PAH-DNA Adducts, Cigarette Smoking, \textit{GST} Polymorphisms, and Breast Cancer Risk

Kathleen M. McCarty

Regina M. Santella

Susan E. Steck

University of South Carolina - Columbia, ssteck@sc.edu

Rebecca J. Cleveland

Jiyoung Ahn

\textit{See next page for additional authors}

Follow this and additional works at: https://scholarcommons.sc.edu/sph_epidemiology_biostatistics_facpub

Part of the Public Health Commons

\textbf{Publication Info}

Published in \textit{Environmental Health Perspectives}, Volume 117, Issue 4, 2009, pages 552-558.

McCarty, K. M., Santella, R. M., Steck, S. E., Cleveland, R. J., Ahn, J., Ambrosone, C. B., ... Gammon, M. D. (2009). PAH-DNA adducts, cigarette smoking, \textit{GST} polymorphisms, and breast cancer risk. \textit{Environmental Health Perspectives, 117}(4), 552-558.

DOI: 10.1289/ehp.0800119

Reproduced with permission from Environmental Health Perspectives

© Environmental Health Perspectives, 2009, National Institute of Environmental Health Sciences

This Article is brought to you by the Epidemiology and Biostatistics at Scholar Commons. It has been accepted for inclusion in Faculty Publications by an authorized administrator of Scholar Commons. For more information, please contact digres@mailbox.sc.edu.
PAH–DNA Adducts, Cigarette Smoking, GST Polymorphisms, and Breast Cancer Risk

**Kathleen M. McCarty,**1,2 **Regina M. Santella,**3 **Susan E. Steck,**4 **Rebecca J. Cleveland,**1 **Jiyoung Ahn,**5 **Christine B. Ambrosone,**6 **Kari North,**1 **Sharon K. Sagiv,**1 **Sybil M. Eng,**7 **Susan L. Teitelbaum,**9 **Alfred I. Neugut,**9,10 and **Marilie D. Gammon**1

1Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; 2Department of Epidemiology and Public Health, Division of Environmental Health Sciences, School of Medicine, Yale University, New Haven, Connecticut, USA; 3Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA; 4Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, USA; 5Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA; 6Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York, USA; 7Epidemiologic Resources, Safety Evaluation, and Epidemiology, Pfizer, Inc., New York, New York, USA; 8Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, New York, USA; 9Department of Epidemiology, Mailman School of Public Health, and 10Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York, USA

**BACKGROUND:** Polycyclic aromatic hydrocarbons (PAHs) may increase breast cancer risk, and the association may be modified by inherited differences in deactivation of PAH intermediates by glutathione S-transferases (GSTs). Few breast cancer studies have investigated the joint effects of multiple GSTs and a PAH biomarker.

**OBJECTIVE:** We estimated the breast cancer risk associated with multiple polymorphisms in the GST gene (GSTT1, GSTM1, GSTP1, and GSTT1) and the interaction with PAH–DNA adducts and cigarette smoking.

**METHODS:** We conducted unconditional logistic regression using data from a population-based sample of women (cases/controls, respectively): GST polymorphisms were genotyped using polymerase chain reaction and matrix-assisted laser desorption/ionization time-of-flight assays (n = 926 of 916), PAH–DNA adduct blood levels were measured by competitive enzyme-linked immunosorbent assay (n = 873 of 941), and smoking status was assessed by in-person questionnaires (n = 943 of 973).

**RESULTS:** Odds ratios for joint effects on breast cancer risk among women with at least three variant alleles were 1.56 (95% confidence interval (CI), 1.13–2.16) for detectable PAH–DNA adducts and 0.93 (95% CI, 0.56–1.36) for no detectable adducts; corresponding odds ratios for three or more variants were 1.18 (95% CI, 0.82–1.69) for ever smokers and 1.44 (95% CI, 0.97–2.14) for never smokers. Neither interaction was statistically significant (p = 0.43 and 0.62, respectively).

**CONCLUSION:** We found little statistical evidence that PAHs interacted with GSTT1, GSTM1, GSTP1, and GSTA1 polymorphisms to further increase breast cancer risk.

**KEY WORDS:** breast cancer, GST, Long Island, PAH–DNA adducts, smoking. Environ Health Perspect 117:552–558 (2009). doi:10.1289/ehp.0800119 available via http://dx.doi.org/ [Online 10 December 2008]

Polycyclic aromatic hydrocarbons (PAHs) are an environmentally ubiquitous class of compounds that are formed during incomplete combustion of organic substances. Several PAHs have been classified as probable human carcinogens (Boffetta et al. 1997; Shimada 2006). In the general population, the major source of exposure is tobacco smoke (Lioy and Greenberg 1990), with diet (grilled/ smoked foods, cereals, and leafy green vegetables) and exposure to fossil fuel combustion by-products contributing to cumulative exposure (Waldman et al. 1991). Although there is strong evidence for the relationship between PAH exposure and lung, skin, and bladder cancer in humans, it is equivocal as to whether PAH exposure is associated with breast cancer (Boffetta et al. 1997; Gammon and Santella 2006; Shimada 2006).

PAH–DNA adducts reflect not only PAH exposure but also the body’s ability to metabolize these compounds. The formation of these carcinogen–DNA adducts is recognized as a key event in the initiation of carcinogenesis (Gammon et al. 2004b; Hecht 2003; Wogan et al. 2004). In the Long Island Breast Cancer Study Project (LIBCSP), a large population-based case–control study, blood levels of PAH–DNA adducts were associated with a modest 29–35% elevation in breast cancer risk among women (Gammon et al. 2004b). These findings are consistent with previously conducted, smaller hospital-based studies (Li et al. 1996, 2002; Rundle et al. 2000a). Animal studies have provided further support for the role of PAHs as mammary carcinogens (Cavalieri et al. 1991; el-Bayoumy et al. 1995). Although a significant association between breast cancer risk and detectable PAH–DNA adducts has been noted, a dose–response relationship was not observed in the LIBCSP. Further stratification by known sources of PAH exposure, such as cigarette smoking or the consumption of PAH-containing foods, did not modify this association (Gammon et al. 2004b). These findings are consistent with those from smaller studies (Hu et al. 2007). The lack of a dose response effect suggests that there may be subgroups of women who are more genetically susceptible to the carcinogenic effects of PAH exposure on breast tissue.

