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Sulfotransferase genetic variation: from cancer risk to treatment response

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Abstract

Cytosolic sulfotransferases (SULTs) are phase II detoxification enzymes that are involved in the biotransformation of a wide variety of structurally diverse endo- and xenobiotics. Single-nucleotide polymorphisms (SNPs) in SULTs can alter the phenotype of the translated proteins. SNPs in some SULTs are fairly uncommon in the population, but some, most notably for SULT isoform 1A1, are commonly found and have been associated with cancer risk for a variety of tumor sites and also with response to therapeutic agents. SNPs in many SULTs vary by ethnicity, another factor that could influence SULT-associated disease risk and pharmacogenetics. This review surveys the current knowledge of *SULT* genetic variability in relation to cancer risk and response to therapy, focusing primarily on *SULT1A1*.

Keywords

Breast cancer; cancer survival; environmental exposures; gene; gene interactions; tamoxifen

Introduction

Human cytosolic sulfotransferases (SULTs) belong to a superfamily of phase II detoxification enzymes that are responsible for the biotransformation of structurally diverse endo- and xenobiotics (Jakoby & Ziegler, 1990). They can be primarily divided into two major subfamilies, the phenol and hydroxysteroid SULTs (SULT1 and SULT2, respectively). SULTs function biologically by catalyzing the transfer of the sulfonyl group from the obligatory co-substrate, 3'-phosphoadenosine-5'-phosphosulfate (PAPS), to acceptor molecules, primarily to hydroxyl, sulfhydryl, amino or *N*-oxide functional moieties. SULTs are widely expressed in human tissues, including liver, but do display tissue-specific distribution. Given their roles in the metabolism of hormones and in the metabolic activation/detoxification of putative carcinogens, genetic variability within this gene family has garnered much attention in molecular epidemiological studies. The term "molecular epidemiology" first appeared in the literature in 1973 in a manuscript addressing the

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Declaration of interest

The authors declare no interests.

molecular epidemiology of influenza (Kilbourne, 1973). Since then, the integration of biomarkers such as single-nucleotide polymorphisms (SNPs) into traditional epidemiological studies has generated a wealth of information on the relationship between human genetic variability and the impact it has on phenotypic variability, and ultimately on disease risk. Early molecular epidemiological approaches examined single variants in candidate genes in relation to disease risk. The human phenol *SULT* gene, *SULT1A1*, was one of the earlier candidate genes examined due to its involvement in the metabolism of putative carcinogens and the existence of a functional, common SNP that conferred decreased enzymatic activity and thermostability of the expressed protein (Ozawa et al., 1998; Raftogianis et al., 1997). This discovery spurred intense efforts to determine the contribution of this SNP to the etiology of various cancers, with more than 200 disease-association studies listed in PubMed.

Subsequently, other SNPs have been identified in *SULT1A1*, as well as other *SULT* isoforms. These SNPs have been examined in relation to disease etiology, as well as in response to therapy, although the preponderance of research has been carried out on *SULT1A1*. *SULT1A1* is the most highly expressed *SULT* in the liver and this isoform has been reported to sulfate a wide variety of phenolic xenobiotics and endogenous iodothyronines (Kester et al., 1999; Li & Anderson, 1999; Visser et al., 1998) and the antiangiogenic estrogen metabolite, 2-methoxyestradiol (Spink et al., 2000). *SULT1A1*-catalysed biotransformation of 2-methoxyestradiol occurs at physiological concentrations. While *SULT1A1* can catalyze the sulfation of other estrogens at non-physiological concentrations (Falany et al., 1994), *SULT1E1* is responsible for the regulation of estrogen responsiveness under normal physiological conditions (Falany et al., 1998). *SULT1A1* is also involved in the bioactivation of *N*-hydroxy heterocyclic and aromatic amines found in the environment, particularly in meat cooked at high temperatures (Chou et al., 1995). For these substrates, sulfation produces an electrophile that can form adducts with cellular macromolecules including DNA, which, if not repaired, can lead to carcinogenesis.

