GST Polymorphism and Excretion of Heterocyclic Aromatic Amine and Isothiocyanate Metabolites after Brassica Consumption

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GST Polymorphism and Excretion of Heterocyclic Aromatic Amine and Isothiocyanate Metabolites after Brassica Consumption

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Abstract
Brassica vegetable intake has been associated with decreased risk and well-done meat intake has been associated with increased risk of cancers at multiple organ sites in epidemiologic studies. Experimental studies suggest a role of modulation of phase I and phase II metabolizing enzymes as one mechanism for these associations. Heterocyclic aromatic amines (HAAs) are carcinogens formed in meat that has been cooked to well-done and at high temperatures. Phase I metabolizing enzymes catalyze the activation of HAAs, and phase II metabolizing enzymes serve to detoxify the active carcinogens. The glutathione S-transferases (GSTs) are a family of phase II metabolizing enzymes that are induced by, and act to conjugate, isothiocyanates (ITCs), phytochemicals found in Brassica vegetables. This review summarizes the results of feeding studies in humans that examine effects of polymorphisms in GSTs on ITC metabolite excretion, reviews the evidence for modulation of HAA mutagenicity by ITCs, and discusses the need for feeding studies examining potential interactions among polymorphic genes encoding phase I and phase II metabolizing enzymes, meat intake, and Brassica intake to elucidate their role in cancer etiology.

Keywords
Brassica; heterocyclic aromatic amines; glutathione S-transferase; isothiocyanate

INTRODUCTION
Brassica vegetables are members of the plant family Brassicaceae. Vegetables of the genus Brassica represent virtually all members of this family that are consumed by humans. The genus includes broccoli, cauliflower, cabbage, kale, collard greens, mustard, watercress, and Brussels sprouts, among others. Isothiocyanates (ITCs) are phytochemicals in Brassica vegetables that have anticarcinogenic properties in cell culture and animal models, and intake of Brassica vegetables is inversely associated with cancer in many epidemiologic studies [Verhoeven et al., 1997; Talalay and Fahey, 2001]. The mechanism of action of these phytochemicals is believed to involve their ability to inhibit phase I and induce phase II metabolizing enzymes, the effect of which may protect cells from the damaging effects of carcinogens, such as heterocyclic aromatic amines (HAAs) found in meat cooked to well-done at high temperatures [Verhoeven et al., 1997]. One class of phase II metabolizing enzymes that has been extensively studied with regard to Brassica vegetables and cancer are the glutathione S-transferases (GSTs). We review here the feeding studies that have examined interactions...
among the GSTs, ITC metabolite excretion, and/or HAA metabolite excretion in humans, providing context for a large and growing cancer epidemiologic literature on the subject. We refer to feeding studies as studies in humans that provide a known dose of a food (in this case, Brassica vegetable) to individuals in a controlled setting over a defined course of time to investigate biologic mechanisms. Outcomes, such as metabolite excretion, gene expression or enzyme activity, are measured to examine effects of the feeding regimen on biologic processes. These studies are typically small in size (less than 100 subjects) and short in duration (e.g., may measure the effects of one meal to up to daily meals for several weeks).

BRASSICA VEGETABLES MAY REDUCE CANCER RISK

Brassica vegetables have been implicated in cancer prevention for a large number of organ sites [van Poppel et al., 1999; Talalay and Fahey, 2001; Lampe and Peterson, 2002; Seow et al., 2005; Higdon et al., 2007; Jeffery and Keck, 2008]. In addition, numerous animal studies have shown that administration of Brassica vegetables or phytochemicals from Brassica vegetables reduces tumor incidence and size [Verhoeven et al., 1997] and has beneficial effects on cell cycle progression and apoptosis [Gamet-Payrastre et al., 2000; Keum et al., 2004; Chiao et al., 2004; Zhang, 2004; Zhang et al., 2006].