Inherited differences in the metabolism of PAHs, interindividual differences in enzyme expression, and induction may be key determinants in individual breast cancer susceptibility (Shimada 2006). Genetic differences in metabolic activation and detoxification of PAHs have been shown to affect differences in phenotypic biomarkers such as urinary metabolites and are hypothesized to influence cancer risk (Brescia et al. 2004; Hatuskami et al. 2006; Hecht et al. 2006; Kuljukka-Rabb et al. 2002; Upadhayaya et al. 2006; Wogan et al. 2004). Further investigation of these genetic differences in the deactivation of PAH metabolites may contribute to our understanding of the lack of a dose–response relationship and increased understanding of breast cancer risk.

The phase II metabolic superfamily of GST enzymes is involved in the metabolic activation and deactivation of PAH metabolites, and polymorphisms in these genes lead to specific changes in enzyme function and the capacity to metabolize PAH compounds (Hecht 1999). The GSTM1 null polymorphism [GenBank BC036805; National Center for Biotechnology Information (NCBI) 2009a] results in the absence of isoenzyme (mu)
expression and reduced glutathione binding efficiency of PAH epoxides and other genotoxic substrates (Hayes and Pulford 1995). The GSTP1 Ile105Val polymorphism [GSTP1; Unigene Hs.523836 (NCBI 2009b)] is associated with reduced isoenzyme (pi) expression and a reduced capacity to inactivate carcinogens, including the diol epoxides created during phase I metabolism of PAHs (Coles and KadiIubar 2003; Pavanello and Clonfero 2000; Ryberg et al. 1997; Watson et al. 1998). The GSTT1 null polymorphism (Genbank X79389) results in the absence of (theta) isoenzyme (Hayes and Pulford 1995), but the role of this polymorphism in relation to PAH metabolism is uncertain (Pavanello and Clonfero 2000). On the one hand, the theta isoenzyme is thought to activate alkylating agents, such as nitrosamines present in tobacco smoke (Hecht 1999; Pavanello and Clonfero 2000); on the other hand, in human erythrocytes, the theta isoenzyme binds reactive conjugates to glutathione, inhibiting genotoxic damage to DNA (Pelin et al. 1996). GSTs conjugate PAH diol epoxides into water-soluble products, and GST enzymes also protect against products of oxidative stress (Mitrunen and Hirvonen 2003). GSTA1 (Unigene Hs.446309) is thought to decrease reactive oxygen species and, via an increase in antioxidant levels, to also play an active role in PAH metabolism (Ahn et al. 2006; Coles et al. 2005; Korabsy and El-Kadi 2006). For GSTA1, two alleles, hGSTA1*A and hGSTA1*B, differ in three linked base changes in the 5′ promoter region of the gene: T→G at nucleotide 567, C→T at nucleotide 69, and G→A at nucleotide 52 (Coles et al. 2001a, 2001b). These substitutions result in differential expression (Coles et al. 2001b), with lower transcriptional activation with GSTA1*B (variant) than with GSTA1*A (common) alleles. It has been demonstrated by our group that the variant GSTA1*B/B genotype is associated with higher risk of breast cancer among smokers compared with nonsmokers with the A/A* genotype (Ahn et al. 2006).

Only one breast cancer study (Rundel et al. 2000b) has reported on a potential interaction between GSTM1 null genotype and PAH–DNA adducts. However, the sample size was small (<100 cases), yielding unstable effect estimates and prohibiting exploration of more than one single nucleotide polymorphism from among the many that contribute to this complex cascade of activation and detoxification. Investigating whether genetically determined differences in multiple GST genotypes modify the association between breast cancer risk and PAH exposure may improve our ability to identify women who are susceptible to the carcinogenic effects of PAHs on breast tissue.

The goal of our present analysis was to investigate whether multiple GST polymorphisms modify the relationship between PAH exposure and breast cancer, using the lymphocyte PAH–DNA adduct biomarker as our primary exposure measure of interest using a large, population-based sample of cases and controls from the LIBCSP. We also evaluated the interaction between GST polymorphisms and smoking status, because smoking behavior was previously identified as the strongest predictor of detectable PAH–DNA adducts (Shantakumar et al. 2005). Finally, we investigated the joint effects of smoking status and GST polymorphisms on detectable PAH–DNA adducts among control women.

Methods

Study population. The population-based sample of cases and controls from the LIBCSP has been described previously (Gammon et al. 2002a). Briefly, cases were defined as English-speaking adult women newly diagnosed with breast cancer residing in Nassau County or Suffolk County in Long Island, New York. Population-based controls were identified through random-digit dialing for women <65 years of age, and by Health Care Finance Rosters for women ≥65 years of age within the same counties, and frequency matched them (by 5-year age groups) to cases. Participants were between 20 and 98 years of age; 94% were white, 4% were black, and 2% other races/ethnicities. The study protocol was approved by the institutional review boards of the collaborating institutions, and written informed consent was obtained from the LIBCSP participants.

Data collection. Respondents to the case-control interview included 1,508 cases and 1,556 controls (Gammon et al. 2002a). The 2-hr in-person structured interview collected data on history of cigarette smoking (current, past), exposure to environmental tobacco smoke in the residential home throughout the life course (Gammon et al. 2004a), and other characteristics potentially relevant to breast cancer risk. Blood samples were obtained from 73% of cases and 73% of controls (Gammon et al. 2004b).

Laboratory assays. We processed the blood samples collected by Gammon et al. (2004b), isolated the DNA and completed genotyping for GSTT1 and GSTM1 as previously described (Steck et al. 2007b), by a multiplex polymerase chain reaction method as previously described (Bell et al. 1992). Genotyping for GSTP1 (Ile105Val; rs1695) (Steck et al. 2007b) and GSTA1 (Ahn et al. 2006) was completed as previously described by matrix-assisted laser desorption/ionization time-of-flight assay (Fannon 2002). We included positive and negative controls in each batch, and a random 10% repeated sampling yielded a 97% concordance. Genotype distributions of GSTA1 (p = 0.81) and GSTP1 (p = 0.38) were in Hardy-Weinberg equilibrium among controls. The number of cases and controls, respectively, for whom genotyping was successful varied with genotype (n = 1,041 and 1,090 for GSTA1, 983 and 1,016 for GSTT1, 975 and 1,001 for GSTM1, and 1,027 and 1,069 for GSTP1). Missing genotype data were primarily due to insufficient DNA (Ahn et al. 2006; Steck et al. 2007b).

