Carcinogenesis, 2016, Vol. 37, No. 11, 1110–1115

doi:10.1093/carcin/bgw090
Advance Access publication August 26, 2016
Original Manuscript

ORIGINAL MANUSCRIPT

Significant interactions between maternal PAH exposure and single nucleotide polymorphisms in candidate genes on B[*a*]P–DNA adducts in a cohort of non-smoking Polish mothers and newborns

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Abstract

Polycyclic aromatic hydrocarbons (PAH) are a class of chemicals common in the environment. Certain PAH are carcinogenic, although the degree to which genetic variation influences susceptibility to carcinogenic PAH remains unclear. Also unknown is the influence of genetic variation on the procarcinogenic effect of *in utero* exposures to PAH. Benzo[*a*]pyrene (B[*a*]P) is a well-studied PAH that is classified as a known human carcinogen. Within our Polish cohort, we explored interactions between maternal exposure to airborne PAH during pregnancy and maternal and newborn single nucleotide polymorphisms (SNPs) in plausible B[*a*]P metabolism genes on B[*a*]P–DNA adducts in paired cord blood samples. The study subjects included non-smoking women (n = 368) with available data on maternal PAH exposure, paired cord adducts, and genetic data who resided in Krakow, Poland. We selected eight common variants in maternal and newborn candidate genes related to B[*a*]P metabolism, detoxification, and repair for our analyses: *CYP1A1*, *CYP1A2*, *CYP1B1*, *GSTM1*, *GSTT2*, *NQO1*, and *XRCC1*. We observed significant interactions between maternal PAH exposure and SNPs on cord B[*a*]P–DNA adducts in the following genes: maternal *CYP1A1* and *GSTT2*, and newborn *CYP1A1* and *CYP1B1*. These novel findings highlight differences in maternal and newborn genetic contributions to B[*a*]P–DNA adduct formation and have the potential to identify at-risk subpopulations who are susceptible to the carcinogenic potential of B[*a*]P.

Introduction

Polycyclic aromatic hydrocarbons (PAH) are a class of chemicals that are products of incomplete combustion reactions, and thus are ubiquitous in the environment. Major sources of PAH include fossil fuel combustion, cigarette smoking, and grilling of meats (1). The common routes of exposure to PAH are inhalation and oral.

Certain PAH are carcinogenic and of these, the best-studied is benzo[*a*]pyrene (B[*a*]P). The metabolic activation of B[*a*]P to form a compound that is highly reactive with DNA has been well elucidated and is diagrammed in Figure 1. The reactive B[*a*]P 7,8-diol-9,10-epoxide (BPDE) metabolite preferentially forms a covalent adduct at the N^2 position of the deoxyguanosine base,

Received: January 29, 2016; **Revised:** August 12, 2016; **Accepted:** August 21, 2016

Abbreviations

B[a]P	benzo[*a*]pyrene
BPDE	B[*a*]P 7,8-diol-9,10-epoxide
ETS	environmental tobacco smoke
GST	glutathione S-transferase
NQO	NAD(P)H:quinone oxidoreductase
PAH	polycyclic aromatic hydrocarbon
SNP	single nucleotide polymorphism
WBC	white blood cell

thus forming a DNA adduct, which can be considered an early risk biomarker of cancer, as well as a biomarker which integrates multiple B[*a*]P exposure routes and reflects a biologically effective dose (2–4). The International Agency for Research on Cancer originally designated B[*a*]P as a Group 2A, or probable, human carcinogen (1). However, based on accumulating evidence, the agency later promoted the classification of B[*a*]P to that of a Group 1, or known, human carcinogen (5,6).

In this study, we have evaluated the interaction between maternal PAH exposure measured by personal air monitoring during pregnancy and both maternal and newborn single nucleotide polymorphisms (SNPs) on B[*a*]P–DNA adducts measured in umbilical cord blood. We have described previously the susceptibility of the human fetus to B[*a*]P–DNA adduction in our epidemiologic cohorts (7,8). Additionally, the formation and persistence of B[*a*]P–DNA adducts and their association with cancer have been described in other experimental (9) and epidemiologic studies (10,11).