The epidemiologic evidence for the association between Brassica intake and cancer risk has been reviewed previously [Higdon et al., 2007], and remains mixed, with most studies showing either an inverse or null association. In our ecological study of breast cancer and nutritional, socioeconomic and reproductive factors using data from 59 countries, we found that on a per-calorie exposure basis, the strongest protective effect was due to Brassica vegetable consumption [Hebert and Rosen, 1996]. In another paper, utilizing data from the Long Island breast cancer study project, we found a borderline significant reduced risk of breast cancer among postmenopausal women, but an increased risk among premenopausal women who consumed ≥6 servings of Brassica vegetables per week as compared with those women consuming 0 or 1 servings per week [Gaudet et al., 2004a]. The increased risk observed in premenopausal women is perplexing as it is inconsistent with other studies (see for example, [Fowke et al., 2003a; Ambrosone et al., 2004]). Inconsistencies in study results may reflect the different dietary assessment tools used or the limited range in intake of some populations studied [Hebert and Miller, 1988; Hebert, 2005]. Some dietary assessment methods may not have included all, or even the most common, Brassica vegetables consumed in the population under study (e.g., kale), whereas others may have include non-Brassica vegetables (e.g., spinach) resulting in inaccurate exposure data or narrow ranges of intake that limit the ability to observe an association if one exists. Intakes of Brassica vegetables are highest in East Asian countries, where individuals eat foods rarely eaten in the West, but only a few studies have tested for associations in populations from this geographic region [London et al., 2000; Seow et al., 2002; Zhao et al., 2001; Fowke et al., 2003b]. Perhaps more importantly, it may be necessary to categorize individuals by genetic susceptibility, such as by polymorphisms for genes encoding phase I or phase II metabolizing enzymes known to be affected by phytochemicals in Brassica vegetables, to clearly observe an effect of Brassica vegetable intake on cancer risk. The interaction between ITCs and polymorphisms in one family of phase II metabolizing enzymes, the GSTs, has been examined in numerous epidemiologic studies in relation to lung [London et al., 2000; Spitz et al., 2000; Zhao et al., 2001; Lewis et al., 2002; Wang et al., 2004; Brennan et al., 2005], colon and colorectal [Lin et al., 1998; Slattery et al., 2000; Seow et al., 2002], prostate [Joseph et al., 2004], head and neck [Gaudet et al., 2004b], renal cell [Moore et al., 2007], and breast [Fowke et al., 2003a; Ambrosone et al., 2004; Steck et al., 2007b; Lee et al., 2008] cancers. However, the mechanisms underlying these associations have been explored in only a few feeding studies, as discussed later.
ITCs ARE PHYTOCHEMICALS RELEASED UPON BRASSICA VEGETABLE CONSUMPTION

Brassica vegetables contain glucosinolates, which upon chewing or chopping, are hydrolyzed into ITCs, indoles, and other substances by an enzyme called myrosinase that is present in a separate cellular compartment in the vegetable. The ITCs are responsible for the pungent flavor or biting taste that is experienced, acutely by many individuals, upon consumption of Brassica vegetables [Zhang and Talalay, 1994]. It is estimated that significant portions of ITCs are released upon intake of average servings of Brassica vegetables. In one study, consumption of 2 oz of watercress resulted in the release of ~12 mg of a specific ITC, phenethyl ITC (PEITC), representing a 30 to 67% conversion rate [Chung et al., 1992]. Brassica vegetables contain varying amounts of different glucosinolates, giving rise to different ITCs [Kushad et al., 1999; Vermeulen et al., 2006; Velasco et al., 2007; Cartea et al., 2008]. See review by Zhang [2004] and study by Shapiro et al. [1998] for chemical structures and metabolic pathways of ITCs. The most commonly studied of the ITCs include sulforaphane (primarily from broccoli), PEITC (from Chinese cabbage, radishes and watercress), and allyl ITC (AITC; from mustard, collard greens and kale). The amount of different glucosinolates, and hence, ITC byproducts, can vary at least 10-fold within and between Brassica vegetables, and even within varieties of a single vegetable type [Finley, 2005]. Cooking reduces ITC availability by inactivating myrosinase [Conaway et al., 2000]. However, even in the absence of myrosinase activity, small amounts of ITCs are released by the gut microflora [Krul et al., 2002]. ITCs are metabolized by the mercapturic acid pathway, which involves initial conjugation with glutathione (GSH) and further enzymatic modification to N-acetylcysteine (NAC) conjugates (mercapturic acids) that are rapidly excreted in the urine [Mennicke et al., 1983; Ye et al., 2002]. The rapid accumulation of ITC in cells is due primarily to this conjugation with GSH [Zhang et al., 2006].

