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[35] Cancer and Molecular Biomarkers of Phase 2

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Abstract

Associations between genotypes of phase 2 enzymes and cancer risk are extracted from epidemiological studies, namely case–control studies. Variant alleles in glutathione *S*-transferase (GST), UDP-glucuronosyltransferase (UGT), sulfotransferase (SULT), and *N*-acetyltransferase (NAT) have been used as molecular genetic biomarkers of risk. GSTM (my)1 has been associated with an increased risk of colorectal cancer, lung cancer, and bladder cancer and GSTP(pi)1 with prostate cancer. UGT1A1*28 and *37 are both associated with an increased risk of breast cancer as is SULT1A1*2. The presence of UGT1A1*28 results in an increased risk of ovarian cancer and NAT2 of colorectal and lung cancer. A high frequency of SULT1A1*1 has been identified in patients with breast cancer; the role in colorectal cancer is more controversial. This chapter discusses the balance between carcinogen activation and detoxification in relation to phase 2 enzymes.

Introduction

Genetic polymorphisms exist in several phase 2 enzymes that catalyze carcinogen activation or detoxification. Although polymorphisms in glutathione *S*-transferase (GST), UDP-glucuronosyltransferase (UGT),

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sulfotransferase (SULT), and *N*-acetyltransferase (NAT) are well established, only few data link a particular genotype to an increased or a decreased risk of cancer. An association between a specific genotype and cancer risk is often found by epidemiological studies, that is, case–control studies. We have identified clinical studies using molecular genetic biomarkers (variant alleles) of phase 2 enzymes as markers of susceptibility to the development of cancer (Table I).

Glutathione *S*-transferase

Glutathione *S*-transferases are a family of inducible enzymes that are important in carcinogen detoxification. They catalyze the conjugation of a variety of different compounds with the endogenous tripeptide glutathione (GSH). Cytosolic GSTs can be divided into four human families (isozymes) with different but sometime overlapping substrate specificities. They are termed A (alpha), M (my), P (pi), and T (theta).

Both the expression and the protein levels of GST isozymes vary between individuals, making them predisposed to the toxic effects of environmental carcinogens. Also, high levels of GSTs (especially GSTP) have been found in human cancer tumors compared with normal tissue (Chang and Yang, 2000; Kelekar and Thompson, 1998; Wolter *et al.,* 1997). Variation in levels of tumor GST may be associated with resistance or susceptibility to chemotherapeutic agents(Lewis *et al.,* 1989).

One of the most studied GSTs is GSTM1, which is only expressed in 50% of the population (Seidegard *et al.,* 1988). Lack of GSTM1 (GST M1 null genotype) is associated with lung cancer. In a meta-analysis of epidemiological studies (Vineis *et al.,* 1999), it was estimated that both Caucasians and Asians had an increased risk of developing lung cancer (OR = 1.21, 95% CI = 1.06–1.39 and OR = 1.45, 95% CI = 1.23–1.70, respectively). Also, bladder cancer was associated with the GSTM1-null genotype. Caucasians had an increased risk of 1.54 (OR) (95% CI = 1.32–1.80) and Asians 1.71 (OR) (95% CI = 1.09–2.91). Other genetic polymorphic GSTs are associated with cancer. In a Japanese case–control study (Nakazato *et al.,* 2003) of patients with familial prostate cancer, it was shown that the GSTP1-valine variant (A-to-C transition at nucleotide 313) was associated with a significant increased risk of prostate cancer in homozygous individuals (OR = 9.31, 95% CI = 0.47–184).

Not only single polymorphisms within each GST class may be used as biomarkers of cancer risk. Combinations of polymorphisms within different GST classes also influence the risk. Individuals with two high-risk genotypes in M1, P1, or T1 have a significantly higher risk of developing prostate cancer (Nakazato *et al.,* 2003), and the risk of CLL is increased

TABLE I
MOLECULAR BIOMARKERS OF PHASE 2 ENZYMES AND RISK OF CANCER IN CASE–CONTROL STUDIES [ODDS RATIO (OR) AND 95% CONFIDENCE INTERVALS (CI)]