***SULT1A1* genetic variation**

In 1996, a common genetic variant was identified in *SULT1A1* that generated an amino acid change in the protein from arginine to histidine at residue 213 of the translated protein. The histidine variant is associated with decreased enzymatic activity and thermostability of the enzyme when measured in liver or in blood platelets in humans (Ozawa et al., 1998; Raftogianis et al., 1996). The common allele has been designated *SULT1A1**1 and the variant as *SULT1A1**2, representing either Arg213 or His213, respectively. Several SNPs have also been identified in both the distal and proximal promoter region of *SULT1A1*, which are associated with platelet enzymatic activity (Lin et al., 2012; Ning et al., 2005). These SNPs were in linkage disequilibrium with each other and with *SULT1A1**1. Haplotype analysis also showed that there was considerable variability in the frequency of the haplotypes among different populations. Copy number variation (CNV) was described in *SULT1A1* in 2007 (Hebbring et al., 2007). It was demonstrated that copy number was associated with enzymatic activity, and that African-American subjects were significantly more likely to have higher CNV than Caucasians, providing a potential biological basis for

the observation that African-Americans tend to have higher basal platelet *SULT1A1* activity than Caucasians (Anderson & Jackson, 1984).

Other SNPs have been identified in the 3'-flanking region of the gene (Yu et al., 2010). These were in linkage with each other and in strong linkage with *SULT1A1**1 ($D' = 0.85$). When the collective effects of 3'-UTR SNPs, *SULT1A1**1/*2, and CNV on *SULT1A1* activity were examined in 498 Caucasian and 127 African-American subjects, *SULT1A1**1 did not significantly contribute to the variation in *SULT1A1* enzymatic activity when the 3'-UTR SNPs were included in the statistical model. Two major haplotypes (ACG and GTA) were significantly associated with *SULT1A1* activity, and when stratified by copy number, the *SULT1A1* 3'-UTR SNPs remain significantly associated with *SULT1A1* enzymatic activity in Caucasians, but not in African-Americans. Functional characterization revealed that the 3'-SNPs disrupted a binding site for the microRNA, miR-631, thus regulating *SULT1A1* expression in a genotype-specific manner. *In vitro* studies suggest a role for these variants in pharmacogenomic studies, as they were shown to be significantly associated with activity toward fulvestrant and the 4-hydroxy metabolite of toremifene, drugs that are used as adjuvant therapy for breast and prostate cancer (Edavana et al., 2011, 2012). To date, however, these variants have not been investigated in disease-association studies.

Genetic variation in other SULT isoforms will likely exert a significant influence on drug metabolism in the individual, but, to date, the low occurrence in the population make them unsuitable for studies where sample size is inadequate. Additionally, the allele frequency of some functional SNPs differs by ethnicity, which could contribute to differential drug responses between ethnic groups. Functional SNPs in SULT enzymes have the potential to alter the pharmacokinetic/pharmacodynamic profiles of drugs metabolized by SULTs, thus altering the efficacy of therapy in addition to their potential role in modifying metabolism.

***SULT1A1* and breast cancer risk and response to therapy**

Due to its role in the potential sulfation of estrogens and anti-estrogens, *SULT1A1* has been most extensively investigated in relation to breast cancer risk and in the pharmacogenomics of tamoxifen response. Table 1 presents the most recent findings from several studies, including meta-analyses of pooled earlier studies. Five studies found no association of *SULT1A1* genetic variation and breast cancer risk (Dumas & Diorio, 2011; Gulyaeva et al., 2008; Reding et al., 2012; Syamala et al., 2010; Wang et al., 2010). Of these five studies, three were performed in mixed populations with fairly large numbers of study subjects, while two were performed in ethnically homogeneous groups. A large analysis of a mixed population of African-American and Caucasian women (1644 cases/1451 controls) found no association between *SULT1A1* and breast cancer risk (Reding et al., 2012). Similarly, a large meta-analysis of 14 case-control studies with a total of 8454 cases and 11 800 controls found no significant main effect overall, but there was some suggestion that *SULT1A1**2 is a breast cancer risk factor for Asian women (Wang et al., 2010). This is in agreement with another meta-analysis of 10 362 cases and 14 250 controls that also reported no main effect (odds ratio (OR) = 1.07, 95% confidence interval (CI): 0.97–1.17, $p = 0.164$). When the analysis was restricted to postmenopausal women, the dominant model suggested increased risk (OR = 1.28, 95% CI: 1.04–1.58, $p = 0.019$; Jiang et al., 2010). Significant associations