HAAs ARE CARCINOGENS FORMED IN WELL-DONE MEAT COOKED AT HIGH TEMPERATURES

HAAs are formed when amino acids pyrolyze in meat juice. Their concentrations are particularly high in panfried, grilled and, to a lesser extent, broiled meat [Knize et al., 1999]. The amount of HAAs formed is dependent upon the method, temperature, and duration of cooking, with greater doneness and higher temperatures associated with higher concentrations of HAAs [Sinha et al., 1998a, b]. Concentrations of three HAAs, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQX), are detectable in meat cooked by various methods [Sinha, 2002]. Foods high in MeIQx include panfried hamburger, sausage, and steak cooked to well-done or very well-done. By contrast, DiMeIQx has been detected in small quantities in pan-fried very well-done steak and in pan-fried and grilled/barbecued chicken [Sinha et al., 1995, 1995b]. Steak cooked to very well-done by frying or grilling/barbecuing and chicken are major contributors to PhIP intake [Sinha et al., 1998b; Skog and Solyakov, 2002]. HAAs are known carcinogens in animals, and are involved in the development of tumors through direct damage to DNA (formation of DNA adducts) [el-Bayoumy et al., 1995; Snyderwine et al., 2002]. MeIQx and PhIP are activated via hydroxylation with CYP1A2 in the liver [Boobs et al., 1994], as well as with other CYPs including CYP1A1 and CYP1B1 in extrahepatic tissue [Crofts et al., 1998]. Additional reactions such as conjugation with sulfotransferases, N-acetyltransferases, UDP-glucuronosyltransferases, and perhaps GSTs then occur to detoxify the active carcinogen [Pool-Zobel et al., 2005; Turesky, 2005].
Dietary intake of these meat and meat-derived HAAs has been linked consistently to colorectal cancer [Cross and Sinha, 2004], and has been linked to breast cancer in some [De Stefani et al., 1997], but not all [Delfino et al., 2000; Sinha et al., 2000] epidemiologic studies. In a previous study, we found that high lifetime intake of grilled/barbecued and smoked meats was associated with increased risk of breast cancer among women consuming few fruits and vegetables [Steck et al., 2007c]. This is consistent with experimental studies that suggest that chemopreventive constituents of fruits and vegetables, such as ITCs, may protect against HAA-induced genotoxicity [Dingley et al., 2003; Conaway et al., 2005].

A few feeding studies in humans have examined the effect of Brassica vegetable intake on HAA metabolism and DNA adduct formation after meat and Brassica consumption [Murray et al., 2001; Steinkellner et al., 2001; Hoelzl et al., 2008]. In one study, excretion of MeIQx and PhIP in urine following a fried meat meal was reduced after 14 days of intake of 250 g each of Brussels sprouts and broccoli compared with a control period in which no Brassica was consumed [Murray et al., 2001]. Hoelzl et al. [2008] found that after consumption of 300 g Brussels sprouts per day for 6 days, PhIP-induced DNA damage was reduced in lymphocytes collected from participants before and after the intervention. Similarly, Steinkellner et al. [2001] report results from feeding studies showing that urinary mutagenicity following meat consumption was decreased with the consumption of red cabbage prior to the meat meals, while a larger portion of the excreted mutagenic substances were conjugated following cabbage consumption. Finally, in one small pilot study, eight individuals were fed fried meat daily for 6 weeks, with half of the subjects consuming Brassica vegetables daily, and the other half consuming no Brassica vegetables [DeMarini et al., 1997]. In that study, conjugated mutagens in urine doubled among the subjects consuming Brassica vegetables but decreased among those not consuming Brassica vegetables. This finding is consistent with the hypothesis that Brassica vegetables are working through a phase II enzyme-inducing mechanism. This study also genotyped participants for GSTM1 and other genes encoding phase II metabolizing enzymes, but because of the small sample size (n = 8), did not allow for characterizing the effect of GST genotype on response to the combination of Brassica vegetable and meat intake. Thus, more work in this area is needed to examine whether these in vivo effects are mediated by genotypes for genes encoding both phase I and phase II metabolizing enzymes.