Disease	Molecular biomarker	OD (95% CI)	Comments
Colorectal cancer	SULT1A1*1	4.4 (1.6–11.8)	Smoking-associated disease
	SULT1A1*1	0.47 (0.27–0.83)	
	NAT2	1.19	Fast metabolizers
	GSTM1	1.78 (1.39–2.17)	
Breast cancer	SULT1A1*2 (both homo- and heterozygous)	2.11 (1.00–4.46)	Premenopausal women smoking >5 cigarettes daily[b]
	SULT1A1*2 (both homo- and heterozygous)	2.83 (1.23–6.54)	Premenopausal women smoking >20 years[b]
	SULT1A1*2	HR[a] 2.9 (1.1–7.6)	Death among tamoxifen-treated women
	UGT1A1*28	1.8 (1.0–3.1)	Invasive disease in premenopausal African-American women
	UGT1A1*37	1.8 (1.0–3.1)	Invasive disease in premenopausal African-American women
Lung cancer	SULT1A1*2 (both homo- and heterozygous)	1.41 (1.04–1.91)	Women and current and heavy smokers
	NAT2	2.0 (1.1–3.7)	Slow-metabolizing Chinese women
	GSTM1	1.21 (1.06–1.39)	Caucasians
	GSTM1	1.45 (1.23–1.70)	Asians
Bladder cancer	NAT2	1.41 (1.23–1.80)	Slow-metabolizing Caucasians
	GSTM1	1.54 (1.32–1.80)	Caucasians
	GSTM1	1.77 (1.09–2.91)	Asians
Familial prostate cancer	GSTP1	9.31 (0.47–1.84)	
Ovarian cancer	UGT1A1*28	7.20 (2.06–25.19)	Mucinous tumors[b]

[a] Hazard ratio.
[b] Case-only study.

2.8-fold if M1, T1, and P1 are ''high-risk'' genotypes (Yuille *et al.,* 2002). It is even more complicated when high-risk genotypes of other phase II enzymes are combined with GSTs. A polymorphic NAT2 combined with a GSTM1 and T1 null genotype changes the risk of development of breast cancer in women (Lee *et al.,* 2003).

UDP-Glucuronosyltransferase

Conjugation with UDP (uridindiphosphate) by UGT (glucuronidation) is one of the major routes of elimination and detoxification of drugs and endogenous compounds. Carcinogens and their reactive metabolites may also be glucuronidated to harmless intermediates that can be eliminated from the body. However, in some cases, glucuronidation may result in the formation of highly reactive species (Li *et al.,* 1999; Marini *et al.,* 1998) with a potential to create neoplastic development. UGTs consist of two multigene families—UGT1 and UGT2 (Burchell *et al.,* 1991)—on the basis of sequence homology, with distinct but overlapping substrate specificity. The UGT2 family is encoded by separate genes clustered on chromosome 4q13 and consists of the UGT2A and UGT2B subfamilies. UGTs are involved in the inactivation of estradiol and its oxidized and methoxylated metabolites. Variation in activity may therefore modify estrogen exposure and consequently estrogen-related cancer risk. In premenopausal African-American women, genetic epidemiological studies have shown that the UGT1A1*28 (A(TA)7TAA) and the UGT1A1*34 (A(TA)8TAA) promoter alleles were associated with an increased risk of developing invasive breast cancer (OR = 2.1, 95% CI = 1.0–4.2) (Guillemette *et al.,* 2000). However, in a major study of white women within the Nurses' Health Study cohort it was not possible to detect a significant risk in the presence of UGT1A1*28 alleles (Guillemette *et al.,* 2001). Estradiol levels were nevertheless increased among women carrying at least one UGT1A1*28 allele, suggesting a contribution of the glucuronidation pathway in the maintenance of hormone homeostasis. Breast density is a predictor of breast cancer and, in addition, is related to the UGT1A1*28 genotype. However, this association depends on the menopausal status. Premenopausal women homozygote for UGT1A1*28 had significantly lower breast density compared to those with the wild-type genotype (minus 43%). In contrast, postmenopausal women homozygote for the UGT1A1*28 genotype had significantly greater breast density (plus 32%) (Haiman *et al.,* 2003).

Estrogens are somehow also involved in ovarian cancer; however, the exact role is not clear. Cecchin *et al.* (2004) could not detect any difference in prevalence of the UGT1A1*28 genotype between patients with ovarian

cancer and controls. However, using a case–case approach it was observed that individuals with a subtype of ovarian cancer (mucinous tumors) had a higher prevalence of the specific genotype compared to patients with the nonmucinous subtype (55% versus 15%) (OR = 7.20, 95% CI = 2.06–25.19), suggesting that UGT1A1*28 could be used as a valuable biomarker when planning ovarian cancer chemotherapy.

