

Association between Polycyclic Aromatic Hydrocarbon-DNA Adduct Levels in Maternal and Newborn White Blood Cells and *Glutathione S-Transferase P1* and *CYP1A1* Polymorphisms¹

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Abstract

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants; a number are carcinogenic. Metabolic polymorphisms may modulate susceptibility to PAH-induced DNA damage and carcinogenesis. This study investigates the relationship between PAH-DNA adduct levels (in maternal and newborn WBCs) and two polymorphisms: (a) an *MspI* RFLP in the 3' noncoding region of cytochrome P4501A1 (*CYP1A1*); and (b) an A→G transition in nucleotide 313 of *glutathione S-transferase P1* (*GSTP1*), resulting in an ile105val substitution. *CYP1A1* catalyzes the bioactivation of PAH; the *CYP1A1 MspI* RFLP has been associated with cancer of the lung. *GSTP1* catalyzes the detoxification of PAH; the *val* allele has greater catalytic efficiency toward PAH diol epoxides. The study involves 160 mothers and their newborns from Poland. Regression models controlled for maternal smoking and other confounders. No association was seen between maternal adduct levels and either polymorphism, separately or combined. However, adduct levels were higher among newborns with the *CYP1A1 MspI* restriction site (heterozygotes and homozygotes combined) compared with newborns lacking the restriction site ($P = 0.06$). Adducts were higher among *GSTP1 ile/val* and *ile/ile* newborns compared with *GSTP1 val/val* newborns ($P = 0.08$). Adduct levels were 4-fold higher among *GSTP1 ile/ile* newborns having the *CYP1A1* restriction site compared with *GSTP1 val/val* newborns

who lacked the *CYP1A1* restriction site ($P = 0.04$). This study demonstrates a significant combined effect of phase I and phase II polymorphisms on DNA damage from PAHs in fetal tissues. It illustrates the importance of considering interindividual variation in assessing risks of transplacental exposure to PAHs.

Introduction

PAHs⁴ are ubiquitous pollutants in indoor and ambient air from the combustion of fossil fuel and tobacco (1–4). A number are mutagenic and carcinogenic and are associated with increased risk of lung cancer in smokers and in nonsmokers exposed to environmental tobacco smoke (5–8). PAHs readily cross the placenta (9, 10) and are transplacental carcinogens in animal models (11–13). PAHs are also developmental toxicants (14, 15). Genetic differences in detoxification capabilities may modulate PAH-induced DNA damage and carcinogenesis (16–18).

This study extends prior evaluations in the current cohort to consider the combined effect of phase I (*CYP1A1 MspI* RFLP) and phase II (*GSTP1*) metabolic enzyme polymorphisms on PAH-DNA adduct levels in WBCs of mothers and newborns. The cohort consisted of 70 mother/newborn pairs from Krakow, Poland [an industrial city with elevated ambient air pollution including PAH from coal-burning for industry and residential heating (19)], and 90 pairs from Limanowa [a small town located 70 km southeast of Krakow with lower ambient pollution levels but 2-fold more frequent use of coal-stoves for indoor home heating (20)]. We have reported previously on the effects of environmental exposures (cigarette smoke and ambient air pollution) on WBC PAH-DNA adduct levels in mothers and newborns (21, 22). Briefly, no difference was seen in adduct levels in mothers and newborns from Krakow compared with Limanowa, possibly because of higher indoor air concentrations of PAHs from coal burning in Limanowa (2). Ambient pollution monitoring data were available for Krakow subjects only. Among Krakow subjects not employed away from home, a significant association was seen between ambient PM₁₀ levels at the woman's residence and adduct levels in both maternal and newborn WBCs. Maternal active and passive cigarette smoking status was significantly associated with maternal, but not newborn, adducts. Newborn adduct levels were significantly inversely associated with birth weight, length, and head circumference (23).

CYP1A1 codes for an inducible enzyme system involved in PAH biotransformation to epoxide-containing metabolites, some of which are mutagenic and carcinogenic (24). An *MspI* RFLP identified in the 3' noncoding region of *CYP1A1* (the

Received 6/30/99; revised 10/28/99; accepted 11/24/99.

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¹ This work was supported by USPHS Grants RO1CA-39174, RO1CA-35809, 1-PO1-ES05294, RO1CA-53772, CA51196, RO1-ES06722, RO1-ES08977, and P50-ES09600; Grant DE-FG02-93ER61719 from the Department of Energy; a grant from the Gladys and Roland Harriman Foundation; a grant from the March of Dimes Birth Defects Foundation; and the Fogarty International Center (NIH).

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⁴ The abbreviations used are: PAH, polycyclic aromatic hydrocarbon; CYP1A1, cytochrome P4501A1; GST, glutathione *S*-transferase.

CYP1A1 MspI RFLP) has been associated with cancer of the lung in some, but not all, studies (reviewed in Ref. 25). The *CYP1A1 MspI* RFLP segregates in linkage disequilibrium with a polymorphism in exon 7 that results in an ile→val substitution in the catalytic region (26). Although the data are inconsistent, the exon 7 polymorphism has been associated with increased *CYP1A1* induction or activity in several studies (27–29). Prior evaluations of the association between each of these polymorphisms and carcinogen-DNA adducts are limited, and results are conflicting (30–33). We have reported previously that PAH-DNA adduct levels were significantly higher in placental tissue of newborns from the current cohort who had the *CYP1A1 MspI* restriction site (heterozygotes and homozygotes combined) compared with newborns without the restriction site (34).