with risk were not found among premenopausal breast cancer women (OR = 1.06, 95% CI: 0.88–1.27, $p = 0.537$). The authors suggested that these differences by menopausal status could be attributed to significant publication bias among the postmenopausal women ($p = 0.002$). Subgroup analysis by race, however, also demonstrated a significant increase in breast cancer risk among Asian women (OR = 2.03, 95% CI: 1.00–4.14, $p = 0.051$) in the recessive model (Jiang et al., 2010). Another large meta-analysis (9881 cases/13 564 controls) found no significant association with breast cancer risk (Sun et al., 2011). Subgroup analysis by the source of controls revealed significant increased risk for hospital-based studies for *SULT1A1**1/*1 homozygous versus heterozygous *SULT1A1**1/*2 (OR = 1.173, 95% CI = 1.000–1.376) and for *SULT1A1**1/*1 homozygous versus *SULT1A1**2/*2 homozygous (OR = 1.600, 95% CI = 1.134–2.256). All of these meta-analyses overlap in study subjects, but differ by selection methods and analysis criteria. Selection bias is also problematic, as is the ability to consider gene–environment interactions that could profoundly alter *SULT1A1* phenotype. Until large-scale studies among different ethnic groups with attendant environmental data can be conducted, it will be difficult to truly elucidate the role of *SULT1A1* genetic variability in relation to breast cancer risk.

An early report in 2002 indicated that *SULT1A1**1 was significantly associated with improved overall survival in breast cancer patients receiving adjuvant tamoxifen therapy (Nowell et al., 2002). A subsequent study examined the impact of both a functional SNP in cytochrome P450 2D6 (*CYP2D6**4), which is responsible for producing the active metabolites of tamoxifen, along with *SULT1A1**1 on disease recurrence in patients treated with tamoxifen. This study found that carriers of the *CYP2D6**4 allele had a decreased risk of recurrence (relative risk = 0.28, 95% CI = 0.11–0.74, $p = 0.0089$). A similar pattern was seen among the *SULT1A1**1 homozygotes (relative risk = 0.48, 95% CI = 0.21–1.12, $p = 0.074$), in agreement with the earlier study (Wegman et al., 2005). A subsequent study in the context of a clinical trial found no association of *SULT1A1* genotype with recurrence-free survival at five years, but did report improved recurrence-free survival associated with the *SULT1A1**1 allele in patients receiving high-dose tamoxifen for two years ($p = 0.03$; Wegman et al., 2007). The mechanistic basis for improved outcomes associated with the high activity allele could be attributed to the observation that sulfated metabolites of tamoxifen induce apoptosis in breast cancer cell lines (Mercer et al., 2010). In this case, rapid sulfation of the active metabolites of tamoxifen in breast tumor cells could result in an increase in apoptosis and, hence, improved survival in individuals with the high activity *SULT1A1* genotype. Later studies, however, have not supported the involvement of *SULT1A1* genotype or copy number in tamoxifen response (Table 2). One study did report improved overall survival with the *SULT1A1**2 allele (Tengstrom et al., 2012) in patients also receiving chemotherapy. All of these studies are small and exhibit heterogeneity in terms of disease stage and patient ethnicity. Larger studies will be necessary to truly define the role of *SULT1A1* in tamoxifen response.

***SULT1A1* genetic variation and prostate cancer risk**

SULT1A1 genetic variability has also been investigated as a potential modifier of risk of other types of hormone-sensitive cancers (Table 3). A small study in a Turkish population could find no evidence of an association of *SULT1A1* and prostate cancer risk, even when