ITCs FROM BRASSICA VEGETABLES MODULATE PHASE I AND PHASE II METABOLIZING ENZYMES AND HAVE ANTICARCINOGENIC PROPERTIES

The biologic rationale supporting the role of ITCs in cancer prevention is related, in part, to their ability to modulate phase I and phase II enzymes [Hecht, 1999; Talalay and Fahey, 2001; Lampe and Chang, 2007; Clarke et al., 2008]; thereby detoxifying carcinogens such as the HAAs (see Fig. 1). The cytochrome P450 enzymes are phase I enzymes that are responsible for transforming precarcinogens to their carcinogenic form(s) and for metabolizing carcinogens to more carcinogenic form(s). In the process, electrophilic intermediates may be formed that can react with macromolecules to form DNA adducts. If not repaired, these DNA adducts can cause mutations in critical genes involved in cell cycle control or tumor suppression. In contrast, phase II enzymes, such as the family of GSTs and NAD(P)H:quinone oxidoreductase (NQO1), are capable of detoxifying these P450-activated carcinogens through the addition of polar moieties that make the carcinogen readily excretable (GSTs) and suppress the creation of reactive oxygen species (NQO1). Thus, inhibiting certain phase I enzymes or inducing the phase II enzymes (to a greater extent than any phase I induction) are two potential ways to reduce carcinogenicity. ITCs have been shown to do both in animal models and in
The effects of specific ITCs on CYP enzymes in cell culture and animal studies have been reported, albeit with mixed results. Sulforaphane has been shown to inhibit CYP1A1 and CYP2B1/2 in rat hepatocytes, and to decrease mRNA levels of CYP3A4 in human hepatocytes [Maheo et al., 1997], as well as inhibit steroid and xenobiotic receptor (SRX)-mediated induction of CYP3A4 in human hepatocytes and intestinal cells [Zhou et al., 2007]. PEITC also has been shown to inhibit CYP1A1, CYP1A2, and CYP2B1 in rat liver microsomes [Conaway et al., 1996], inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4 human isoforms in baculovirus-infected insect cells, and function as a mechanism-based inactivator of CYP2E1 [Nakajima et al., 2001]. Similarly, another ITC, BITC, was shown to be a mechanism-based inactivator of CYP2E1 [Moreno et al., 1999]. However, sulforaphane had no effect on CYP activity in human or rat liver in another study [Hanlon et al., 2008]. In contrast to previous studies, sulforaphane induced hepatic CYP1A2 in rats fed sulforaphane for 10 days [Yoxall et al., 2005], and PEITC was shown to upregulate CYP1A1 and activate CYP1A2 transcription in human hepatocytes [Gross-Steinmeyer et al., 2004]. Thus, the variation in Phase I enzyme response to ITCs appears to depend on experimental conditions and the different assays used to measure enzyme activity.

In human feeding studies, Brassica vegetables have the effect of upregulating CYP1A2 activity. This has been reported for intake of broccoli [Vistisen et al., 1992; Kall et al., 1996; Lampe et al., 2000b], cabbage and Brussels sprouts combined [Pantuck et al., 1979], and broccoli and Brussels sprouts combined [Murray et al., 2001]. Given the variety of phytochemicals present in Brassica vegetables, this effect may not entirely be contradictory to the cell culture studies showing inhibition of CYP1A2 by ITCs, if, in fact, other compounds in Brassica vegetables (such as indole-3-carbinol) have the effect of upregulating CYP1A2 beyond the inhibition exhibited by the ITCs.

In humans, a few feeding studies have reported changes in GST activity upon Brassica consumption [Bogaards et al., 1994; Steereama et al., 1995; Lampe et al., 2000a; Lampe et al., 2000b]. In one study of males only, GST-α was increased in plasma following consumption of 300 g/d cooked Brussels sprouts for 2 weeks [Bogaards et al., 1994]. Similarly, Nijhoff et al. [1995b], found that plasma GST-α was increased in males, but not in females, after 6 days of consuming 300 g/d cooked Brussels sprouts, while urinary GST-alpha and both plasma and urinary GST-pi levels were not significantly changed by the intervention. A study by Lampe et al. [2000a], found that GST-α activity was increased in fasting blood samples from GSTM1-null women (but not in GSTM-positive women or in men of either genotype) after consuming Brassica vegetables for 6 days. One small crossover feeding study also found increased GST-α and -π levels in rectal biopsies from humans after intake of 300 g/d Brussels sprouts for 7 days [Nijhoff et al., 1995a]. However, a recent feeding study showed no change in expression of GSTs in human gastric mucosa after one dose of standard broccoli or high-glucosinolate broccoli [Gasper et al., 2007]. Possible reasons for this discrepant result may be the fact that only a single dose of broccoli was administered in that study precluding the examination of effects of more chronic intake.