PAH–DNA adducts were measured in peripheral mononuclear cell DNA using competitive enzyme-linked immunosorbent assay as previously described (Gammon et al. 2002b). PAH–DNA adduct measurements were available for 873 cases and 941 controls who donated sufficient blood volume for the assay, as described previously (Gammon et al. 2004b).

Statistical methods. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression using SAS version 9.0 (SAS Institute Inc., Cary, NC). All models were adjusted for age at reference (date of diagnosis for cases and date of identification for controls), the frequency-matching factor. Covariates considered as potential confounders included race, family history of breast cancer, parity, age at menarche, age at first pregnancy, menopausal status, lifetime alcohol intake, education, and smoking status. We considered a covariate a confounder and included it in the models if it changed the ORs by more than 10% (Hosmer and Lemeshow 1989); however, adjustment by these potential confounders did not appreciably change the ORs, and therefore only the age-adjusted estimates are shown.

For our first set of analyses, our goal was to determine whether breast cancer risk is associated with the GST polymorphisms and whether they interact with PAH exposures, either alone or jointly, to affect breast cancer risk. We previously reported that the ORs for the association between breast cancer and individual GST genotypes were not substantially elevated (Ahn et al. 2006; Steck et al. 2007b), although risk was elevated when we considered multiple GSTs (Ahn et al. 2006; Steck et al. 2007b). Here, we focus primarily on the analyses that examine the interaction of GSTs with adducts and smoking, using the following methods.

We estimated the ORs for breast cancer in relation to potential interactions between various PAH measures and the GST polymorphisms, (a) considering each polymorphism separately (Table 1), and (b) by grouping individuals based on the number of variant alleles for any of the four GST polymorphisms considered (Tables 2 and 3). For this group of analyses, the reference group included women with GSTT1 present, GSTM1 present, GSTP1 common (AG or GG), or GSTA1 common (A/A*) genotypes. Using this approach, we explored the effect of even a single at-risk genotype, among those who carried common alleles for the other GSTs considered.
We chose to group the genes this way based on experimental evidence indicating reduced or no enzyme activity for the variant and null genotypes. In terms of metabolism, the GSTP1 valine genotype is thought to be associated with lower glutathione S-transferase pi enzyme activity compared with the GSTP1 isoleucine genotype, which plays a key role in the detoxification of benz[a]pyrene diol epoxide, a major carcinogen present in tobacco smoke (Fields et al. 1998; Hecht 1999; Nakajima et al. 1995). To explore these potential gene–PAH interactions, we developed separate models for women based on the presence or absence of the PAH exposure measure [PAH–DNA adducts (detectable/not detectable); self-reported cigarette smoking status (ever/never, or current/past/never)] or pack years of smoking history (< 15 years, 15–30 years, > 30 years). We also developed models for all women that included multiplicative interaction terms (Hosmer and Lemeshow 1989); gene–environment interactions were formally assessed by examining departures from multiplicity by comparing models with and without the interaction term using the likelihood ratio test (LRT) (Hosmer and Lemeshow 1989). In addition, we investigated potential interactions on the additive scale (Hosmer and Lemeshow 1989) using joint indicator terms for genotype only, for PAH measure only, and for both genotype and PAH measure (Tables 3 and 4). Interaction contrast ratios (ICRs) and their 95% CIs were calculated to measure the relative excess risk due to interaction (Assmann et al. 1996; Rothman and Greenland 1998). We also considered other categorizations of smoking exposure status that incorporated information collected by the questionnaire on environmental tobacco smoke (Gammon et al. 2004a), but the cell sizes were too small to yield meaningful results, so we do not show these data.

For our second set of analyses, our goal was to determine the association between PAH–DNA adducts and the GST variant alleles among control women only. We used unconditional logistic regression with detectable adducts as the dependent variable, and GSTs as the independent variable, controlling for age at reference and season of blood draw (Table 4). We also investigated the main effect of each genotype or number of variant alleles on the outcome of detectable PAH–DNA adducts in a multivariate model adjusted for age, smoking status, and season of blood draw. In a previous study (Shantakumar et al. 2005), we found that cigarette smoking was a significant predictor of detectable PAH–DNA adducts among this population-based sample; thus, we also explored whether the GST genotypes modified the association between smoking status and detectable adducts. We also considered potential interactions with cigarette smoke because of its link to our biomarker, although we recognize that other PAH sources and other constituents of tobacco smoke could potentially interact with GST polymorphisms to affect risk; however, these other constituents of tobacco smoke have not been linked to breast cancer risk in a human study.

**Results**

**Individual GSTs, PAHs, and breast cancer risk.** As shown in Tables 1 and 2, we did not observe substantial effect modification, on a multiplicative or additive scale, by any of the individual genotypes on the associations between breast cancer risk and PAH exposure (PAH–DNA adducts or cigarette smoking).

**Multiple GSTs and breast cancer risk.** The ORs for the association between breast cancer risk and multiple GST variant alleles were 1.10 (95% CI, 0.77–1.57) for three or more variants, 0.76 (95% CI, 0.56–1.03) for two variants, and 0.80 (95% CI, 0.59–1.08) for one variant. When we considered the combined effects of GSTM1, -PI, -T1, and -A1 variants that are coded based on their PAH-related biologic activity (rather than for their isothiocyanate-related activity), we did not find a significant association between the number of variant GST alleles and breast cancer risk.