We previously reported a statistically significant association between maternal PAH exposure, characterized by tertiles, and paired cord blood B[*a*]P–DNA adducts in our Polish cohort of mothers and newborns (12). We also found a statistically significant correlation between paired maternal and newborn B[*a*]P–DNA adducts (12). In that study, our multivariable linear regression model estimated that 3% of cord blood adduct variance could be attributed to maternal PAH exposure above 5.70 ng/m^3, and that 14.8% of cord blood adduct variance could be attributed to the level of maternal B[*a*]P–DNA adducts (12). As we discussed in that publication, DNA adduct formation is subject to greater variability than external exposure, as individuals vary in their rates of adduct formation and DNA repair (12). Therefore in this study, we hypothesize that common genetic variation in candidate genes could account for a fraction of the cord blood B[*a*]P–DNA adduct variance that we previously observed. This study is an extension of a prior analysis in which we examined interactions between maternal PAH exposure during pregnancy and genetic variation on B[*a*]P–DNA adducts in n = 328 mothers for whom we had PAH exposure data and n = 255 newborns for whom we had B[*a*]P–DNA adduct data. Our current study involves a larger number of subjects (n = 424 Polish mothers for whom we had PAH exposure data, and n = 445 newborns for whom we had B[*a*]P–DNA adduct data) and a greater number of genetic polymorphisms evaluated.

The metabolic roles of each of the genes selected for this interaction study are shown in Figure 1. B[*a*]P, the parent compound, is primarily metabolized by the cytochrome P450 (CYP) isoform 1A1, though isoforms 1A2 and 1B1 are also capable of metabolizing the parent compound. Following the formation of the B[*a*]P 7,8-epoxide metabolite, the epoxide hydrolase enzyme catalyzes the hydrolysis of the epoxide to form the B[*a*]P 7,8-diol. A second CYP reaction results in the formation of BPDE. This metabolite is the ultimate reactive carcinogen, which harbors an electrophilic center at the C^{10} position. The sterics of BPDE coupled with its electrophilicity can result in covalent adduction with the nucleophilic N^2 of the deoxyguanosine base. The deoxyguanosine moiety is depicted in the black outline in Figure 1.

In addition to this central metabolic activation pathway, it is also possible for reactive B[*a*]P quinone metabolites to be formed from the B[*a*]P diols. NAD(P)H:quinone oxidoreductase (NQO) is a protective enzyme which catalyzes the 2-electron reduction of quinones back to the diol metabolites. B[*a*]P metabolites can also be conjugated by glutathione S-transferase (GST) and UDP-glucuronosyl transferase enzymes, respectively, to generate readily excretable metabolites.

Here, we report interactions between maternal PAH exposure and common SNPs in selected B[*a*]P metabolism genes (*CYP1A1*, *CYP1A2*, *CYP1B1*, *GSTM1*, *GSTM3*, *GSTT2*, *NQO1*, and *XRCC1*) on B[*a*]P–DNA adducts in paired umbilical cord blood samples. As detailed above, CYP1A1, CYP1A2, and CYP1B1 are involved in metabolizing the parent B[*a*]P compound to BPDE, which is involved in the formation of the B[*a*]P–DNA adduct. In contrast, GSTM1, GSTM3, GSTT2, and NQO1 are involved in shunting B[*a*]P metabolism so as to prevent formation of the reactive BPDE.

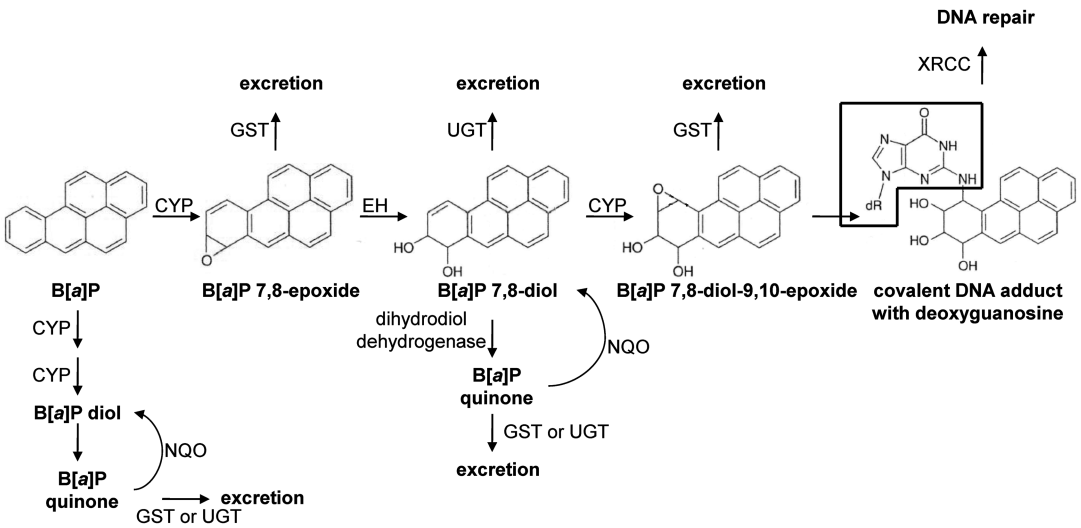

Figure 1. Metabolic scheme showing activation and detoxification pathways of B[*a*]P (adapted from Boelsterli, 2003).

