*, 2001(87)	Turkish	121	121	PCR	20/17	1.2 (0.6−2.2)
	Lee *et al*, 2002(88)	Korean	232	165	PCR	58/52	1.3 (0.9−2.0)
GSTP1 Ile-Val polymorphism[6] (exon 5)	Harries *et al*, 1997(91)	British	71	155	PCR	65/49	1.9 (1.1−3.4)
	Katoh *et al*, 1999(92)	Japanese	106[5]	122	PCR	29/24	1.3 (0.7−2.4)
	Martone *et al*, 2000(81)	Italian	45	0	PCR	60/*[3]	The frequency of GSTP1 rapid genotype with p53 mutation was 3.5-fold higher than that of GSTP1 slow genotype with p53 mutation (P=0.03)
	Peluso *et al*, 2000(83)	Italian	123	54	PCR	59/41	2.1 (1.1−4.1)
	Steinhoff *et al*, 2000(85)	German	135	127	PCR	50/45	1.2 (0.8−2.0)
	Toruner *et al*, 2001(87)	Turkish	121	121	PCR	45/31	1.8 (1.0−2.9)

[1]Cases were bladder cancer patients, [2]Cases were renal pelvis cancer patients, [3]There were no controls, [4]Cases were 112 bladder cancer, 12 ureter cancer, 10 renal pelvis cancer and 11 overlapping cancer patients, [5]Cases were 73 bladder cancer, 9 ureter cancer, 13 renal pelvis cancer and 11 overlapping cancer patients, [6]Variant genotypes were GSTP1A/G or G/G, respectively

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Table 3. Previous reports of association between NAT1 polymorphisms and urothelial cancer

Author, year of publication (reference number)	Population	Number of cases	Number of controls	Phenotyping and genotyping (drug used for phenotyping or mutant allele)	Crude OR or results OR (95%CI)
Okkels *et al*, 1997(96)	Danish	254[1]	242	Genotyping (*NAT1*3,10,11*)	0.99 (0.98–1.01) (rapid vs slow acetylators) 3.76 (1.07–13.31) (NAT2 slow/NAT1 rapid vs NAT2 rapid/NAT1 slow)
Bringuier *et al*, 1998(21)	Australian	105[2]	0	Genotyping (*NAT1*10,11*)	No association between p53 mutation and NAT1 polymorphism among cancer cases.
Taylor *et al*, 1998(95)	American	230[1]	203	Genotyping (*NAT1*3,10,11*)	3.8 (2.1–7.1) (NAT1*10(+)/smoker vs NAT1*10(−)/nonsmoker) 5.7 (1.9–17.7) (NAT1*10(+)/NAT2 slow/smoker vs NAT1*10(−)/NAT2 rapid/nonsmoker)
Hsieh *et al*, 1999(97)	Taiwanese	74[1]	184	Genotyping (*NAT1*3,10,11*)	2.34 (1.03–5.31) (NAT1*10/NAT2 slow ever smoker vs never smoker)
Katoh *et al*,1999(94)	Japanese	116[3]	122	Genotyping (*NAT1*3,10*)	2.09 (1.02–4.35 ((NAT1*10/*10 vs *4/*4) 7.28 (2.13–32.06) (NAT2 slow/NAT1*10 vs NAT2 rapid/-NAT1*4)
Cascorbi *et al*, 2001(98)	German	425[1]	343	Genotyping (*NAT1*3,10,11,14,15,17,22*)	0.53 (0.20–1.40) (NAT1*10/*10 vs *4/*4) 2.09 (1.36–3.22) (NAT2 slow/NAT 1 *4 vs NAT2 rapid/NAT 1 *10)

[1]Cases were bladder cancer patients, [2]Cases were renal pelvic cancer patients, [3]Cases were 96 bladder cancer, 7 renal pelvis and 13 ureter cancer patients

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allele and were slow *NAT2* acetylators. In the two latter studies, significant differences were found by a combination of *NAT1*10* allele and slow *NAT2* acetylator and smoking. They suggested that higher levels of NAT1-catalyzed activation (*O*-acetylation) within the urothelial increase risk. On the other hand, Cascorbi *et al.* [98] reported that genotypes including *NAT1*10* were significantly less frequent among the cases (P=0.013). Furthermore, the bladder cancer risk for *NAT2* slow acetylators combined with *NAT1*4* was increased 2.3 times compared with *NAT2* rapid acetylators with *NAT*10* genotypes (P=0.0001). Perhaps *NAT1*10* allele might affect urothelial cancer development, but few studies and small sample size might cause the discrepancy in the results.