### Table 1. Age-adjusted ORs (95% CIs) for the individual GST genotypes on the associations between smoking status and breast cancer risk.

| Genotype | Smoking status | Cases (n) | Controls (n) | OR (95% CI) | P-Value * |
|----------|----------------|-----------|--------------|-------------|-----------|
| GSTT1    | Present        | Never     | 351          | 341         | 1.0       | 0.27      |
|          |                | Ever      | 423          | 454         | 0.94 (0.80–1.11) | 0.74     |
|          | Null           | Never     | 97           | 112         | 0.97 (0.86–1.16) | 0.63     |
|          |                | Ever      | 112          | 109         | 1.04 (0.79–1.37) | 0.50     |
| GSTM1    | Present        | Never     | 227          | 247         | 1.0       | 0.62      |
|          |                | Ever      | 278          | 300         | 0.98 (0.81–1.19) | 0.45     |
|          | Null           | Never     | 218          | 201         | 1.14 (0.92–1.42) | 0.21     |
|          |                | Ever      | 252          | 253         | 1.06 (0.86–1.30) | 0.29     |
| GSTP1    | AA (common)    | Never     | 236          | 242         | 1.0       | 0.86      |
|          |                | Ever      | 275          | 309         | 0.91 (0.75–1.10) | 0.50     |
|          | AG or GG       | Never     | 239          | 234         | 1.04 (0.85–1.28) | 0.50     |
|          |                | Ever      | 278          | 284         | 1.01 (0.83–1.22) | 0.79     |
| GSTA1    | A1/A1* (common)| Never     | 145          | 168         | 1.0       | 0.60      |
|          |                | Ever      | 150          | 191         | 0.96 (0.77–1.20) | 0.66     |
|          | A1* or B1/B1*  | Never     | 335          | 328         | 1.06 (0.88–1.28) | 0.27     |
|          |                | Ever      | 362          | 376         | 1.02 (0.85–1.22) | 0.82     |

Common alleles: GSTT1 present, GSTM1 present, GSTP1 (AA), GSTA1 (A1/A1). Variant alleles: GSTT1 null, GSTM1 null, GSTP1 (A1 or B1), GSTA1 (A1/B1). Symbols: +, PAH–DNA adducts detected; −, PAH–DNA adducts not detected.

*From likelihood ratio test.

### Table 2. Age-adjusted ORs (95% CIs) for the individual GST genotypes on the associations between PAH–DNA adducts and breast cancer risk.

| Genotype | PAH–DNA adducts | Cases (n) | Controls (n) | OR (95% CI) | P-Value * |
|----------|-----------------|-----------|--------------|-------------|-----------|
| GSTT1    | Present         | −         | 165          | 204         | 1.0       | 0.22      |
|          | +               | 463       | 474          | 1.01 (0.87–1.19) | 0.68     |
|          | Null            | −         | 40           | 61          | 0.68 (0.45–1.03) | 0.16     |
|          | +               | 134       | 124          | 1.14 (0.87–1.48) | 0.26     |
| GSTM1    | Present         | −         | 104          | 146         | 1.0       | 0.75      |
|          | +               | 301       | 320          | 0.99 (0.82–1.19) | 0.98     |
|          | Null            | −         | 100          | 114         | 0.93 (0.70–1.23) | 0.62     |
|          | +               | 293       | 274          | 1.13 (0.93–1.37) | 0.14     |
| GSTP1    | AA (common)     | −         | 107          | 133         | 1.0       | 0.77      |
|          |                | +         | 320          | 293         | 0.94 (0.78–1.13) | 0.68     |
|          | AG or GG        | −         | 106          | 153         | 0.83 (0.63–1.09) | 0.44     |
|          |                | +         | 304          | 333         | 1.15 (0.95–1.38) | 0.25     |
| GSTA1    | A1/A1*          | −         | 75           | 111         | 1.0       | 0.53      |
|          |                | +         | 211          | 223         | 0.97 (0.79–1.20) | 0.89     |
|          | A1* or B1/B1*   | −         | 145          | 179         | 0.83 (0.65–1.05) | 0.14     |
|          |                | +         | 416          | 413         | 1.03 (0.86–1.22) | 0.45     |

Common alleles: GSTT1 present, GSTM1 present, GSTP1 (AA), GSTA1 (A1/A1). Variant alleles: GSTT1 null, GSTM1 null, GSTP1 (A1 or B1), GSTA1 (A1/B1 or B1/B1). Symbols: +, PAH–DNA adducts detected; −, PAH–DNA adducts not detected.

*From likelihood ratio test.
Multiple GSTs, PAHs, and breast cancer risk. Table 3 illustrates the potential joint effects of PAH–DNA adducts and the number of GST polymorphisms (one, two, or three or more variants) and breast cancer risk. We observed a 56% increase in risk (OR = 1.56; 95% CI, 1.13–2.16) among women with detectable adducts and three or more GST variants (GSTT1 null variant, GSTM1 null variant, GSTP1 AG/GG genotype, GSTA1 common (A*B* or B*B*) genotypes) compared with those with all common genotypes and no detectable PAH–DNA adducts. The corresponding OR for three or more variants and no detectable adducts was 0.93 (95% CI, 0.56–1.56). Women with one variant allele and no detectable adducts had a 44% reduced risk of breast cancer compared with women with all common alleles and no detectable adducts (OR, 0.56; 95% CI, 0.40–0.77); the corresponding OR for detectable adducts was not significant (OR, 0.97; 95% CI, 0.78–1.20; Table 3).

As shown in Table 4, the ORs for the association between breast cancer risk and the number of GST variants varied little with smoking status, and results for interactions on either a multiplicative or additive scale were not statistically significant. For example, the OR associated with three or more GST variants was 1.18 among ever smokers (95% CI, 0.82–1.69) but was 1.44 among never smokers (95% CI, 0.97–2.14). Results for the interaction between multiple GST variants and pack-years of smoking (data not shown) are similar to those shown in Table 4.

When we categorized ever smokers by whether they were current or past smokers, the OR for the association between breast cancer risk and three or more GST variants was 0.62 (95% CI, 0.27–1.43) among current smokers, and 1.66 (95% CI, 0.93–2.97) among past smokers, compared with never smokers with all four common alleles. However, the category sizes upon which these estimates are based were small (data not shown), and the p-value for the interaction on a multiplicative scale was 0.31.