XRCC1 is involved is involved in the repair of B[*a*]P-adducted DNA.

Materials and methods

Study participants

Study subjects were selected from a longitudinal cohort study in Krakow, Poland; the study design details have been published previously (13). Study subjects were recruited between 2000 and 2003 through the Jagiellonian University. The women are of European ancestry, drawn from a homogeneous population in Krakow, Poland. Pregnant women were considered eligible for the study if they were not currently smoking, were registered at prenatal health care clinics, had lived at their present address for at least a year before the initial interview, were ≥18 years of age, had no history of illicit drug use, or pregnancy-related diabetes or hypertension, and had a valid estimate of gestational age.

Maternal PAH exposure assessment

During the second or third trimesters of pregnancy, the study participants carried a backpack containing a portable personal exposure air monitor during the day and kept it near their beds at night over a consecutive 48-h period for personal PAH exposure measurements. Air extracts were analyzed at the Southwest Research Institute in San Antonio, TX, for levels of pyrene and the following eight carcinogenic PAH: benzo(*a*)anthracene, chrysene, benzo(*b*)fluoranthene, benzo[*k*]fluoranthene, B(*a*)P, indeno(1,2,3-*cd*)pyrene, dibenz(*a*,*h*)anthracene, and benzo(*g*,*h*,*i*)perylene. These methodological details have been previously described (14,15). The sum of these PAH measurements was used to generate the final values for maternal PAH exposure. Supporting the validity of the 48-h personal monitoring of PAH, sequential 2-week indoor residential monitoring (four 2-week periods from the 32nd to the 42nd weeks of pregnancy) in the Columbia Center for Children's Environmental Health (CCCEH) cohort showed that the overall mean indoor level was significantly correlated with the individual 48-h personal monitor estimate of PAH exposure (16).

B[*a*]P–DNA adduct quantitation

Umbilical cord blood (30–60 ml) was collected at delivery. White blood cells (WBCs) were isolated from the blood samples, and total DNA was harvested from the cells. B[*a*]P–DNA adducts in WBC DNA samples were measured and quantified using a high-performance liquid chromatography-fluorescence detection method described previously, which detects B[*a*]P tetrols specifically measuring B[*a*]P–DNA adducts (17). This detection method has a coefficient of variation of 12% and a lower limit of detection of 0.25 adducts per 10^8 nucleotides DNA. As in prior analyses, samples falling below the limit of detection were assigned a value midway between the limit of detection and 0 (0.125 adducts per 10^8 nucleotides DNA). In order to minimize batch effects, a standard curve was generated for each batch of samples analyzed and cross-batch comparisons were also conducted.

Genetic polymorphism selection

A total of 32 SNPs from eight genes related to PAH metabolism, detoxification, and repair were selected for the analyses: *CYP1A1*, *CYP1A2*, *CYP1B1*, *GSTM1*, *GSTM3*, *GSTT2*, *NQO1*, and *XRCC1*. The specific SNPs analyzed were selected from the SNP500Cancer resource (18). DNA sequence analysis was performed on WBC DNA from umbilical cord blood and also on WBC DNA isolated from maternal blood, which was collected (30–35 ml) within 1 day postpartum.

Interaction analyses between maternal PAH exposure and SNPs on newborn B[*a*]P–DNA adducts

The previously listed eight PAH measured were significantly correlated, so a composite PAH variable was computed, as done previously (19–21). As in prior studies (19–21), this summed measure was dichotomized at the median (22.11 ng/m^3) to obtain a binary PAH exposure, defined as either 'PAH high' or 'PAH low'. We examined 32 SNPs from the eight genes of interest.