stratifying by smoking status (Arslan, 2010). A larger study found a risk of biochemical recurrence (OR 1.43, 95% CI 1.05–1.95) associated with the *SULT1A1**1 allele (Borque et al., 2013) in over 700 men undergoing radical prostatectomy after five years follow-up. One of the first reports of *SULT1A1* and prostate cancer risk found that Caucasians homozygous for the *SULT1A1**1 high activity allele were at increased risk for prostate cancer (OR 1.68; 95% CI 1.05–2.68) but the association in African-Americans did not reach significance (OR, 1.60; 95% CI, 0.46–5.62; Nowell et al., 2004). This study also reported on *SULT1A1* platelet activity and found a strong association between increased *SULT1A1* activity and prostate cancer risk in Caucasians (OR, 3.04; 95% CI, 1.8–5.1 and OR, 4.96; 95% CI, 3.0–8.3, for the second and third tertiles of *SULT1A1* activity, respectively) compared with individuals in the low enzyme activity tertile. A similar association was also found in African-American patients, with ORs of 6.7 and 9.6 for the second and third tertiles of *SULT1A1* activity (95% CI, 2.1–21.3 and 2.9–31.3, respectively). This association was further modified by consumption of well-done meat (OR, 1.42; 95% CI, 1.01–1.99 and OR, 1.68; 95% CI, 1.20–2.36 for the second and third tertiles, respectively). A later study from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial used a tagSNP approach to comprehensively examine genetic variability, meat consumption and prostate cancer risk (Koutros et al., 2009). This approach did not identify an association of *SULT1A1* with prostate cancer risk nor did it indicate an interaction with meat consumption. The disparities in these studies could be due to the differences in SNPs examined and in data collection differences in dietary assessments.

***SULT1A1* genetic variants and risk of lung, bladder and colorectal cancer**

SULT1A1 has long been demonstrated to play a role in the metabolism of environmental carcinogens thought to be involved in the etiology of various cancers (Arlt et al., 2002, 2005; Coughtrie & Johnston, 2001; Nishiyama et al., 2002; Sugahara et al., 2003; Zhang et al., 2012). *SULT1A1* genetic variability seems to show fairly consistent results as a significant risk factor for lung cancer (Table 4). However, a recent meta-analysis that included a total of five publications covering 1669 cases and 1890 controls (Liao et al., 2012) found no overall association between *SULT1A1**1 and lung cancer risk in all genetic models (dominant model: OR = 1.33, 95% CI = 1.00–1.76, $p = 0.05$; additive model: OR = 1.30, 95% CI = 0.93–1.81, $p = 0.12$; recessive model: OR = 1.21, 95% CI = 0.89–1.66, $p = 0.23$). Subgroup analysis revealed an elevated risk in mixed populations with *SULT1A1**2 in the dominant model (OR = 1.66, 95% CI = 1.06–2.62, $p = 0.03$) and an increased risk of lung cancer in both females and males in the dominant model (females: OR = 1.72, 95% CI = 1.29–2.27, $p = 0.001$; males: OR = 1.46, 95% CI = 1.19–1.78, $p = 0.00$). These associations were also not modified by smoking status.

Smoking is also considered a risk factor for bladder cancer. Several studies have failed to find an association between *SULT1A1* genotype, smoking status and bladder cancer risk (Table 4; Figueroa et al., 2008; Fortuny et al., 2006; Kellen et al., 2006). Others, however, have found increased risk for bladder cancer among ever/heavy smokers (Kellen et al., 2007; Wang et al., 2008a).

SULT1A1 has been shown to be responsible for catalyzing the activation of *N*-hydroxy heterocyclic amines (Chou et al., 1995), which are food-borne carcinogens thought to be involved in colorectal cancer risk. Earlier studies of *SULT1A1* and colorectal cancer risk have produced conflicting results; later analyses have also not been entirely consistent (Table 4). One meta-analysis of 12 different studies failed to find an association (Zhang et al., 2011). Another study found no main effect of *SULT1A1* genotype, but risk associated with frequent consumption of red meat was significantly elevated among carriers of the *SULT1A1**2 allele (OR 2.1, 95% CI 1.1–4.1; Lilla et al., 2007). Fan et al. reported significant gene-gene interactions between a phase I metabolic enzyme involved in the activation of aromatic and polycyclic aromatic amines, CYP1B1, and *SULT1A1**1 in a case-only study of colorectal cancer risk in a Chinese population (Fan et al., 2007). Two other studies from the Ontario Familial Colorectal Cancer Registry have reported significant findings for *SULT1A1*. Colorectal cancer risk increased significantly with well-done meat intake (OR 1.57, 95% CI 1.27–1.93). They also reported that the *CYP1B1* variant and *SULT1A1**2 significantly modified the association between red meat doneness intake and colorectal cancer risk with individuals homozygous for both variants exhibiting the highest colorectal cancer risk (Cotterchio et al., 2008). Another report from this group (Cleary et al., 2010) found that smoking for >27 years was associated with a statistically significant increased colorectal cancer risk and interactions were observed between smoking status and *SULT1A1**1 ($p = 0.02$).