**ITCs ARE SUBSTRATES FOR GSTs WHICH ARE POLYMORPHIC IN HUMAN POPULATIONS**

In addition to inducing GSTs, ITCs are known substrates for the GSTs (see Fig. 1). Functional polymorphisms in the GST family of genes have been identified and the frequencies of some of these differ by race, as found in the Carolina Breast Cancer Study [Millikan et al., 2000]. The most studied of the GST genes in relation to Brassica vegetables and cancer are GSTM1,
GSTT1, and GSTP1. A deletion in both alleles of GSTM1 results in no enzyme activity in an estimated 52% of European Americans but only 28% of African Americans. A deletion in both alleles of GSTT1 exists equally among African Americans and European Americans at ~20%. For GSTP1, an amino acid substitution (Ile105Val) is associated with alterations in enzyme activity; approximately 49% of European Americans and 55% of African Americans are heterozygous, whereas 11% of European Americans and 23% of African Americans carry the homozygous variant. The functional effect of this polymorphism is not entirely clear, as there is evidence that the Val allele has reduced specific activity to sulforaphane as compared with the Ile allele in one study [Lin et al., 2003], whereas the Ile allele has lower activity toward detoxifying benzo(a)pyrene (BaP) compared with the Val allele in another study [Sundberg et al., 1998].

In vitro studies reveal that different classes of GSTs are more efficient catalysts for specific ITCs than others, with GSTM1 and GSTP1 being the most efficient, GSTA1 less efficient, and GSTM2 and GSTM4 least efficient for each of four ITCs studied (AITC, benzyl-ITC, PEITC, and sulforaphane) [Kolm et al., 1995; Zhang et al., 1995]. There is evidence from controlled feeding studies that individuals can be separated into high and low excreters of ITC, even at constant dosing [Shapiro et al., 1998]. One hypothesis to explain is that having the inactive form of GSTs may result in reduced excretion of ITC metabolites due to reduced metabolism of these phytochemicals. This hypothesis was supported in one observational study, where the null genotype for GSTT1, as compared with non-null genotype, was associated with lower ITC excretion levels in Singapore Chinese, eating mostly green leafy crucifers such as Chinese cabbage [Seow et al., 1998]. However, more recently, a broccoli feeding study in the UK found that individuals with the GSTM1-null genotype had significantly higher excretion of sulforaphane metabolites following broccoli intake than GSTM1-positive subjects [Gasper et al., 2005]. We conducted a one-meal feeding study examining the relationship between polymorphisms in GSTM1, GSTT1, GSTP1, and GSTA1, and ITC metabolite excretion after broccoli consumption in humans [Steck et al., 2007a]. Similar to the Gasper et al. study, we did not observe an increase in ITC metabolite excretion in individuals with the non-null or more active genotypes.

Even within a single family of vegetables, such as the crucifers and a specific genus, Brassica, effects may differ between different vegetables, and there may be alternative routes of metabolism for the different ITC (namely sulforaphane in the broccoli studies). There is speculation that there may be differential effects of different Brassica vegetables on cancer risk because of differences in their phytochemical constitution [Gasper et al., 2005]. Other factors that may explain the differential excretion of ITCs between individuals include the amount of chewing, which affects the release of myrosinase from the vegetable. In the case of cooked vegetables, where myrosinase has been inactivated, conversion of glucosinolates to ITCs still occurs via the gastrointestinal microflora, so differences in ITC excretion between individuals also may be related to differences in the gastrointestinal microflora. Finally, there is speculation that the GSTs affect the rate of ITC excretion, rather than the absolute amount excreted; in which case, a single urinary measurement of ITC excretion would have little value within either a feeding study or epidemiologic study designed to account for this difference in rate. The relationship between GST genotypes and excretion of specific ITC from other Brassica vegetables besides broccoli has not been tested in human feeding studies. These types of feeding studies are needed to identify whether certain GSTs are more important in specific ITC metabolism and excretion than others in vivo, and whether one class of GSTs may compensate when another class is missing or less active. Interestingly, sulforaphane was the poorest substrate for GSTM1, GSTP1, GSTA1, and GSTM2 enzymes, yet was the most potent inducer as compared with three other ITC in vitro [Zhang et al., 1995]. This suggests that it may be sulforaphane’s ability to induce the GSTs rather than its role as a substrate for the GSTs that
is most crucial in cancer prevention. This is consistent with findings from some studies in the United States showing that intake of Brassica vegetables (the majority being broccoli) is associated with greater cancer risk reduction in individuals with the active forms of the GST genes as compared with individuals with the inactive forms [Spitz et al., 2000; Joseph et al., 2004; Wang et al., 2004].