GSTs, smoking, and PAH–DNA adducts among control women. We did not observe a significant association between any single GSTT1, GSTM1, GSTP1, or GSTA1 polymorphism and detectable PAH–DNA adducts among the control women (GSTT1; OR, 1.09; 95% CI, 0.77–1.56; GSTM1; OR, 0.93; 95% CI, 0.69–1.25; GSTP1; OR, 0.95; 95% CI, 0.72–1.27; GSTA1; OR, 1.15; 95% CI, 0.86–1.53) or the number of variant genotypes and detectable PAH–DNA adducts (one variant compared with all common alleles: OR, 1.60; 95% CI, 0.92–2.79; two variants compared with all common alleles: OR, 1.35; 95% CI, 0.77–2.36; three or more variants compared with all common alleles: OR, 1.45; 95% CI, 0.75–2.82). Table 5 shows the

| Genotype | Smoking status | Adducts not detected | Adducts present | OR (95% CI) | p-Value | ICR (95% CI) |
|----------|----------------|----------------------|-----------------|-------------|----------|-------------|
| GSTT1    | Present        | Never                | 73              | 1.0         | 0.18     | 0.28        |
|          |                | Ever                 | 80              | 1.0         | 0.18     | 0.28        |
| GSTM1    | Present        | Never                | 75              | 1.0         | 0.41     | 0.17–0.96   |
|          |                | Ever                 | 80              | 1.0         | 0.41     | 0.17–0.96   |
| GSTP1    | AA (common)    | Never                | 97              | 1.0         | 0.41     | 0.17–0.96   |
|          |                | Ever                 | 82              | 1.0         | 0.41     | 0.17–0.96   |
| GSTA1    | A*G (common)   | Never                | 97              | 1.0         | 0.41     | 0.17–0.96   |
|          |                | Ever                 | 82              | 1.0         | 0.41     | 0.17–0.96   |

Table 3. Age-adjusted ORs (95% CIs) for the effects of number of variant genotypes, PAH–DNA adducts, and risk of breast cancer.

| No. of variants | PAH–DNA adduct status | Cases (n) | Controls (n) | OR (95% CI) | p-Value | ICR (95% CI) |
|-----------------|-----------------------|-----------|-------------|-------------|----------|-------------|
| Four variants   |                       | 28        | 20          | 1.00        | Referent |             |
| One variant     |                       | 215       | 219         | 0.97 (0.78 to 1.20) | 0.60 (0.23 to 0.97) |
| Two variants    |                       | 183       | 222         | 0.82 (0.66 to 1.03) | 0.36 (–0.12 to 0.84) |
| Three variants  |                       | 29        | 31          | 0.93 (0.56 to 1.56) | 0.43     |             |

Common alleles: GSTT1 present, GSTM1 present, GSTP1 (AA), GSTA1 (A*G*). Variant alleles: GSTT1 null, GSTM1 null, GSTP1 (AG or GG), GSTA1 (A*B* or B*B*). Symbols: +, PAH–DNA adducts detected; −, PAH–DNA adducts not detected.

*From likelihood ratio test.

Table 4. Age-adjusted ORs (95% CIs) for the effect of number of variant genotypes, smoking status, and risk of breast cancer.

| No. of variants | Smoking status | Cases (n) | Controls (n) | Total | OR (95% CI) | p-Value | ICR (95% CI) |
|-----------------|----------------|-----------|-------------|-------|-------------|----------|-------------|
| Four variants   | Never          | 73        | 143         | 1.0   | 0.20        | –0.37 (–1.04 to 0.31) |
|                 | Ever           | 80        | 190         | 1.0   | 0.18        | –0.28 (–1.10 to 0.62) |
| One variant     | Never          | 75        | 125         | 1.0   | 0.41        | –0.17 (–0.96 to 0.89) |
|                 | Ever           | 80        | 190         | 1.0   | 0.41        | –0.17 (–0.96 to 0.89) |
| Two variants    | Never          | 97        | 180         | 1.0   | 0.41        | –0.17 (–0.96 to 0.89) |
|                 | Ever           | 82        | 233         | 1.0   | 0.41        | –0.17 (–0.96 to 0.89) |
| Three variants  | Never          | 54        | 97          | 1.0   | 0.41        | –0.17 (–0.96 to 0.89) |
|                 | Ever           | 57        | 126         | 1.0   | 0.41        | –0.17 (–0.96 to 0.89) |

Common alleles: GSTT1 present, GSTM1 present, GSTP1 (AA), GSTA1 (A*G*). Variant alleles: GSTT1 null, GSTM1 null, GSTP1 (AG or GG), GSTA1 (A*B* or B*B*). *From likelihood ratio test.

Table 5. Age-adjusted ORs (95% CIs) for the joint effect of GST polymorphisms and smoking on the outcome of detectable PAH–DNA adducts among control women.

We adjusted data for age at reference and for season of blood draw. Common alleles: GSTT1 present, GSTM1 present, GSTP1 (AA), GSTA1 (A*G*). Variant alleles: GSTT1 null, GSTM1 null, GSTP1 (AG or GG), GSTA1 (A*B* or B*B*). *From likelihood ratio test.
association between GST polymorphisms and PAH–DNA adducts among control women stratified by smoking status. Women who ever smoked and had the GSTM1 present genotype had a 35% reduced odds (OR, 0.65; 95% CI, 0.45–0.93) of having detectable PAH–DNA adducts compared with never smokers with the same genotype. We noted similar results for ever smokers with the GSTM1 null genotype compared with never smokers with the GSTM1 common genotype (OR, 0.64; 95% CI, 0.43–0.93). Ever smokers with the GSTT1 present genotype had a 27% reduced odds of PAH–DNA adducts among control women who were smokers regardless of whether they had the same genotype. We also report for the first time that among controls with the A*/A* GSTT1 genotype, ever smokers had lower odds of having detectable PAH–DNA adducts than did never smokers with the same genotype (OR, 0.62; 95% CI, 0.41–0.92).

**GST polymorphisms and breast cancer risk.** A few previous studies (Helzlsouer et al. 1998; van der Hel et al. 2005) including our own have found that individual polymorphisms in GSTT1 (Ahn et al. 2006), GSTM1 (Helzlsouer et al. 1998; Spurdle et al. 2007), and GSTT1 null (van der Hel et al. 2005) and GSTP1 (heterozygote or homozygote valine) (Helzlsouer et al. 1998) are modestly associated with breast cancer, although others have reported no association with GSTT1 (García-Closas et al. 1999; Helzlsouer et al. 1998; Vogl et al. 2004), GSTP1 (Vogl et al. 2004), or GSTM1 (Ambrosone et al. 1995; García-Closas et al. 1999; Vogl et al. 2004). Effects of multiple combinations of GST polymorphisms on breast cancer risk have previously been conducted in smaller studies, with conflicting findings (Helzlsouer et al. 1998; Steck et al. 2007b; van der Hel et al. 2005; Vogl et al. 2004). Combined effect of all three GSTT1, GSTM1, and GSTP1 variants have been reported to have greater than a 3-fold increase in breast cancer risk compared with women with the common genotype for all three polymorphisms (Helzlsouer et al. 1998; Steck et al. 2007b). In this analysis, in which we considered the combined effects of the GSTT1, -M1, -P1, and -A1 variants that are coded based on their PAH-related biologic activity (rather than for their isothiocyanate-related activity), we did not find a significant association between the number of variant GST alleles and breast cancer risk.