Taken together, these studies tend to support a role for interactions between carcinogen exposure and *SULT1A1* genetic variability. Some of the inconsistent findings could be due to underpowered studies, inconsistent collection of exposure data or selection bias. Perhaps well-designed future studies with sufficient power can overcome these limitations.

Genetic variability in other SULT isoforms

The SULT1C subfamily has been recently cloned and two major isoforms identified in humans (Sakakibara et al., 1998). *SULT1C2* is primarily expressed in the thyroid, stomach and kidney and is involved in the sulfation of xenoestrogens and toxicants in cigarette smoke (Pai et al., 2001, 2002; Yasuda et al., 2007). Two recent studies (Table 5) have indicated that genetic variability in *SULT1C2* might be involved in response to therapy for castration-resistant prostate cancer (Deeken et al., 2010). Associations were also identified for *SULT1C2* heterozygosity and relapse from acute myeloblastic leukemia (relative risk = 4.1; $p = 0.004$; Monzo et al., 2006).

SULT1E1 is the primary SULT involved in estrogen homeostasis in physiological conditions (Falany & Falany, 1996a,b). Studies of genetic variability in *SULT1E1* in relation to cancer risk have been hampered by the low population frequency of known variants, which highlights the importance of this enzyme. Variants in *SULT1E1* have been investigated in relation to breast cancer, mammographic density, endometrial cancer and testicular germ cell tumors (Table 5). In all of these studies, no significant associations could be identified. Although no statistically significant findings have been reported thus far, future genome-wide SNP scans may provide clues on the involvement of *SULT1E1* and disease risk.

Summary

SULTs are an integral component of human metabolism of endogenous compounds and xenobiotics. The most consistent role for *SULT1A1* genetic variation thus far is in association with lung cancer risk. However, *SULT1A1* genetic variation has been suggested to play a minor role in breast cancer risk, but should be considered for postmenopausal as well as Asian women. Prostate, bladder and colorectal cancer risk and pharmacogenomic studies have provided us with conflicting results involving *SULT1A1*. Undoubtedly, the lack of cohesiveness between studies is multifactorial. More comprehensive studies that are well designed and adequately powered need to be conducted to either corroborate or contradict the existing findings. In light of the most recent functional genetic variations of *SULT1A1* including copy number and 3'UTR SNPs, future analyses are necessary to fully describe the extent to which it is involved in carcinogenesis and treatment. While most research has focused on *SULT1A1*, recent tools may shed light on variability in other isoforms. The search for the genetic basis of human population variability has greatly accelerated within the past few years with the completion of the human genome project. Future studies of the functional consequences of common variants may provide better models to genetically explain phenotypic variability in SULTs, and thus, to better predict disease risk and drug response. Examination of variability in sufficiently powered studies with quality exposure data will facilitate the examination of gene–environment interactions involving SULTs, as well as other enzyme families. The next major question in this field may involve epigenetic regulation of SULTs and other metabolizing enzymes as well as an observation of the differences between normal and tumor tissue in the microenvironment.

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Table 1

SULT1A1 genetic variability and breast cancer risk.