2. *NAT2*

Slow NAT2 acetylator status as a risk factor for urothelial cancer was first proposed in the late 1970s and early 1980s [99, 100]. Since then, a large number of studies have appeared in the literature confirming or refuting an association between NAT2 status and urothelial cancer risk (Table 4) [20, 24, 80, 81, 83, 84, 92, 97, 99−126]. Recently, some meta-analyses of published studies have been reported. Green *et al.* [127] (21 studies, 2700 cases, 3426 controls) and Johns *et al.* [128] (21 studies, 2462 cases, 3450 controls) suggested that NAT2 slow acetylator may be associated with a small increase in bladder cancer risk, and these effects may be greater in smokers than in non-smokers. Marcus *et al.* [129] (22 studies, 2496 cases, 3340 controls) reported that slow acetylators had an approximately 40% increase in risk compared with rapid acetylators (OR=1.4, 95% CI=1.2−1.6). However, studies conducted in Asia generated a summary OR of 2.1 (95% CI=1.2−3.8); in Europe, a summary OR of 1.4 (95% CI=1.2−1.6); and in the USA, a summary OR of 0.9 (95% CI=0.7−1.3). In addition, a case series meta-analysis using data from 16 bladder cancer studies conducted in the general population (n=1999 cases) has been published [130]. The case-series design can be used to assess multiplicative gene-environment interaction without inclusion of control subjects. There was a weak interaction between smoking and NAT2 slow acetylation (OR=1.3, 95% CI=1.0−1.6) that, again, was stronger when analyses were restricted to studies conducted in Europe (OR=1.5, 95% CI=1.1−1.9). The meta-analyses mentioned above were based on both phenotype and genotype. Vineis *et al.* [131] reported a pooled analysis of *NAT2* genotype-based studies in Caucasian populations (6 studies, 1530 cases, 731 controls), and a significant association between *NAT2* and bladder cancer (OR=1.42, 95% CI=1.14−1.77). The risk of cancer was elevated in smokers and occupationally exposed subjects, with the highest risk among slow acetylators. They suggested that *NAT2* was not a risk factor but modulated the effect of carcinogens contained in tobacco smoke (probably arylamines) or associated with occupational exposures.

Sulfotransferases (SULT)

SULT catalyze both the bioactivation and detoxification of a wide range of promutagens and procarcinogens. SULT1A1 appears to be an important phenol SULT because of its abundance and distribution in many tissues and wide substrate specificity. The *SULT1A1* gene

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Table 4. Previous reports of association between NAT2 polymorphisms and urothelial cancer