Sulfotransferase

Cytosolic sulfotransferase enzymes catalyze the sulfation of a large variety of drugs and endogenous substances. The thermostable phenol SULT (encoded by SULT1A1) is a key enzyme in the metabolism of aryl amines and polycyclic hydrocarbons (PAHs), constituents of tobacco smoke. The gene contains several polymorphic sites with a high prevalence of a G-to-A transition at nucleotide 638 in exon 7, leading to an arginine-to-histidine substitution. It occurs at a frequency of 0.3 (Carlini *et al.,* 2001). The variant SULT1A1*2 allele is associated with decreased activity compared with the wild-type SULT1A1*1 allele.

In a Dutch case–control study (Tiemersma *et al.,* 2004), the association between smoking and colorectal adenomas and the potential of a specific SULT1A1 genotype to modify this association was investigated. In the study, 431 adenoma cases and 432 polyp-free controls were examined and a multivariate analysis, including age, sex, and endoscope indication, as well as alcohol and smoking habits, was performed. The study showed that smoking for more than 25 years more than doubled the adenoma risk (OR = 2.4, 95% CI = 1.4–4.1) compared with never smoking. Presence of the SULT1A1*1 fast sulfation allele modestly increased the risk of smoking-associated colorectal adenomas (from an OR = 3.5, 95% CI = 0.9–12.4 to an OR = 4.38, 95% CI = 1.6–11.8). However, the difference was not significant. Findings of an additive effect of smoking and the SULT1A1 fast sulfation genotype are consistent with results from biochemical studies indicating that SULT1A1 may activate procarcinogens in cigarette smokers (Chou *et al.*, 1995; Gilissen *et al.*, 1994; Glatt, 2000). The definite role of SULT in the risk of developing colorectal cancer is, however, not yet clarified. Leukocyte DNA from 226 unrelated cases of histological-confirmed colorectal cancers was genotyped for the SULT1A1 allele and compared with 293 controls (Bamber *et al.,* 2001). When the population was considered overall, there was no significant difference in the occurrence of the SULT1A1*1 and SULT1A1*2 alleles, and there was no association between SULT1A1 genotypes and various clinical parameters, including tumor stage and site. However, when data were analyzed matching for age, it was shown that the most common

SULT1A1*1 allele was associated with a significant reduced risk of colorectal cancer (OR = 0.47, 95% CI = 0.27–0.83), suggesting that the high-activity SULT1A1 enzyme protects against dietary and/or environmental chemicals involved in the pathogenesis of colorectal cancer. In this study, SULT1A1*1 was not a risk-carrying gene as in the aforementioned study. However, patients were not matched for smoking habits, and they were generally older than in the Bamber study. A possible explanation may be related to different functions of phase 2 enzymes under different circumstances. SULT is able to act as a bioactivation enzyme (cigarette smoke) or detoxification enzyme (dietary carcinogens), suggesting that the balance of SULT1A1 function is in favor of detoxification and chemical defense in the latter study and in favor of bioactivation of smoke constituents in the first study.

Interaction between smoking habits and gene polymorphism of SULT1A1 and the risk of breast cancer has also been studied. In a case-only study of 288 women with breast cancer (Saintot *et al.,* 2003), it was shown that a SULT1A1*1/*2 or *2/*2 genotype induces an individual susceptibility to breast cancer among premenopausal currently smoking women. A daily cigarette consumption of more than five, as well as duration of smoking of more than 20 years, increased the risk of breast cancer in women carrying the His SULT1A1 allele (OR = 2.11, 95% CI = 1.00–4.46 and OR = 2.83, 95% CI = 1.23–6.54, respectively). In contrast to colorectal cancers, the variant SULT1A1 genotype is the breast cancer risk-carrying gene in young female smokers, indicating that variation in estrogen metabolism due to differences in sulfation capacity may be an important future biomarker.

A very interesting study from Nowell *et al.* (2002) found an association between risk of death among breast cancer patients receiving tamoxifen therapy and low SULT1A1 activity. Patients homozygous for the low-activity SULT1A1*2 allele had approximately three times the risk of death [hazard ratio (HR) = 2.9, 95% CI 1.1–7.6] as those who were homozygous or heterozygous for the SULT1A1*1 allele. Among patients who did not receive tamoxifen, there was no association between survival and SULT1A1 genotype (HR = 0.7, 95% CI = 0.3–1.5). SULT catalyzes sulfation of the active metabolite of tamoxifen, 4-OH tamoxifen, which has a much greater affinity for the estrogen receptor than the parent compound. It was quite unexpected that fast sulfation of 4-OH tamoxifen was associated with a clinical benefit. The authors explain their findings by alterations in the bioavailability of the active metabolite or to an undefined estrogen receptor-mediated event. About 13% of the Caucasian population carries the low activity SULT1A1 genotype, consequently possessing a risk of decreased efficacy of tamoxifen. Although this study

needs to be confirmed by other studies, changes in strategy in breast cancer therapy may have to be considered.