Author, year	Cancer site	Population	Cases/controls (n)	Main finding	References
Reding, 2012	Breast (risk)	African-American and Caucasian American	1644/1451	NA	Reding et al. (2012)
Lee, 2012	Breast (risk)	Mixed (meta-analysis)	400/400	Increased risk with <i>SULT1A1</i> *2 in women overall Increased risk with <i>SULT1A1</i> *2 in postmenopausal women	Lee et al. (2012)
Khvostova, 2012	Breast (risk)	Siberian	335/530	Increased risk for <i>SULT1A1</i> *2	Khvostova et al. (2012)
Dumas, 2011	Breast (risk)	Mixed		NA	Dumas & Diorio (2011)
Jiang, 2010	Breast (risk)	Mixed	10 362/14 250	Increased risk with <i>SULT1A1</i> *2 in postmenopausal women and Asian women	Jiang et al. (2010)
Sun, 2011	Breast (risk)	Mixed	9881/13 564	Increased risk with <i>SULT1A1</i> *2 using hospital based controls	Sun et al. (2011)
Yong, 2010	Breast (risk)	Mixed Seattle, WA	175 women with screening mammogram within 1 y	16% lower percent breast density with <i>SULT1A1</i> *2 compared to <i>SULT1A1</i> *1 after controlling for ethnicity, $p = 0.001$	Yong et al. (2010)
Wang, 2010	Breast (risk)	Mixed	8454/11 800	NA	Syamala et al. (2010); Wang et al. (2010)
Syamala, 2010	Breast (risk)	South Indian	359/367	NA	Syamala et al. (2010)
Kotnis, 2008	Breast (risk)	Mixed	132/198	Increased risk for <i>SULT1A1</i> *2 in Asian women	Kotnis et al. (2008)
Gulyaeva, 2008	Breast (risk)	Russian	118/180	NA	Gulyaeva et al. (2008)

NA: no association.

Table 2

SULT1A1 genetic variation and response to therapy for breast cancer.

Author, year	Cancer site	Population	Cases/controls (n)	Main finding	References
Moyer, 2011	Breast (treatment)	Mixed, but 95% Caucasian	190 on tamoxifen monotherapy	NA with <i>SULT1A1</i> copy number and either disease free survival or recurrence	Moyer et al. (2011)
Serrano, 2011	Breast (treatment)	Caucasian	47/135	NA	Serrano et al. (2011)
Knechtel, 2010	Breast (treatment)	Austrian	216 LN+ cases	NA	Knechtel et al. (2010)
Tengström, 2012	Breast (treatment)	Finnish	412 (76 treated with cyclophosphamide, 65 with TAM, 4 with both)	Improved overall survival associated with <i>SULT1A1</i> *2	Tengstrom et al. (2012)
Gjerde, 2008	Breast (treatment)	Caucasians in Norway	151 Tamoxifen treated cases	NA for both genotype and copy number	Gjerde et al. (2008)
Wegman, 2007	Breast (treatment)	Swedish	677 Tamoxifen treated cases	NA	Wegman et al. (2007)
Grabinski, 2006	Breast (treatment)	Caucasian & Hispanic	296 Tamoxifen treated cases	NA	Grabinski et al. (2006)

NA: no association.

Table 3

SULT1A1 genetic variation and other steroid-related cancers.

Author, year	Cancer type	Population	Cases/controls (n)	Main finding	References
<i>SULT1A1</i>					
Arslan, 2011	Prostate	Turkish	104/151	NA between <i>SULT1A1</i> *1 and prostate cancer incidence ($p = 0.24$) or between smokers and non-smokers	Arslan et al. (2011)
Borque, 2013	Prostate	Caucasian American	703 cases with radical prostatectomy and 5 year follow-up data	<i>SULT1A1</i> *1 was associated with increased risk for biochemical recurrence, $p = 0.025$	Borque et al. (2013)
Koutros, 2009	Prostate	Mixed	1126/1127	NA between <i>SULT1A1</i> SNPs, HCA intake, and risk	Koutros et al. (2009)
Koike, 2008	Prostate	Japanese	126/119	NA	Koike et al. (2008)
Ferlin, 2010	Testicular germ cell tumor (TGCT)	Italian	234/218	NA	
O'Mara, 2011	Endometrial	Australian National Endometrial Cancer Study Polish Endometrial Cancer Study	1597/1507	NA	O'Mara et al. (2011)
Gulyaeva, 2008	Endometrial (risk)	Russian	154/180	NA	Gulyaeva et al. (2008)
Hirata, 2008	Endometrial	Caucasian	150/165	Increased risk with <i>SULT1A1</i> *1 and SNPs in the 3' flanking region (14A/G & 85C/T)	Hirata et al. (2008)
Gulyaeva, 2008	Ovarian (risk)	Russian	96/180	<i>SULT1A1</i> *2 higher in cases	Gulyaeva et al. (2008)

NA: no association.

Table 4

SULT1A1 genetic variants and risk of lung, bladder and colorectal cancer.