Author, year of publication (reference number)	Population	Number of cases[1]	Number of controls	Phenotyping and genotyping (drug used for phenotyping or mutant allele)	Frequencies of NAT2 slow cases/controls(%)	Crude OR or results OR (95%CI)
Lower *et al*, 1979(99)	Swedish	115	118	Phenotyping (Sulphamethazine)	70/67	1.1 (0.7–2.0)
Lower *et al*, 1979(99)	Danish	71	74	Phenotyping (Sulphamethazine)	65/51	1.8 (0.9–3.4)
Lower *et al*, 1979(99)	American	34	41	Phenotyping (Sulphamethazine)	65/51	1.5 (0.6–3.8)
Wolf *et al*, 1980(100)	Danish	71	74	Phenotyping (Sulphamethazine)	65/51	1.7 (0.9–3.4)
Cartwright *et al*, 1982(101)	British	111	95	Phenotyping (Dapsone)	67/57	1.5 (0.9–2.7)
Evans *et al*, 1983(102)	British	100	852	Phenotyping (Sulphamethazine)	66/60	1.3 (0.8–2.0v
Miller *et al*, 1983(103)	American	26	26	Phenotyping (Sulphamethazine)	46/69	0.4 (0.1–1.2)
Cartwright *et al*, 1984(104)	Portuguese	47	35	Phenotyping (not stated)	30/29	1.1 (0.4–2.8)
Hanssen *et al*, 1985(105)	German	105	42	Phenotyping (Sulphamethazine)	62/43	2.2 (1.1–4.5)
Ladero *et al*, 1985(106)	Spanish	130	157	Phenotyping (Dapsone)	64/57	1.3 (0.8–2.1)
Mommsen *et al*, 1985(107)	Danish	228	100	Phenotyping (Sulphamethazine)	51/46	1.5 (0.9–2.4)
Karakaya *et al*, 1986(108)	Turkish	23	109	Phenotyping (Sulphamethazine)	39/62	0.4 (0.2–0.9)
Kaisary *et al*, 1987(109)	British	98	110	Phenotyping (Dapsone)	60/49	1.6 (0.9–2.7v
Bicho *et al*, 1988(110)	Portuguese	49	84	Phenotyping (Sulphamethazine)	43/42	1.1 (0.5–2.1)
Horai *et al*, 1989(111)	Japanese	51	203	Phenotyping (Dapsone)	6/6	0.9 (0.3–3.3)
Hanke *et al*, 1990(112)	Polish	67	22	Phenotyping (Isoniazid)	70/45	2.8 (1.1–7.5)
Hayes *et al*, 1993(113)	Chinese	38	43	Phenotyping (Dapsone) Genotyping (*NAT2*5;6;7*)	13/23	0.3 (0.1–1.1) (Phenotype) 0.5 (0.2–1.6) (Genotype)
Lee *et al*, 1994(24)	Korean	98	84	Phenotyping (Isoniazid)	16/17	1.0 (0.4–2.1)
Dewan *et al*, 1995(114)	Indian	77	80	Phenotyping (Isoniazid)	60/35	3.3 (1.8–6.6)
Ishizu *et al*, 1995(115)	Japanese	71	91	Phenotyping (Isoniazid)	28/14	2.4 (1.1–5.2)
Risch *et al*, 1995(116)	British	189	59	Genotyping (*NAT2*5A,B,C; 6A; 7B*)	67/44	2.6 (1.4–4.7)
Brockmoller *et al*, 1996(20)	German	374	373	Genotyping (*NAT2*5A,B,C; 6A; 7B*)	62/58	1.2 (0.9–1.6)
Golka *et al*, 1996(117)	German	196	0	Genotyping (*NAT2*5A,B,C; 6A;7B*)	55/*[2]	No significant excess of NAT2 slow in cases who worked in chemical production(P=0.123)or chemical or rubber industry (P=0.141)

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Table 4. Previous reports of association between NAT2 polymorphisms and urothelial cancer(continued)

Author, year of publication (reference number)	Population	Number of cases[1]	Number of controls	Phenotyping and genotyping (drug used for phenotyping or mutant allele)	Frequencies of NAT2 slow cases/controls(%)	Crude OR or results OR (95%CI)
Okkels *et al*, 1997(118)	Danish	254	242	Genotyping (*NAT2*5A,B,C; 6A; 7*)	61/56	1.2 (0.9−1.7)
Peluso *et al*, 1998(119)	Italian	114	46	Genotyping (*NAT2*5A; 6A; 7A*)	67/57	1.5 (0.8−3.1)
Schnakenberg *et al*, 1998(120)	German	60	154	Genotyping (*NAT2*5A,B,C; 6A,B; 7B; 13*)	70/61	1.5 (0.8−2.8)
Su *et al*, 1998(121)	Taiwanese	27	60	Genotyping (*NAT2*5; 6; 7*)	30/12	3.3 (1.0−9.9)
Taylor *et al*, 1998(122)	American	230	203	Genotyping (*NAT2*5; 6; 7; 14*)	53/54	1.0 (0.7−1.4)
Filiadis *et al*, 1999(123)	Greek	89	147	Genotyping (*NAT2*5; 6; 7*)	58/38	2.3 (1.3−3.9)
Hsieh *et al*, 1999(97)	Taiwanese	74	184	Genotyping (*NAT2*5; 6; 7; 14*)	21/24	0.8 (0.4−1.6)
Inatomi *et al*, 1999(124)	Japanese	85	146	Genotyping (*NAT2*5; 6; 7*)	20/7	4.2 (1.8−10.8)
Katoh *et al*, 1999(94)	Japanese	116[3]	122	Genotyping (*NAT2*5; 6; 7*)	19/6	3.8 (1.6−9.0)
Kim *et al*, 2000(80)	Korean	112	219	Genotyping (*NAT2*5; 6; 7*)	7/11	0.6 (0.3−1.4)
Martone *et al*, 2000(81)	Italian	44	0	Genotyping (*NAT2*5A,B; 6A,B; 7A,B*)	80/*[2]	No association between p53 mutation and NAT2 polymorphism among cancer cases
Peluso *et al*, 2000(83)	Italian	123	54	Genotyping (*NAT2*5A; 6A; 7A*)	68/56	1.7 (0.9−3.3)
Schnakenberg *et al*, 2000(84)	German	157	223	Genotyping (*NAT2*5A,B,C; 6A,B; 7B; 13*)	73/66	1.3 (0.9−2.1)
Cascorbi *et al*, 2001(125)	German	425	343	Genotyping (*NAT2*5A,B,C; 6A; 12A; 14B*)	63/57	1.3 (1.0−1.8)
Kontani *et al*, 2001(126)	Japanese	149	163	Genotyping (*NAT2*5A,B,C; 6A; 7B*)	7/6	1.1 (0.4−2.7)