CONCLUSION

Intake of Brassica vegetables in relation to GST polymorphisms represents a well-studied gene-diet interaction in cancer epidemiology. As described earlier, interaction between GSTs, HAAs, and ITCs may exist and two possible mechanisms include: (1) polymorphisms in GSTs that reduce enzyme activity may predispose meat-eaters to cancer by reducing HAA detoxification; in turn, intake of Brassica vegetables may counteract this effect because of the ability of ITCs to induce GSTs and other phase II metabolizing enzymes and enhance HAA detoxification; (2) polymorphisms in GSTs that reduce enzyme activity may enable individuals consuming high amounts of Brassica vegetables to sequester ITCs in the body to act via chemopreventive mechanisms; these individuals may then be more protected against meat-derived HAA intake than individuals with the fully active enzymes and low Brassica vegetable intake. Of course, these mechanisms are not mutually exclusive. One small pilot study in humans provides suggestive evidence that both GST polymorphism and ITC intake may modulate effects of HAA on urinary mutagenicity [DeMarini et al., 1997]. More work is needed to elucidate the full capabilities of these interactions to beneficially affect health and disease risk. Feeding studies that enroll adequate numbers of individuals of varying genotypes; and then examine the effects of cooked vs. raw Brassica vegetables, of different types of ITCs from various Brassica vegetables, and both ITC and HAA metabolite excretion patterns by genotype are warranted as these factors cannot be controlled in observational epidemiologic studies.

Intake of Brassica vegetables is estimated to be low in the American population. Based on data from the Continuing Survey of Food Intakes by Individuals on over 4,800 Americans, fewer than 20% of the study sample consumed a Brassica vegetable (broccoli, cauliflower, kale or Brussels sprouts) in the two-day reporting period [Johnston et al., 2000]. Given the substantial scope for increasing intake of Brassica vegetables in the American population, efforts to increase consumption may be more effective and economical if tailored to individuals who will receive the most benefit, i.e., those who are genetically susceptible to the benefits of Brassica vegetable intake. Thus, it is extremely important to study the biologic mechanisms linking ITCs to inhibition of carcinogenicity by HAAs and to study the effect of GST genotype on response to ITC and HAA intake in humans to determine whether the observational data on the association between ITC, GST genotype and cancer are merely chance findings or whether they have etiologic implications.

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AITC</td>
<td>allyl isothiocyanate</td>
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<td>BaP</td>
<td>benzo(a)pyrene</td>
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<td>DiMeIQX</td>
<td>2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline</td>
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<td>GSH</td>
<td>glutathione</td>
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<td>GST</td>
<td>glutathione S-transferase</td>
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<td>HAA</td>
<td>heterocyclic aromatic amine</td>
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<td>ITC</td>
<td>isothiocyanate</td>
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<td>MeIQx</td>
<td>2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline</td>
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<td>Acronym</td>
<td>Description</td>
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<tr>
<td>NAC</td>
<td>N-acetylcysteine</td>
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<td>NQO1, NAD(P)H</td>
<td>quinone oxidoreductase</td>
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<td>PEITC</td>
<td>phenethyl isothiocyanate</td>
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<tr>
<td>PhIP</td>
<td>2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine</td>
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<tr>
<td>SXR</td>
<td>steroid and xenobiotic receptor</td>
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**References**


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Environ Mol Mutagen. Author manuscript; available in PMC 2010 October 22.
Fig. 1.
Biologic pathways relating ITCs, HAAs, GSTs, and primary cancer. Isothiocyanates are substrates for GSTs. Isothiocyanates may inhibit or induce phase I metabolizing enzymes (CYPs such as CYP1A1, CYP1A2, CYP2A1, CYP2A6, CYP2B1, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4) that activate heterocyclic aromatic amines into active mutagens, and induce phase II metabolizing enzymes, such as the GSTs, that detoxify the active mutagens. Adapted with permission from Lin HJ, et al. 1998. Glutathione transferase null genotype, broccoli, and lower prevalence of colorectal adenomas. Cancer Epidemiol Biomarkers Prev 7:647–652, American Association for Cancer Research.