Author, year	Cancer type	Population	Cases/controls (n)	Main finding	References
Liao, 2012	Lung	Mixed	1669/1890	Significant association between <i>SULT1A1</i> *2 and lung cancer risk NA between smokers and non-smokers	Liao et al. (2012)
Ihsan, 2011	Lung	Indian	188/290	Significant association with risk	Ihsan et al. (2011)
Tamaki, 2011	Lung	Japanese	192/203	NA	Tamaki et al. (2011)
Arslan, 2009	Lung	Turkish	106/271	Significant association with risk	Arslan et al. (2009)
Pachouri, 2006	Lung	North Indians	103/122	Significant association with increasing <i>SULT1A1</i> */ alleles	Pachouri et al. (2006)
Huang, 2009	Bladder	Taiwanese	112 cases	<i>SULT</i> SNPs might modify the arsenic methylation profile and UC progression	Huang et al. (2009)
Figueroa, 2008	Bladder	Spanish Bladder Cancer Study	1150/1149	NA after adjusting for age, gender, region, and smoking status between <i>SULT1A1</i> and bladder cancer	Figueroa et al. (2008)
Wang, 2008	Bladder	Taiwanese	300/300	Significantly increased risk with <i>SULT1A1</i> *1 in ever smokers and heavy smokers (28 pack-years)	Wang et al. (2008b)
Kellen, 2007	Bladder	Belgians	200/385	Increased risk with <i>SULT1A1</i> */1 in ever exposure by false-positive report probability	Kellen et al. (2007)
Kellen, 2006	Bladder	Belgians	200/385	NA	Kellen et al. (2006)
Fortuny, 2006	Bladder	Spaniards	958/1029	NA	Fortuny et al. (2006)
Zhang, 2011	Colorectal	12 study meta-analysis	3549/5610	NA	Zhang et al. (2011)
Cleary, 2010	Colorectal	Canadian (Ontario Familial Colorectal Cancer Registry)	1174/1293	Increased risk with <i>SULT1A1</i> */1 in smokers.	Cleary et al. (2010)
Cotterchio, 2008	Colorectal	Canadian (Ontario Familial Colorectal Cancer Registry)	842/1251	<i>SULT1A1</i> */2 significantly modified the association between red meat doneness intake and CRC risk	Cotterchio et al. (2008)
Fan, 2007	Colorectal	Chinese	207 w/ sporadic CRC	Gene-gene interaction between CYP1B1 1294G & <i>SULT1A1</i> */1	Fan et al. (2007)
Lilla, 2007	Colorectal	German	604/505	CRC risk elevated with frequent consumption of red meat + carriers of <i>SULT1A1</i> */2 allele	Lilla et al. (2007)
				CRC risk elevated with 30+ pack-years of active smoking + carriers of <i>SULT1A1</i> */2 allele	

NA: no association.

Table 5

Genetic variability in other *SULT* isoforms and disease risk or response to therapy.

Author, year	Cancer type	Population	Cases/controls (n)	Main finding	References
SULT1C					
Deeken, 2010	Castration-resistant prostate cancer	Randomized phase II trial with docetaxel ± thalidomide		10 SNPs in 3 genes were potentially associated with response to therapy: SULT1C2, PPAR- δ & CHST3	Deeken et al. (2010)
Monzo, 2006	Intermediate-risk acute myeloblastic leukemia (AML)	French-American-British in the CEFAM-99 prospective trial	110 adults with AML	Increased relapse risk was associated with SULT1C2 heterozygosity	Monzo et al. (2006)
SULT1E1					
Yong, 2010	Mammographic breast density	Mixed Seattle, WA	175	NA	Yong et al. (2010)
Ferlin, 2010	Testicular germ cell tumor (TGCT)	Italian	234/218	NA	Ferlin et al. (2010)
Hirata, 2008	Endometrial	Caucasian	150/165	NA	Hirata et al. (2008)
O'Mara, 2011	Endometrial	Australian National Endometrial Cancer Study & Polish Endometrial Cancer Study	1597/1507	NA	O'Mara et al. (2011)
Udler, 2009	Breast	SEARCH	4470	NA observed between SULT1E1 and survival after breast cancer diagnosis	Udler et al. (2009)

NA: no association.