With respect to covariates, although environmental tobacco smoke (ETS) was not significantly associated with B[*a*]P–DNA adducts, it was included in the model to be consistent with other studies. Other covariates, such as maternal age, dietary PAH, and maternal body mass index, were not confounders of B[*a*]P–DNA adducts nor were they significantly associated with B[*a*]P–DNA adducts at the significance level of $P \leq 0.05$ and so were not included in the model (12). Because the B[*a*]P–DNA adducts reflect exposure over the prior 4 months and therefore reflect any recent heating, we did not adjust for heating season versus non-heating season in order to avoid over-controlling.

Only those maternal PAH exposure × SNP interactions on cord blood B[*a*]P–DNA adducts that achieved statistical significance ($P \leq 0.05$) are reported here. A further requisite for reporting the interaction was an observed SNP frequency of ≥5%. Associations of significant interactions with either increased or decreased levels of adducts are reported. The analyses did not apply Bonferroni or another type of correction because of the exploratory nature of the study.

Assessment of functional implications of interaction analysis results

In order to interpret the significant interactions between maternal PAH exposure and SNPs in terms of their impact on function of the B[*a*]P metabolism, detoxification, and repair enzymes we assessed, we utilized interaction coefficients to determine the fold change in the original level of adducts with the SNPs and wild-type nucleotides under either high or low PAH exposure conditions. This was based on linear regressions of logarithm-transformed B[*a*]P–DNA adduct levels. To determine the fold change in the level of adducts formed with the wild-type nucleotide under high PAH exposure conditions compared with the level of adducts formed under low PAH exposure conditions, we used the formula:

$$[e^{\wedge}(\beta_{PAH})]$$

To determine the fold change in the level of adducts formed with the SNP under high PAH exposure conditions compared with the level of adducts formed under low PAH exposure conditions, we used the formula:

$$[e^{\wedge}(\beta_{PAH} + \beta_{interaction})]$$

Depending on the role of the enzyme in B[*a*]P metabolism and detoxification, the calculated fold change for the SNP was identified as having either a 'protective' or 'not protective' effect on adduct formation based on whether the fold change was higher or lower than the fold change for the wild-type nucleotide.

Results

The study population from which samples were collected for analysis is described in Table 1. Four hundred and twenty-four mothers in the cohort had data on maternal PAH exposure, 445 newborns in the cohort had data on cord adducts, and 368 pairs of mothers and newborns for whom we had maternal PAH exposure data, maternal, and cord adduct data and data on one or more candidate genes. The mean maternal PAH exposure based on personal monitoring, newborn B[*a*]P–DNA adducts in cord blood, gestational age, relative serving frequency of dietary PAH, and maternal exposure to ETS (yes/no) are shown in Table 1.

Table 2 displays the statistically significant PAH exposure × SNP interactions identified in our analysis, as well as the SNP frequencies and interaction coefficients. The nucleotides distinguishing the wild-type from the SNP are also listed. We identified two significant PAH × maternal SNP interactions (*CYP1A1* and *GSTT2*) and three significant PAH × newborn SNP interactions (one in *CYP1A1* and two in *CYP1B1*) on cord B[*a*]P–DNA adducts. The identical *CYP1A1* SNP was involved in the significant interaction for both mothers and newborns.

Figure 2 graphically depicts examples of significant PAH × SNP exposure interaction effects on cord B[*a*]P–DNA adducts.

Here, we show the significant interaction results for the *CYP1A1* SNP in newborns. The figure illustrates that, under 'PAH low' conditions, cord adducts are lower in newborns harboring the SNP, as compared with those newborns bearing the wild-type nucleotide. Under 'PAH high' conditions, cord adducts are higher in newborns bearing the SNP as compared with newborns with the wild-type nucleotide.

The suggested biologic impact of the identified SNPs involved in significant interactions with high maternal PAH exposure on cord B[*a*]P–DNA adducts are summarized in Table 3, based on the known function of each enzyme in B[*a*]P metabolism and detoxification. The information presented in Table 3 offers our hypotheses about the effect each SNP could be having on cord B[*a*]P–DNA adduct formation, under conditions of high maternal PAH exposure. We interpret our results to suggest that the *GSTT2* SNP in mothers is protective with regard to cord B[*a*]P–DNA adduct formation. The maternal and newborn *CYP1A1* SNP, and the newborn *CYP1B1* SNPs are not protective with regard to cord B[*a*]P–DNA adduct formation.