[1]Cases were bladder cacer patients, [2]There were no controls, [3]Cases were 96 bladder cancer, 7 renal pelvis cancer and 13 ureter cancer patients

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possesses G to A polymorphism that results in an Arg213 to His amino acid substitution, and the His213 allele has been shown to have low activity and low thermal stability. Studies by Hung *et al.* [132] in a north Italian population have reported a marginal protective effect of *SULT1A1* Arg213His polymorphism. However, Tsukino *et al.* reported there is no significant association between urothelial cancer and *SULT1A1* Arg213His polymorphism in Japanese [133].

Conclusion

A number of independent studies have now demonstrated the importance of polymorphisms in xenobiotic metabolism as risk factors in the development of urothelial cancer associated with chemical exposure. It has been revealed that *GSTM1* null genotype or *NAT2* slow acetylator genotype may be associated with a small increase in urothelial cancer risk. Associations between other polymorphisms of metabolic enzymes and urothelial cancer were not well-known or inconsistent. One of the reasons for these discrepancies may be insufficient study power or bad study design or a bias against publishing the absence of correlations. International Agency for Research on Cancer (IARC) [15] and Bartsch *et al.* [134] provided state-of-the art reviews of the application of biomarkers and the design and analysis of molecular epidemiological studies. The prerequisites for proper study design and conduct include: (a) clear definition of representative study populations and controls; (b) a sample size adequate to provide enough statistical power; (c) proper documentation (or measurement) of exposure; (d) avoidance of confounding because of use of study subjects of mixed ethnic background; and (e) study only of gene polymorphisms that have been shown to lead to altered phenotypic expression. The rigor and size of study designs will need to increase, as multiple comparison and power issue dictate. In parallel with these studies, a clearer understanding of the genetic bias of the polymorphisms has emerged, together with more accurate and less invasive methods for screening of populations.

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分子疫学と尿路上皮がん

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要　　旨：喫煙は尿路上皮がんの主要な原因の一つであるが,すべての喫煙者ががんに罹患するわけではない．この事象から,尿路上皮がんのリスク要因として,遺伝的背景の存在が示唆されてきた．タバコの煙には多くのがん原性化学物質が含まれており,これらは第Ⅰ相,第Ⅱ相の薬物代謝酵素によって活性化,解毒される．従ってDNAと反応する究極がん原性物質の量は,活性化と解毒の代謝的バランスによって決定されると考えられる．近年,薬物代謝酵素には遺伝子多型の存在が明らかとなり,シトクロームP450,グルタチオンS-トランスフェラーゼ (GST),N-アセチルトランスフェラーゼ(NAT),スルフォトランスフェラーゼの遺伝子多型と尿路上皮がんとの関連性に関する多数の分子疫学研究が実施されている．GSTM1遺伝子欠損型,NAT２遅延型では軽度のリスクの上昇が報告されているが,他の薬物代謝酵素との関連性については一致した結果が得られていない．これらの関連性を明らかにするためには,優れた研究デザインによる大規模研究が必要である．

キーワード：分子疫学，膀胱がん，シトクロームP450，グルタチオンS-トランスフェラーゼ，N-アセチルトランスフェラーゼ．

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