Very few studies have described the relationship between the SULT1A1*2 polymorphism and the risk of lung cancer. In a case–control study from Wang *et al.* (2002), 948 Caucasian subjects (463 cases and 485 controls) were available for analysis, suggesting that individuals with the heterozygous variant allele (SULT1A1*1/*2) or the homozygous variant allele (SULT1A1*2/*2) had a modestly increased risk of developing lung cancer of 41% (OR = 1.41, 95% CI = 1.04–1.91). Subgroup analysis showed that women (OR = 1.64, 95% CI = 1.06–2.56), current smokers (OR = 1.74, 95% CI = 1.08–2.79), and heavy smokers (OR = 1.45, 95% CI = 1.05–2.00) were at elevated risk.

N-Acetyltransferase

These enzymes catalyze the transfer of an acetyl group to the xenobiotic or carcinogen that has to be detoxified. The substrates are often strong carcinogens used in industrial processes or are formed during cooking or cigarette smoking. The human NAT genes consist of two different forms–NAT1 and NAT2–of which NAT1 is monomorphically and NAT2 polymorphically distributed. The acetylation polymorphism in humans is regulated at the NAT2 gene locus on the short arm of chromosome 8 (Blum *et al.,* 1990). The NAT2 polymorphism may have a significant effect on individual susceptibility to the development of cancer diseases. Much of the evidence derives from epidemiological studies in which bladder cancer patients and controls with high exposure to aromatic amines were analyzed for their NAT phenotype. Patients with the slow NAT2 phenotype are associated with an increased risk of bladder cancer (Cartwright *et al.,* 1982), suggesting that acetylation is important in the protection of bladder carcinogenesis by an ability to inactivate carcinogens. In nonsmoking Chinese women, the proportion of a slow acetylator genotype in a group of lung cancer patients was higher (38%) compared with controls (24%) (OR = 2.0, 95% CI = 1.1–3.7) (Seow *et al.*, 1999). No effect of NAT2 genotype was seen among smokers. However, the exact role of NAT in human carcinogenesis is not entirely clear. In contrast to bladder cancer, the development of colon cancer appears to be associated with individuals possessing the fast NAT phenotype (Smith *et al.,* 1995). This is in accordance with *in vitro* studies in *Salmonella typhimurium* strains where it looks as if NAT activates carcinogens (Grant *et al.,* 1992), presumably by *O*-acetylation, which appears to be an activating step, instead of the normal inactivating *N*-acetylation (Hein, 1988). The role of NATs in chemical carcinogenesis is therefore many sided, depending on the type of

exposure (type of reaction catalyzed), the type of cancer, and a possible contribution of other metabolic pathways competing with the same substrate as NATs. It has been shown that that hydroxylation of heterocyclic amines is catalyzed by CYP1A2 in addition to NAT (Kadlubar *et al.,* 1992).

Conclusion

Most of the cited studies are case–control studies trying to find associations between metabolic gene polymorphisms and cancer of various sites. Data often derive from populations with very common cancer diseases, such as colorectal or breast cancer. Individual susceptibility to cancer may result from differences in metabolism, DNA repair, altered protooncogene of tumor suppressor gene expression, and nutritional status. Most carcinogens require metabolic activation before binding to DNA, and individuals with elevated or decreased metabolic capacity may have an increased risk. Phase 2 enzymes conjugate metabolites (i.e., detoxification of carcinogens or activated carcinogens) with glucuronide, glutathione, or sulfate to produce hydrophilic nontoxic products excreted easily in urine or bile. A decreased activity of phase 2 enzymes (a poor metabolizer due to a variant allele genotype) may therefore lead to the opposite effect observed by phase 1 metabolism, namely a decreased capacity to detoxify carcinogens and an increased risk of cancer development. Consequently, a very subtle threshold value between activating and detoxifying enzymes of specific carcinogens and a risk of initiation of cancer development may exist. Existence of defect enzymes due to generic polymorphisms may disrupt this balance in one direction or the other depending on the site of the defect.

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