**GST polymorphisms, PAHs, and breast cancer.** Previous studies have differed on whether GST polymorphisms modify the association between cigarette smoking and breast cancer risk (Millikan et al. 2000; Terry and Goodman 2006; van der Hel et al. 2005; Vogl et al. 2004; Zheng et al. 2002). Smaller studies have reported that smoking did not modify associations between GSTT1 (Vogl et al. 2004), GSTM1 (van der Hel et al. 2005; Vogl et al. 2004), or GSTP1 polymorphisms (Vogl et al. 2004) and breast cancer, whereas former smokers with GSTT1 null were found to have an increased risk of breast cancer compared with never smokers with GSTT1 present (van der Hel et al. 2005). For example, one recent breast cancer meta-analysis reported no interaction between individual GST polymorphisms and smoking, whereas another meta-analysis reported positive associations between breast cancer risk and GSTT1 present and GSTM1 null genotypes among smokers (Terry and Goodman 2006; Vogl et al. 2004). In contrast, we observed an increased risk of breast cancer with three or more variant GST alleles in a previous analysis (Steck et al. 2007b), but no increased risk with number of variant alleles as defined by low PAH-metabolizing activity, and no evidence of gene–environment interaction with PAH exposure. Our present findings are unique in that we investigated four GST polymorphisms simultaneously in a single large study.

To the best of our knowledge, this is the first study to examine the interaction between PAH–DNA adducts and individual/combined effects of GSTT1, GSTM1, GSTP1, and GSTT1 genotypes on breast cancer risk. We found no pronounced adverse effect for the genotype–PAH exposure interaction, regardless of the PAH measure. Given that the genetic polymorphisms we examined are known to be functionally associated with deactivation of the active intermediates of PAHs, our findings are not easily interpreted. It is possible that the PAH–DNA adduct biomarker effect estimates already reflect any effects associated with metabolic variation; however, if this were true, then any apparent interaction between PAHs and GSTs should have been evident when examining the joint effects with smoking. We found a reduction in risk among women with at least one variant allele and no detectable adducts, but we did not find a similar reduction among these same women in relation to no smoking. Thus, we do not report evidence that PAHs interacted with these polymorphisms to further increase risk.

We acknowledge that expression of GSTs can be modulated by a variety of factors, including diet. There is extensive literature on animal studies demonstrating an interaction between isothiocyanates and PAHs on cancer risk, and the induction of phase II enzymes by isothiocyanates (Hecht 1996, 2000). The interaction between GSTs and isothiocyanates does not appear to interact to affect breast cancer risk in humans or the variations in the urinary metabolites of isothiocyanates in our data (Steck et al. 2007a, 2007b). Whether cruciferous vegetable intake would further interact with PAHs and GSTs to affect breast cancer risk is unclear. Unfortunately, this study was underpowered to explore such three way interactions despite a large sample size. Nevertheless, it may be theoretically possible that breast cancer risk is influenced by a potential three-way interaction of PAH–DNA adducts, GST polymorphisms, and cruciferous vegetable intake, although our current available data do not support this hypothesis (Steck et al. 2007a, 2007b).

**GST polymorphisms, smoking, and PAH–DNA adducts among control women.** We considered the PAH–DNA adduct outcome as both a continuous and a dichotomous variable (detected/not detected), although the latter may be more informative given the lack of a dose–response relationship between adducts...
and breast cancer risk (Gammon et al. 2002b). In our analyses among control women, individual GSTT1, GSTM1, GSTP1, and GSTA1 genotypes were not associated with detectable PAH–DNA adducts, nor was the number of variant GST alleles. Even after stratification on smoking, the number of variant GST alleles was not associated with detectable PAH–DNA adducts; however, ever smokers with either the GSTM1 null or GSTTM1 present genotype had a reduced risk of detectable PAH–DNA adducts (Table 5). We observed a similar finding within the strata of ever smokers and the GSTP1 common genotype compared with never smokers with the common genotype. Our results are the first published findings regarding GSTA1 polymorphisms and PAH–DNA adducts. Our findings related to polymorphisms in GSTM1 and PAH–DNA adduct formation are in contrast with one study (Rundle et al. 2003), while being consistent with others that report no significant difference in detectable PAH–DNA adducts based on GSTTM1 status (Grinyer-Funes et al. 1994; Reithman et al. 1995; Weisbergs et al. 2003). However, the LIBCSP results reported here are based upon a much larger sample size than previous analyses, which yields more stable effect estimates. Additionally, we used different methods to measure the PAH–DNA adducts in the various studies, possibly influencing the results.

**Methodological considerations.** In an epidemiologic study, the use of a biomarker of exposure, such as PAH–DNA adducts, is considered superior because exposure assessment is not based on self-report, eliminating concerns for recall bias. Reliability in the measurement of genotype and adducts was high. Measurement error was possible, although unlikely with genotyping and analysis of adducts; however, because the laboratory was blinded to status of samples, any measurement error in measuring genotype and of PAH–DNA adduct status was independent of case–control status. Therefore, any resulting bias would have been nondifferential.

Our study power was limited when we examined interactions within subgroups of women, such as those with PAH–DNA adducts. However, the LIBCSP is the largest study conducted to date with information on PAH–DNA adducts with which to evaluate these associations, and thus our study power was better than that of previously reported studies.

We selected the GST polymorphisms because of their role in phase II metabolism, specifically metabolism of PAH-reactive intermediates. Because PAH–DNA adducts may be related to inherited differences in the metabolism of PAHs, this pathway was hypothesized to be important in individual breast cancer susceptibility. GSTP1 and GSTM1 have been shown to have a role in detoxification of PAH carcinogenic intermediates produced by cytochrome P450 in phase I metabolism (Bukiewicz et al. 2000). GSTT1 and GSTA1 have also been implicated in the metabolism of PAH intermediates (Garte et al. 2007; Hayes and Pulford, 1995; Korashy and El-Kadi 2006).