GST consists of a superfamily of phase II enzymes that catalyze the conjugation of reduced glutathione with electrophilic compounds, including many environmental mutagens and carcinogens (35). The currently identified cytosolic GSTs are categorized into four main classes, α , μ , θ , and π , based on biochemical characteristics (36). Human α , μ , and θ families contain multiple genes, whereas the π family consists of a single gene, *GSTP1*. PAH epoxides are substrates for both class μ and π GSTs (36–38). *GSTP1* is widely expressed in human epithelial tissue and is the dominant GST present in lung, brain, esophagus, and erythrocytes (38, 39). π is also the major GST expressed in fetal tissues including liver, lung, kidney, and placenta (38, 40–42). A coding sequence polymorphism in *GSTP1*, an A→G transition in nucleotide 313, has been identified. It results in a change in codon 105 from ile to val in the hydrophobic binding site and impacts catalytic efficiencies (43). The effect of the *105val* allele appears to differ by substrate. Compared with the *GSTP1 ile* allele, the *GSTP1 105val* allele has decreased activity toward 1-chloro-2,4-dinitrobenzene (39, 44, 45) but greater activity toward PAH diol-epoxides (46–48). Thus, it has been hypothesized that *105val* homozygotes will be more susceptible to certain mutagens/carcinogens but less susceptible to PAH-induced DNA damage and carcinogenesis (46, 47). Prior data on the association between the polymorphism and cancer risk have been conflicting. The *105val* allele was associated with increased risk of lung, upper aerodigestive tract, bladder, and testicular cancers in some, but not all, studies (45, 49–55). Among lung cancer patients, a significant association was seen between the *105val* allele and DNA-adducts measured in lung tissue of current smokers by a method that detects a complex mixture of aromatic and/or hydrophobic compounds (49). The present study is the first to evaluate the association between the polymorphism and PAH-DNA adducts in fetal tissue.

Materials and Methods

Field studies were conducted in Poland during January–March 1992 under the direction of Dr. W. Jedrychowski in accordance with current guidelines for human subjects. Enrollment was restricted to women who had resided in Krakow or Limanowa for at least 1 year and was limited to vaginal deliveries. Samples of umbilical cord blood (20–60 ml) were collected at delivery, and a maternal blood sample was collected 1–2 days postpartum. Samples were processed as described previously (20).

A detailed, validated questionnaire administered to the mother within 2 days postpartum included information on smoking (active and passive), residential and employment histories, use of coal stoves for residential heating, and other environmental exposures. Data on the average number of

weekly servings of specific PAH-containing foods consumed during pregnancy, such as broiled and smoked meats and fish and smoked cheese, were also collected. In addition, subjects were asked about exposure to sources of PAHs either at home or in the workplace as well as pesticides and other organic chemicals as potential inducers of *CYP1A1*.

PAH-DNA Adducts. DNA was extracted from maternal and umbilical cord WBCs by standard phenol/chloroform extraction and RNase treatment. Quantity obtained ranged from 16 to 2900 μg DNA. PAH-DNA adducts were measured by a competitive ELISA with fluorescence endpoint detection, essentially as described previously (56). The detection limit of the assay is 2 adducts per 10^8 nucleotides. Samples were assayed in triplicate at 50 μg of DNA/well and 150 μg of DNA/plate; the median values were used to determine the percentage of inhibition. When sufficient DNA was available (63% of samples), the assay was repeated. Laboratory personnel were blinded to subject status. The antiserum was elicited against benzo(*a*)pyrene diol-epoxide-DNA but recognizes other structurally related PAH diol-epoxide-DNA adducts, including those formed by benz[*a*]anthracene and chrysene (57). Thus, positive reaction with the antiserum may indicate the presence of multiple PAH-DNA adducts in the sample; values are expressed as the amount of benzo(*a*)pyrene diol-epoxide-DNA that would cause a similar inhibition in the assay. PAH-DNA adduct levels were determined for 135 maternal and 135 umbilical cord WBC samples, including 112 mother/newborn pairs.

***CYP1A1 MspI* RFLP.** The *CYP1A1 MspI* genotype was determined using one of two methods at either the New York University or National Institute of Environmental Health Sciences laboratories. At New York University, prior to the development of a PCR-based assay, high molecular weight genomic DNA from placental villus (fetal) samples was digested with *MspI*, and resultant fragments were electrophoretically separated and visualized by autoradiograph after hybridization with radiolabeled cDNA probes (20). A simpler PCR-based RFLP procedure was implemented at the National Institute of Environmental Health Sciences laboratory utilizing DNA from umbilical cord and maternal blood samples as described previously (20, 34). As a validation and quality control procedure, 131 samples were analyzed by both methods, and the concordance was 100%. The *CYP1A1 MspI* RFLP was determined for 142 mothers and 158 newborns.

***GSTP1*.** The *GSTP1* (ile105val) genotype was determined by use of the PCR-RFLP method of Watson *et al.* (39) and Helzlsouer *et al.* (35) as described previously. Briefly, genomic DNA (50 ng) was added to a PCR mix of *GSTP1* primers 2306F (5'-GTA GTT TGC CCA AGC TCA AG) and 2721R (5'-AGC CAC CTG AAG GGT AAG; 15 pmol each) and other PCR reagents as described previously (35). PCR products were digested overnight with the restriction enzyme *Alw26I*, which distinguishes between the restriction sites on the *ile* allele (ATC) and the *val* allele (GTC). For all genotype analysis, laboratory personnel were blinded to subject status; photographs were interpreted by at least two independent readers, and ~10% of samples were tested a second time as a quality control measure. The *GSTP1* genotype was determined for 142 mothers and 143 newborns.

Statistical Analyses. PAH-DNA adduct levels were log-transformed to stabilize the variance and obtain a more symmetrical distribution. For samples below the detection limit (34% of maternal and 42% of infant samples), a value of half the detection limit was assigned prior to transformation. Means and SDs are presented as untransformed values for ease of inter-

Table 1 Age,^a smoking status,^b and coal use^b of mothers

	Krakow (n = 70)	Limanowa (n = 90)
Mother's age (yr)	27.6 ± 5.3 ^c	25.4 ± 4.1
Current smokers	12 ^c (17%)	4 (4%)
Ex-smokers	20 (29%)	18 (20%)
Nonsmokers	38 (54%)	68 (76%)
ETS ^d exposure (nonsmokers only)	22 (58%)	42 (62%)
Heating by coal stove (yes)	16 ^c (23%)	45 (50%)

^a Mean ± SD.^b Number of subjects (%).^c P < 0.01 Krakow compared with Limanowa.^d ETS, environmental tobacco smoke.Table 2 *CYP1A1* and *GSTP1* genotype frequencies in mothers and newborns

Genotype	Mothers	Newborns
<i>CYP1A1</i> <i>MspI</i> RFLP		
Group I: <i>MspI</i> site absent	118/142 (83%)	126/158 (80%)
Group II: <i>MspI</i> site present (heterozygotes)	24/142 (17%)	29/158 (18%)
Group III: <i>MspI</i> site present (homozygotes)	0/142 (0%)	3/158 (2%)
<i>GSTP1</i>		
Group I: <i>val/val</i>	18/142 (13%)	17/143 (12%)
Group II: <i>ile/val</i>	59/142 (41%)	79/143 (55%)
Group III: <i>ile/ile</i>	65/142 (46%)	47/143 (33%)

pretation. Associations between adduct levels and the *CYP1A1* and *GSTP1* polymorphisms were evaluated by multiple linear regression. All models controlled for place of residence (Krakow versus Limanowa), cigarette smoking status, average number of servings per week during pregnancy of foods high in PAH (smoked meat, cheese, and fish), use of coal stoves for residential heating, and home/occupational exposures to PAH and other organics (21). Maternal age was not included in the models because it was not associated with PAH-DNA adduct levels in either maternal or newborn WBCs. Ethnicity was not controlled for because the Polish population is ethnically homogeneous and subjects were predominantly Slavic. Associations of borderline significance ($0.1 > P > 0.05$) are reported but are considered statistically significant at $P \leq 0.05$.

Results

Data on demographic variables and smoking status are summarized in Table 1. Table 2 shows the frequency of the *CYP1A1* and *GSTP1* genotypes in mothers and newborns. Table 3 presents maternal and newborn WBC PAH-DNA adduct levels stratified by each genotype separately. There was no significant association between maternal WBC PAH-DNA adduct levels and either the mother's *CYP1A1* *MspI* or *GSTP1* genotype (Table 3). Nor was there a significant association between the mother's *CYP1A1* *MspI* RFLP or *GSTP1* genotype and adduct levels in the newborn (data not shown).

WBC PAH-DNA adduct levels were higher in newborns who had the *CYP1A1* *MspI* restriction site (heterozygotes and homozygotes combined) compared with newborns who lacked the restriction site, a difference that was of borderline significance controlling for potential confounders ($P = 0.06$; Table 3). Newborn adduct levels did not differ significantly between *GSTP1* *ile/val* and *ile/ile* newborns. However, adduct levels were somewhat higher among *GSTP1* *ile/ile* and *ile/val* new-

Table 3 WBC PAH-DNA adduct levels for mothers and newborns by *CYP1A1* and *GSTP1* genotypes analyzed separately^a

Genotype	Maternal Mean ± SD per 10 ⁸ nucleotides (n) ^b	Newborn Mean ± SD per 10 ⁸ nucleotides (n) ^b
Total	6.4 ± 9.2 (135)	7.6 ± 9.6 (135)
<i>CYP1A1</i> <i>MspI</i> RFLP		
Group I: <i>MspI</i> restriction site absent	6.9 ± 10.1 (107)	7.0 ± 8.9 (106) ^d
Group II: <i>MspI</i> restriction site present ^c	4.7 ± 4.3 (21)	9.8 ± 11.7 (28)
<i>GSTP1</i>		
Group I: <i>val/val</i>	7.4 ± 10.8 (15)	3.5 ± 3.6 (16) ^{e,f}
Group II: <i>ile/val</i>	7.0 ± 10.4 (54)	8.9 ± 10.2 (70)
Group III: <i>ile/ile</i>	5.9 ± 8.0 (60)	7.7 ± 10.2 (42)

^a Maternal adduct levels are stratified by the mother's genotype, and newborn adduct levels are stratified by the newborn's genotype; all models are controlled for place of residence, cigarette smoking, dietary PAHs, use of coal stoves for residential heating, and home/occupational exposures. Associations of borderline significance ($0.1 > P > 0.05$) are reported but are considered statistically significant at $P \leq 0.05$.