**Conclusion**

Our previous analyses have shown that breast cancer risk was modestly elevated in relation to PAH–DNA adducts (Gammon et al. 2002b, 2004b), among certain subgroups of smokers (Gammon et al. 2004a), and among women with multiple variant alleles in GST genes (Steck et al. 2007b). In this analysis, however, we did not find strong evidence for further elevation of breast cancer risk, either on a multiplicative or on an additive scale, when we considered the joint effect of multiple GSTS and PAHs (cigarette smoking or PAH–DNA adducts), despite the biologic plausibility of such an interaction. These findings are based upon the largest population-based study of breast cancer conducted to date with a biomarker of PAH exposure. Further study may be warranted incorporating other biologic measures of PAH metabolism.

**References**

Ahn J, Gammon MD, Sartella RM, Gaudet MM, Britton JA, Teitelbaum SL et al. 2006. Effects of glutathione S-transferase A1 (GSTA1) genotype and potential modifiers on breast cancer risk. Carcinogenesis 27:137–142.

Ambrose CB, Freudenheim J, Graham S, Marshall JR, Vena JE, Brasure JR et al. 1995. Cytochrome P4501A1 and glutathione S-transferase M1 (GSTM1) genetic polymorphisms and postmenopausal breast cancer risk. Cancer Res 55:1634–1636.

Assmann SF, Hosmer DW, Lemeshow S, Mundt KA. 1996. Confidence intervals for measures of interaction. Epidemiology 7:162–169.

Bell DA, Thompson CL, Taylor J, Miller CR, Perera F, Huie LL et al. 1992. Genetic monitoring of human pulmonary cancer susceptibility genes by polymerase chain reaction: application to tobacco smoke exposure. Environ Health Perspect 98:113–117.

Boffetta P, Jourdenkov N, Dussenvoux P. 1997. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 8:444–472.

Brescia G, Celotti L, Clonfero E, Neumann GH, Forno A, Foà V et al. 2004. The influence of cytochrome P450 1A1 and glutathione S-transferase M1 genotypes on biomarker levels in coke-oven workers. Arch Toxicol 78:431–439.

Butkiewicz D, Grzybowska E, Phillips DH, Hemminki K, Chorazy MM, Ambrosone CB, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR et al. 1995. Cytochrome P4501A1 and glutathione S-transferase M1 genotypes on biomarker levels (GSTA1, GSTM1, GSTP1, and GSTT1) in a cohort of female coke-oven workers. Arch Toxicol 73:431–439.

Coles BF, Kadlubar FF, Sies H, Teitel CH, Hecht SS, et al. 2001. Effect of polymorphism in the human glutathione S-transferase A1 promoter on hepatic GSTA1 and GSTA2 expression. Pharmacogenetics 11:663–669.

Gammon MD, Addink A, Sorenson K, Kurtzke J, Hecht SS. 1995. Comparative tumorigenicity of benzo[α]pyrene, 1-nitropyrene and 2-amino-1-methyl-6-phenylimidazol(4,5-b)pyridine administered by gavage to female CD rats. Carcinogenesis 16:431–434.

Fannon WR. 2002. Single nucleotide polymorphism (SNP) analysis of a variety of non-ideal DNA sample types by SEQUENOM MassARRAY matrix assisted laser desorption/ionization time of flight (MALDI-TOF). Proc Am Assoc Cancer Res 44:323.

Fields WR, Morrow CS, Assaj D, Sundberg K, Jernstrom B, Townsend AJ. 1998. Overexpression of stably transfected human glutathione S-transferase P1-1 protects against DNA damage by benzo[α]pyrene dialdehyde in human 1470 cells. Mol Pharmacol 54:289–304.

Gammon MD, Eng SM, Teitelbaum SL, Britton JA, Kabat GC, Hatch M, et al. 2004a. Environmental tobacco smoke and breast cancer incidence. Environ Res 96:178–185.

Gammon MD, Neugut AI, Eng SM, Teitelbaum SL, Britton JA, Terry MB, et al. 2002a. The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. Breast Cancer Res Treat 74:229–235.

Gammon MD, Sagiv SK, Eng SM, Shantakumar S, Gaudet MM, Teitelbaum SL et al. 2004a. Polycyclic aromatic hydrocarbon–DNA adducts and breast cancer: a pooled analysis. Arch Environ Health 59:540–549.

Gammon MD, Sartella RM. 2008. PAH, genetic susceptibility, and breast cancer risk: an update from the Long Island Breast Cancer Study Project. Eur J Cancer 44:636–640.

Gammon MD, Sartella RM, Neugut AI, Eng SM, Teitelbaum SL, Paykin A, et al. 2002b. Environmental Toxins and Breast Cancer on Long Island. Polycyclic aromatic hydrocarbon–DNA adducts. Cancer Epidemiol Biomarkers Prev 11:877–895.

Garcia-Closas M, Kelsey KT, Hankinson SE, Spiegelman D, Springer K, Willett WC, et al. 1999. Glutathione S-transferase mu and theta polymorphisms and breast cancer susceptibility. J Natl Cancer Inst 91:1960–1964.

Garte S, Taiso E, Popov T, Kalina I, Sram R, Farmer P. 2007. Role of GSTT1 deletion in DNA oxidative damage by exposure to polycyclic aromatic hydrocarbons in humans. Int J Cancer 121:2499–2503.

Grinyer-Funes RA, Singh VN, Perera FB, Bell DA, Young TL, Dickey C, et al. 1999. Polycyclic aromatic hydrocarbon–DNA adducts in smokers and their relationship to micro-nutrient levels and the phase I metabolizer phenotype. Carcinogenesis 20:1249–2454.

Hatsukami DK, Benowitz N, Rennard S, Oncken C, Hecht SS. 2006. Biomarkers to assess the utility of potential reduced exposure tobacco products. Nicotine Tob Res 8:593–622.

Hayes JD, Pulford DJ. 1995. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol 30:465–600.

Hecht SS. 1995. Chemoprevention of lung cancer by isothiocyanates. Adv Exp Med Biol 401:1–11.

Hecht SS. 1999. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91(4):1194–1210.

Hecht SS. 2000. Inhibition of carcinogenesis by isothiocyanates. Drug Metab Rev 32(3–4):395–411.

Hecht SS. 2003. Tobacco carcinogens, their biomarkers, and tobacco induced cancer. Nature Rev Cancer 3:733–744.