^b Number of subjects.^c Homozygotes and heterozygotes combined.^d Newborn *CYP1A1* group I versus group II ($P = 0.06$).^e Newborn *GSTP1* group I versus group II newborns ($P = 0.07$).^f Newborn *GSTP1* group I versus group II + group III ($P = 0.08$).

borns compared with *GSTP1* *val* homozygotes ($P = 0.08$; Table 3).

Relationships between maternal and newborn WBC PAH-DNA adduct levels and the combined *CYP1A1/GSTP1* genotypes are presented in Table 4. There was no significant difference in maternal WBC PAH-DNA adduct levels between any of the maternal genotype combinations (groups I–VI). However, PAH-DNA adducts were 4-fold higher ($P = 0.04$) among *GSTP1* *ile/ile* newborns with the *CYP1A1* restriction site (group VI, the highest adduct group) compared with *GSTP1* *val/val* newborns who lacked the *CYP1A1* restriction site (group I, the lowest adduct group). Compared with group I, adduct levels were also significantly higher among *GSTP1* *ile/val* newborns with the *CYP1A1* *MspI* restriction site (group V, $P = 0.02$) and without the *CYP1A1* *MspI* restriction site (group II, $P = 0.04$). Compared with adduct levels in group I, newborn adducts were also significantly higher in all other genotype groups combined (groups II–VI; $P = 0.03$; Table 4). There was no significant difference in newborn adduct levels between any other newborn genotype combinations. Nor was the association between the interaction term (*CYP1A1***GSTP1*) and newborn adduct levels statistically significant.

Discussion

This study demonstrates a significant combined effect of phase I (*CYP1A1* *MspI*) and phase II (*GSTP1*) polymorphisms on PAH-DNA adduct levels in the WBCs of newborns. Our findings are biologically plausible because the *GSTP1* *val* allele has been shown to be more efficient at detoxifying PAH diol-epoxides (46–48), and some prior data suggest that the *CYP1A1* *MspI* RFLP is linked to increased enzyme activity (27–29). Our results are also consistent with our prior report of a significant association between the *CYP1A1* *MspI* RFLP and PAH-DNA adduct levels in placental tissue of newborns from the current cohort (34). However, they differ from a recent lung cancer case-control study in which adduct levels measured by ³²P-postlabeling in lung tissue of 70 smokers were found to be significantly higher among *GSTP1* *val* homozygotes compared

Table 4 WBC PAH-DNA adduct levels for mothers and newborns by the *CYP1A1* and *GSTP1* genotypes analyzed in combination^a

	Maternal WBC adduct levels	Newborn WBC adduct levels
	Mean \pm SD per 10 ⁸ nucleotides (n) ^b	Mean \pm SD per 10 ⁸ nucleotides (n) ^b
Group I: <i>GSTP1 val/val</i> + <i>CYP1A1 MspI</i> restriction site absent	8.4 \pm 11.4 (13)	2.6 \pm 2.3 (14) ^{c,d,e,f}
Group II: <i>GSTP1 ile/val</i> + <i>CYP1A1 MspI</i> restriction site absent	7.5 \pm 11.5 (43)	8.6 \pm 10.0 (53)
Group III: <i>GSTP1 ile/ile</i> + <i>CYP1A1 MspI</i> restriction site absent	6.0 \pm 8.5 (51)	7.0 \pm 8.6 (35)
Group IV: <i>GSTP1 val/val</i> + <i>CYP1A1 MspI</i> restriction site present ^g	1.0 \pm 0.0 (2)	9.3 \pm 6.7 (2)
Group V: <i>GSTP1 ile/val</i> + <i>CYP1A1 MspI</i> restriction site present ^g	4.6 \pm 4.3 (10)	9.8 \pm 11.0 (17)
Group VI: <i>GSTP1 ile/ile</i> + <i>CYP1A1 MspI</i> restriction site present ^g	4.9 \pm 4.6 (8)	11.3 \pm 16.4 (7)

^a Maternal adduct levels are stratified by the mother's genotype, and newborn adduct levels are stratified by the newborn's genotype; all models are controlled for place of residence, cigarette smoking, dietary PAHs, use of coal stoves for residential heating, and home/occupational exposures. Associations of borderline significance (0.1 > P > 0.05) are reported but are considered statistically significant at $P \leq 0.05$.

^b Number of subjects.

^c Newborn group I versus group VI ($P = 0.04$).

^d Newborn group I versus group V ($P = 0.02$).

^e Newborn group I versus group II ($P = 0.04$).

^f Newborn group I versus group II-VI ($P = 0.03$).

^g Homozygotes and heterozygotes combined.

with *GSTP1 ile* homozygotes (49). As will be discussed, gene-environment interactions may vary between the adult and the fetus. In addition, the fact that the two studies measure a different spectrum of adducts may contribute to these inconsistent findings. The ³²P-postlabeling method detects a complex mixture of aromatic and/or hydrophobic compounds bound to DNA (49). By contrast, the ELISA used in the current study recognizes structurally related PAH diol-epoxide-DNA adducts (57). Enzyme studies suggest that *GSTP1 val* homozygotes will be more susceptible to the effects of carcinogens that share structural similarity to 1-chloro-2,4-dinitrobenzene but less susceptible to the effects of PAH diol epoxides (37, 47, 48). Specifically, the residue at 105 appears to define the geometry of the hydrophobic substrate-binding site such that enzyme activity toward small substrates will be greater with isoleucine at 105 and toward larger substrates such as PAH greater with valine at 105 (43, 46).

The current study saw a significant effect of the combined *CYP1A1* and *GSTP1* polymorphisms on DNA damage in newborn WBCs, whereas there was no significant association between the polymorphisms and DNA damage in maternal WBCs. Possible explanations for this difference include the lack of expression in the fetus of the other class of GST (GST μ) capable of detoxifying PAHs (36, 38). *GSTP1* is the major GST expressed in all fetal tissues tested, including fetal liver. The μ class genes are expressed rarely and not at all in fetal liver (38). By contrast, GST μ genes are widely expressed in adult tissues, including the liver. Thus, there is greater redundancy in PAH detoxification capabilities in adults that may compensate for the effects of the *CYP1A1/GSTP1* genotype.

Similarly, the lower DNA repair efficiency in the fetus relative to the adult (58–60) may render the fetus more sensitive to the effects of the polymorphisms. Our prior finding of higher PAH-DNA adduct levels in newborn WBCs compared with paired maternal WBCs (21) lends support to this hypothesis.

Although maternal adducts were not significantly associated with the *CYP1A1* or *GSTP1* polymorphisms, it is interesting that the genotype associated with the highest level of DNA damage in maternal tissue (the *GSTP1 val/val* with the *CYP1A1 MspI* restriction site absent) corresponds to the genotype associated with the lowest level of DNA damage in fetal tissues. The possibility exists that during human evolution, selection could maintain "deleterious" metabolism gene alleles in a population when they are protective during fetal development.

Conversely, there may be combinations of maternal/fetal genotypes that result in a high-risk situation for the fetus if the mother is exposed to specific chemicals.

To our knowledge, this is the first study to demonstrate a significant combined effect of phase I and phase II polymorphisms on DNA damage from PAH in fetal tissues. As with any initial finding, the associations seen here require confirmation to rule out the possibility that they are attributable to chance or uncontrolled confounding. If real, it is likely that the genotype acts by modifying the relationship between PAH exposure and net DNA adduct formation. A limitation of the current study is that, because of the small sample size and limited ambient monitoring data, we did not have the power to test for effect modification. Nonetheless, these results suggest that cancer risks from transplacental exposure to PAH may be greater in a subset of infants with the combined phase I and II polymorphisms. They are of concern in light of the association seen previously between PAH-DNA adducts and cancer risk (18, 61) and illustrate the importance of considering multigene effects on genetic damage from transplacental exposure to these common environmental contaminants. If confirmed, they have implications for risk assessment, which currently does not adequately take into account sensitive subsets of the population.

Acknowledgments

We acknowledge the assistance of T. Randall, A. Rundle, Q. Wang, D. Allen, W. Y. Tsai, F. Crofts, and R. Lonow.

References

- IARC. International Agency for Research on Cancer (IARC) Technical Report No. 53/001. Lyon, France: IARC, 1983.
- Perera, F. P., Hemminki, K., Grzybowski, E., Motykiewicz, G., Michalska, J., Santella, R. M., Young, T. L., Dickey, C., Brandt-Rauf, P., DeVivo, I., Blaner, W., Tsai, W. Y., and Chorazy, M. Molecular and genetic damage from environmental pollution in Poland. *Nature (Lond.)*, 360: 256–258, 1992.
- Chuang, J. C., Mack, G. A., Kuhlman, M. R., and Wilson, N. K. Polycyclic aromatic hydrocarbons and their derivatives in indoor and outdoor air in an eight-home study. *Atmos. Environ.*, 25B: 369–380, 1991.
- Lewtas, J. Human exposure to complex mixtures of air pollutants. *Toxicol. Lett.*, 72: 163–169, 1994.
- IARC. Tobacco smoking. In: D. G. Zaridze and R. Péro (eds.), IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, pp. 3–323. Lyon, France: IARC, 1986.
- Denissenko, M. F., Paio, A., Tang, M. S., and Pfeifer, G. P. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in p53. *Science (Washington DC)*, 274: 430–432, 1996.