Hecht SS, Carmella SG, Yoder A, Chen M, Li Z, Le C, et al. 2006. Comparison of polymorphisms in genes involved in polycyclic aromatic hydrocarbon metabolism with urinary phenanthrene metabolite ratios in smokers. Cancer Epidemiol Biomarker Prev 15:1196–1206.

Heiltsuor KJ, Selmin O, Huang HY, Strickland PT, Hoffman S, Alberg AJ, et al. 1998. Association between glutathione S-transferase M1, PI, and T1 genetic polymorphisms and development of breast cancer. J Natl Cancer Inst 90:512–518.

Hosmer DW, Lemeshow S. 1989. Applied Logistic Regression. New York: John Wiley and Sons.

Hu Y, Li G, Xue K, Zhou Z, Li X, Fu J, et al. 2007. PAH-DNA adducts, GSTs, and breast cancer.
Pelin K, Hirvonen A, Norppa H. 1996. Influence of erythrocyte glutathione-S-transferase T1 on sister chromatid exchanges induced by diepoxybutane in cultured human lymphocytes. Mutagenesis 11:213–215.

Rothman KJ, Greenland S. 1998. Modern Epidemiology. Philadelphia: Lippincott-Raven Publishers.

Rothman N, Shields PG, Poinier MC, Harrington AM, Ford DP, Strickland PT. 1995. The impact of glutathione S-transferase M1 and cytochrome P450 1A1 genotypes on white-blood-cell polycyclic aromatic hydrocarbon-DNA adduct levels in humans. Mol Carcinog 14:1163–68.

Rundle A, Tang D, Hibschooh H, Estabrook A, Schnabel F, Cao W, et al. 2000a. The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. Carcinogenesis 21:1281–1289.

Rundle A, Tang D, Mooney L, Grumet S, Perera FP. 2003. The interaction between alcohol consumption and GSTM1 genotype on polycyclic aromatic hydrocarbon-DNA adduct levels in breast tissue. Cancer Epidemiol Biomarkers Prev 12(9):911–914.

Rundle A, Tang D, Zhou J, Cho S, Perera FP. 2000b. The association between glutathione S-transferase M1 genotype and polycyclic aromatic hydrocarbon-DNA adducts in breast tissue. Cancer Epidemiol Biomarkers Prev 9:1079–1085.

Ryberg D, Skaug V, Heaver A, Philips DH, Harries LW, Wolf CR, et al. 1997. Genotypes of glutathione transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. Carcinogenesis 18:1285–1289.

Shantakumar S, Gammon MD, Eng SM, Savig SK, Gaudent MM, Teitelbaum SL, et al. 2005. Residential environmental exposures and other characteristics associated with detectable PAH-DNA adducts in peripheral mononuclear cells in a population-based sample of adult females. J Expo Anal Environ Epidemiol 15:482–490.

Shimada T, 2006. Xenobiotic-metabolizing enzymes involved in the activation and detoxification of carcinogenic polycyclic aromatic hydrocarbons. Drug Metab Pharmacokinet 24:257–276.

Spurdle AB, Chang JH, Byrnes GB, Chen X, Dite GS, McCredie MR, et al. 2007. A systematic approach to analyzing gene-environment interactions: polymorphisms at the microsomal epoxide hydrolase EPHX and glutathione S-transferase GSTM1, GSTT1, and GSTP1 loci and breast cancer risk. Cancer Epidemiol Biomarkers Prev 16(9):769–774.

Steck SE, Gaudent MM, Hebert JR, Wall DE, Zeisel SH. 2007a. GSTM1, GSTT1, GSTP1, and GSTA1 polymorphisms and urinary isothiocyanate metabolites following broccoli consumption in humans. J Nutr 137(4):804–809.

Steck SE, Gaudent MM, Britton JA, Teitelbaum SL, Terry MB, Neugut AI, et al. 2007b. Interactions among GSTM1, GSTT1, and GSTP1 polymorphisms, cruciferous vegetable intake and breast cancer risk. Carcinogenesis 28(9):1954–1959.

Terry PD, Goodman M. 2006. Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. Cancer Epidemiol Biomarkers Prev 15(4):602–611.

Upadhyaya P, Rao P, Hochalter JB, Li Z, Vallata PW, Hecht SS. 2006. Quantitation of N-acetyl-S-(9,10-dihydro-9-hydroxy-10-phenanthryl)-L-cysteine in human urine: comparison of glutathione-S-transferase genotypes in smokers. Chem Res Toxicol 19:1234–1240.

van der Heijden P, van den Broek-Schouten JJ, Bijlsma CH, Dirven AM, van Schie TH, Roest M, Schouten B, Grobbe DE, et al. 2005. Cumulative genetic defects in carcinogen metabolism may increase breast cancer risk (The Netherlands). Cancer Causes Control 16(6):675–681.

Vogel FD, Taitel E, Maugard C, Zheng W, Pinto LF, Ambrosone C, et al. 2004. Glutathione S-transferases M1, T1, and P1 and breast cancer: a pooled analysis. Cancer Epidemiol Biomarkers Prev 13(9):1473–1479.

Waldman JM, Lioy PJ, Greenberg A, Butler JP. 1991. Analysis of human exposure to benzo[a]pyrene via inhalation and food ingestion in the Total Human Environmental Exposure Study (THEES). J Expo Anal Environ Epidemiol 1:193–235.

Watson MA, Stewart RK, Smith GB, Massey TE, Bell DA. 1998. Human glutathione S-transferase P1 polymorphism: relationship to lung tissue enzyme activity and population frequency distribution. Carcinogenesis 19:275–280.

Weisburger JF, Jacobson JS, Begg MD, Wang LW, Wang Q, Agrawal M, et al. 2003. A cross-sectional study of polycyclic aromatic hydrocarbon-DNA adducts and polymorphism of glutathione S-transferases among heavy smokers by race/ethnicity. Biomarkers 8(2):142–155.

Wogan GM, Hecht SS, Conney AH, Loeb LA. 2004. Environmental and chemical carcinogenesis. Semin Cancer Biol 14:473–486.

Zhang Y, Yang W, Gilman DS, Gross M, Cerhan JR, Folsom AR. 2002. GSTM1 and GSTT1 polymorphisms and postmenopausal breast cancer risk. Breast Cancer Res Treat 74(1):9–16.