7. Surgeon General. The Health Consequences of Smoking: Cancer. A Report of the Surgeon General. Washington, DC: United States Department of Health and Human Services, United States Government Printing Office, 1982.
8. National Research Council, National Academy of Sciences. Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects, 1-337. Washington, DC: National Academy Press, 1986.
9. Srivastava, V. K., Chauhan, S. S., Srivastava, P. K., Kumar, V., and Misra, U. K. Fetal translocation and metabolism of PAH obtained from coal fly ash given intratracheally to pregnant rats. *J. Toxicol. Environ. Health*, *18*: 459-469, 1986.
10. Neubert, D., and Tapken, S. Transfer of benzo(a)pyrene into mouse embryos and fetuses. *Arch. Toxicol.*, *35*: 2943-2953, 1988.
11. Bulay, O. M., and Wattenberg, L. W. Carcinogenic effects of polycyclic aromatic hydrocarbon carcinogens administered to mice during pregnancy on the progeny. *J. Natl. Cancer Inst.*, *46*: 397-402, 1971.
12. Vesselinovich, S. C., Kyriazis, A. P., Nihailovich, N., and Rao, K. V. Conditions modifying development of tumors in mice at various sites by BaP. *Cancer Res.*, *35*: 2948-2953, 1975.
13. Nikonova, T. V. Transplacental action of benzo(a)pyrene and pyrene. *Bull. Exp. Biol. Med.*, *84*: 1025-1027, 1977.
14. Bui, Q. Q., Tran, M. B., and West, W. L. A comparative study of the reproductive effects of methadone and benzo(a)pyrene in the pregnant and pseudopregnant rat. *Toxicology*, *42*: 195-204, 1986.
15. Barbieri, O., Ognio, E., Rossi, O., Astigiano, S., and Rossi, L. Embryotoxicity of benzo(a)pyrene and some of its synthetic derivatives in Swiss mice. *Cancer Res.*, *46*: 94-98, 1986.
16. Perera, F. P. Environment and cancer: who are susceptible? *Science (Washington DC)*, *278*: 1068-1073, 1997.
17. Mooney, L. A., Bell, D. A., Santella, R. M., Van Bennekum, A. M., Ottman, R., Paik, M., Blaner, W. S., Lucier, G. W., Covey, L., Young, T. L., Cooper, T. B., Glassman, A. H., and Perera, F. P. Contribution of genetic and nutritional factors to DNA damage in heavy smokers. *Carcinogenesis (Lond.)*, *18*: 503-509, 1997.
18. Tang, D. L., Rundle, A., Warburton, D., Santella, R. M., Tsai, W.-Y., Chiamprasert, S., Hsu, Y. Z., and Perera, F. P. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. *Carcinogenesis (Lond.)*, *19*: 1949-1953, 1998.
19. Jedrychowski, W., Becher, H., Wahrendorf, J., and Basa-Cierpialek, Z. A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *J. Epidemiol. Community Health*, *44*: 114-120, 1990.
20. Whyatt, R. M., Garte, S. J., Cosma, G., Bell, D. A., Jedrychowski, W., Wahrendorf, J., Randall, M. C., Cooper, T. B., Ottman, R., Tang, D., Tsai, W.-Y., Dickey, C. P., Manchester, D. K., Crofts, F., and Perera, F. P. CYP1A1 messenger RNA levels in placental tissue as a biomarker of environmental exposure. *Cancer Epidemiol. Biomark. Prev.*, *4*: 147-153, 1995.
21. Whyatt, R. M., Santella, R. M., Jedrychowski, W., Garte, S. J., Bell, D. A., Ottman, R., Gladek-Yarborough, A., Cosma, G., Young, T.-L., Cooper, T. B., Randall, M. C., Manchester, D. K., and Perera, F. P. Relationship between ambient air pollution and procarcinogenic DNA damage in Polish mothers and newborns. *Environ. Health Perspect.*, *106* (Suppl. 3): 821-826, 1998.
22. Perera, F. P., Jedrychowski, W., Rauh, V., and Whyatt, R. M. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environ. Health Perspect.*, *107*: 451-460, 1999.
23. Perera, F. P., Whyatt, R. M., Jedrychowski, W., Rauh, V., Manchester, D., Santella, R. M., and Ottman, R. Recent developments in molecular epidemiology: a study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. *Am. J. Epidemiol.*, *147*: 309-314, 1998.
24. Nebert, D. W. Role of genetics and drug metabolism in human cancer risk. *Mutat. Res.*, *247*: 267-281, 1991.
25. Garte, S. The role of ethnicity in cancer susceptibility gene polymorphisms: the example of CYP1A1. *Carcinogenesis (Lond.)*, *19*: 1329-1332, 1998.
26. Hayashi, S. I., Watanabe, J., and Nakachi, K. Genetic linkage of lung cancer-associated *MspI* polymorphism with amino acid replacement in the heme binding region of the human cytochrome *P450IA1* gene. *J. Biochem.*, *110*: 407-411, 1991.
27. Cosma, G., Crofts, F., Taioli, E., Toniolo, P., and Garte, S. Relationship between genotype and function of the human *CYP1A1* gene. *J. Toxicol. Environ. Health*, *40*: 309-316, 1993.
28. Crofts, F., Taioli, E., Trachman, J., Cosma, G. N., Currie, D., Toniolo, P., and Garte, S. J. Functional significance of different human *CYP1A1* genotypes. *Carcinogenesis (Lond.)*, *15*: 2961-2963, 1994.
29. Kawajiri, K., Nakachi, K., Imai, K., Watanabe, J., and Hayashi, S. The *CYP1A1* gene and cancer susceptibility. *Crit. Rev. Oncol.-Hematol.*, *14*: 77-87, 1993.
30. Rothman, N., Shields, P. G., Poirier, M. C., Harrington, A. M., Ford, D. P., and Strickland, P. T. The impact of glutathione *S*-transferase M1 and cytochrome *P450IA1* genotypes on white-blood-cell polycyclic aromatic hydrocarbon-DNA adduct levels in humans. *Mol. Carcinog.*, *14*: 63-68, 1995.
31. Shields, P. G., Bowman, E. D., Harrington, A. M., Doan, V. T., and Weston, A. Polycyclic aromatic hydrocarbon-DNA adducts in human lung and cancer susceptibility genes. *Cancer Res.*, *53*: 3486-3492, 1993.
32. Ichiba, M., Hagmar, L., Rannug, A., Högstedt, B., Alexandrie, A.-K., Carstensen, U., and Hemminki, K. Aromatic DNA adducts, micronuclei and genetic polymorphism for *CYP1A1* and *GST* in chimney sweeps. *Carcinogenesis (Lond.)*, *15*: 1347-1352, 1994.
33. Mooney, L. A., Bell, D. A., Santella, R. M., Van Bennekum, A. M., Ottman, R., Paik, M., Blaner, W. S., Lucier, G. W., Covey, L., Young, T. L., Cooper, T. B., Glassman, A. H., and Perera, F. P. Contribution of genetic and nutritional factors to DNA damage in heavy smokers. *Carcinogenesis (Lond.)*, *18*: 503-509, 1997.
34. Whyatt, R. M., Bell, D. A., Santella, R. M., Garte, S. J., Jedrychowski, W., Gladek-Yarborough, A., Cosma, G., Manchester, D. K., Young, T.-L., Wahrendorf, J., Cooper, T. B., Ottman, R., and Perera, F. P. Polycyclic aromatic hydrocarbon-DNA adducts in human placenta and modulation by CYP1A1 induction and genotype. *Carcinogenesis (Lond.)*, *19*: 1389-1392, 1998.
35. Helzlsouer, K. I., Selmin, O., Huang, H. Y., Strickland, P. T., Hoffman, S., Alberg, A. J., Watson, M., Comstock, G. W., and Bell, D. Association between glutathione *S*-transferase M1, P1 and T1 genetic polymorphisms and development of breast cancer. *J. Natl. Cancer Inst.*, *90*: 512-518, 1998.
36. Hayes, J. D., and Pulford, D. J. 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*: 445-600, 1995.
37. Hu, X., Ji, X., Srivastava, S. K., Xia, H., Awasthi, S., Nanduri, B., Awasthi, Y. C., Zimniak, P., and Singh, S. Mechanism of differential catalytic efficiency of two polymorphic forms of human glutathione *S*-transferase P1 in the glutathione conjugation of carcinogenic diol epoxide of chrysene. *Arch. Biochem. Biophys.*, *345*: 32-38, 1997.
38. Robertson, I. G. C., Guthenberg, C., Mannervik, B., and Jernstrom, B. Differences in stereoselectivity and catalytic efficiency of three human glutathione transferases in the conjugation of glutathione with 7 β ,8 α -dihydroxy-9 α ,10 α -oxy-7,8,9,10-tetrahydrobenzo(a)pyrene. *Cancer Res.*, *46*: 2220-2224, 1986.
39. Watson, M. A., Stewart, R. K., Smith, G. B. J., Massey, T., and Bell, D. Human glutathione *S*-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. *Carcinogenesis (Lond.)*, *19*: 275-280, 1998.
40. Kashiwada, M., Kitada, M., Shimada, T., Itahashi, K., Sato, K., and Kamataki, T. Purification and characterization of acidic form of glutathione *S*-transferase in human fetal livers: high similarity to placental form. *J. Biochem.*, *110*: 743-747, 1991.
41. Hiley, C., Bell, J., Hume, R., and Strange, R. Differential expression of α and π isoenzymes of glutathione *S*-transferase in developing human kidney. *Biochim. Biophys. Acta*, *990*: 321-324, 1989.
42. Cossar, D., Bell, J., Strange, R., Jones, M., Sandison, A., and Hume, R. The α and π isoenzymes of glutathione *S*-transferase in human fetal lung: *in utero* ontogeny compared with differentiation in lung organ culture. *Biochim. Biophys. Acta*, *1037*: 221-226, 1990.
43. Zimniak, P., Nanduri, B., Pikula, S., Bandorowicz-Pikula, J., Singhal, S. S., Srivastava, S. K., Awasthi, S., and Awasthi, Y. C. Naturally occurring human glutathione *S*-transferase GSTP1-1 isoforms with isoleucine and valine in position 104 differ in enzymic properties. *Eur. J. Biochem.*, *224*: 893-899, 1994.
44. Ali-Osman, F., Akande, O., Antoun, G., Mao, J. X., and Buolamwini, J. Molecular cloning, characterization, and expression in *Escherichia coli* of full-length cDNAs of three human glutathione *S*-transferase Pi gene variants. *J. Biol. Chem.*, *272*: 10004-10012, 1997.
45. van Lieshout, E. M. M., Roelofs, H. M. J., Dekker, S., Mulder, C. J. J., Wobbes, T., Jansen, J. B. M. J., and Peters, W. H. M. Polymorphic expression of the glutathione *S*-transferase P1 gene and its susceptibility to Barrett's esophagus and esophageal carcinoma. *Cancer Res.*, *59*: 586-589, 1999.
46. Hu, X., Xia, H., Srivastava, S. K., Herzog, C., Awasthi, Y. C., Ji, X., Zimniak, P., and Singh, S. V. Activity of four allelic forms of glutathione *S*-transferase hGSTP1-1 for diol epoxides of polycyclic aromatic hydrocarbons. *Biochem. Biophys. Res. Commun.*, *238*: 397-402, 1997.
47. Sundberg, K., Johansson, A. S., Stenberg, G., Widersten, M., Seidel, A., Mannervik, B., and Jernstrom, B. Differences in the catalytic efficiencies of allelic variants of glutathione transferase P1-1 towards carcinogenic diol epoxides of polycyclic aromatic hydrocarbons. *Carcinogenesis (Lond.)*, *19*: 433-436, 1998.
48. Sundberg, K., Seidel, A., Mannervik, B., and Jernstrom, B. Detoxication of carcinogenic fjord-region diol epoxides of polycyclic aromatic hydrocarbons by glutathione transferase P1-1 variants and glutathione. *Fed. Eur. Biochem. Soc. Lett.*, *438*: 206-210, 1998.
49. Ryberg, D., Skaug, V., Hewer, A., Phillips, D. H., Harries, L. W., Wolf, C. R., Ogreid, D., Ulvik, A., Vu, P., and Haugen, A. Genotypes of glutathione

transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. *Carcinogenesis (Lond.)*, *18*: 1285–1289, 1997.

50. Matthias, C., Bockmuhl, U., Jahnke, V., Harries, L. W., Wolf, C. R., Jones, P. W., Alldersea, J., Worrall, S. F., Hand, P., Fryer, A. A., and Strange, R. The glutathione *S*-transferase *GSTP1* polymorphism: effects on susceptibility to oral/pharyngeal and laryngeal carcinomas. *Pharmacogenetics*, *8*: 1–6, 1998.

51. Saarikoski, S. T., Voho, A., Reinikainen, M., Anttila, S., Karjalainen, A., Malaveille, C., Vainio, H., Husgafvel-Pursiainen, K., and Hirvonen, A. Combined effect of polymorphic *GST* genes on individual susceptibility to lung cancer. *Int. J. Cancer*, *77*: 516–521, 1998.

52. Harris, M. J., Coggan, M., Langton, L., Wilson, S. R., and Board, P. G. Polymorphism of the pi class glutathione *S*-transferase in normal populations and cancer patients. *Pharmacogenetics*, *8*: 27–31, 1998.

53. Harries, L. W., Stubbs, M. J., Forman, D., Howard, G. C. W., and Wolf, C. R. Identification of genetic polymorphisms at the glutathione *S*-transferase pi locus and association with susceptibility to bladder, testicular and prostate cancer. *Carcinogenesis (Lond.)*, *18*: 641–644, 1997.

54. Lin, D. X., Tang, Y. M., Peng, Q., Lu, S. X., Ambrosone, C., and Kadlubar, F. F. Susceptibility to esophageal cancer and genetic polymorphisms in glutathione *S*-transferases T1, P1 and M1 and cytochrome P450 2E1. *Cancer Epidemiol. Biomark. Prev.*, *7*: 1013–1018, 1998.

55. Jourenkova-Mironova, N., Voho, A., Bouchardy, C., Wikman, H., Dayer, P., Benhamou, S., and Hirvonen, A. Glutathione *S*-transferase *GSTM3* and *GSTP1* genotypes and larynx cancer risk. *Cancer Epidemiol. Biomark. Prev.*, *8*: 185–188, 1999.

56. Perera, F. P., Hemminki, K., Young, T. L., Brenner, D., Kelly, G., and Santella, R. M. Detection of polycyclic aromatic hydrocarbon-DNA adducts in white blood cells of foundry workers. *Cancer Res.*, *48*: 2288–2291, 1988.

57. Santella, R. M., Gasparro, F. P., and Hsieh, L. L. Quantitation of carcinogen-DNA adducts with monoclonal antibodies. *Prog. Exp. Tumor Res.*, *31*: 63–75, 1987.

58. Calabrese, E. J. *Age and Susceptibility to Toxic Substances 1–296*. New York: John Wiley and Sons, 1986.

59. National Research Council, National Academy of Sciences. *Pesticides in the Diets of Infants and Children*. Washington, DC: National Academy Press, 1993.

60. Laib, R. J., Klein, K. P., and Bolt, H. M. The rat liver foci bioassay: age dependence of induction by vinyl chloride of ATP-deficient foci. *Carcinogenesis (Lond.)*, *6*: 65–68, 1985.

61. Tang, D., Santella, R. M., Blackwood, A., Young, T. L., Mayer, J., Jaretzki, A., Grantham, S., Carberry, D., Steinglass, K. M., Tsai, W. Y., and Perera, F. P. A case-control molecular epidemiologic study of lung cancer. *Cancer Epidemiol. Biomark. Prev.*, *4*: 341–346, 1995.

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Cancer Epidemiol Biomarkers Prev 2000;9:207-212.

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