Table 1. Exposure, biomarker, and demographic characteristics of the study population with mother and/or newborn SNPs (mean ± SD)

	Study participants (mean ± SD)	Sample size (*n*)
Maternal PAH exposure (ng/m^3)	44.05 ± 55.61	424
Newborn B[*a*]P–DNA adducts (adducts/10^8 nucleotides DNA)	0.27 ± 0.15	445
Gestational age (weeks)	39.33 ± 1.57	505
Dietary PAH[a] (relative serving frequency)	2.01 ± 0.73	528
Maternal exposure to ETS (% reporting household ETS)	22	528

Subjects included in the present analysis are mothers with both genotype data and paired cord blood B[*a*]P–DNA adduct data, and newborns with both genotype data and cord blood B[*a*]P–DNA adduct data.

[a]Relative PAH exposure from dietary consumption of smoked meat, cheese, and fish. This value is a composite score from a dietary questionnaire administered to the study participants. Each of 27 questions regarding the participants' dietary habits related to PAH were scored on consumption frequency (1: never; 2: rarely or <1 time/month; 3: 1–2 times/month; 4: 1–2 times/week; 5: >2 times/week; 6: daily), and the sum of these 27 individual scores is represented in the dietary PAH value.

Discussion

In this study, we evaluated the role of common genetic variation in maternal and newborn B[*a*]P metabolism genes in interacting with maternal PAH exposure because B[*a*]P–DNA adduct formation is most likely driven by genetic factors in addition to PAH exposure. We found novel interactions between maternal PAH exposure and common genetic variants in plausible B[*a*]P metabolism genes on fetal B[*a*]P–DNA adduct levels, which are displayed in Tables 2 and 3. Our findings suggest that both maternal and fetal metabolism are involved in the generation of B[*a*]P–DNA adducts in cord blood.

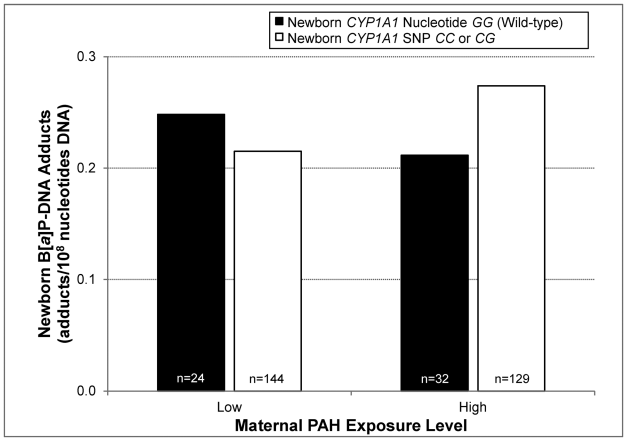

Figure 2. Interaction between maternal PAH exposure and newborn *CYP1A1* SNP (rs2198843) on B[*a*]P–DNA adducts in cord blood. The significance of the newborn *CYP1A1* SNP (rs2198843) is shown. Cord blood adducts are lower when newborns harbor the SNP *CC* or *CG* and are within the low PAH exposure group, but cord blood adducts are higher when this SNP is harbored and the study participants are within the high PAH exposure group (the interaction coefficient $\beta = 0.40$, $P < 0.01$; $n = 329$).

Table 2. Statistically significant ($P \leq 0.05$) SNP × PAH interactions on B[*a*]P–DNA adducts in cord blood

Maternal gene	SNP500Cancer SNP ID	Chromosome position	Wild-type nucleotide	SNP	High PAH exposure with wild-type nucleotide (*n*) Low PAH exposure with wild-type nucleotide (*n*)	High PAH exposure with SNP (*n*) Low PAH exposure with SNP (*n*)	Interaction coefficient (β)[a]	*P*
CYP1A1	rs2198843	75001230	C	G	24 24	135 145	0.57	<0.01
GSTT2	rs2719	24325950	G	T	41 44	104 111	-0.33	0.01
Newborn gene	SNP500Cancer SNP ID	Chromosome position	Wild-type nucleotide	SNP	High PAH exposure with wild-type nucleotide (*n*) Low PAH exposure with wild-type nucleotide (*n*)	High PAH exposure with SNP (*n*) Low PAH exposure with SNP (*n*)	Interaction coefficient (β)[a]	*P*
CYP1A1	rs2198843	75001230	C	G	32 24	129 144	0.40	<0.01
CYP1B1	rs10012	38302390	C	G	16 19	164 166	0.50	<0.01
	rs2617266	38302544	C	T	12 19	134 135	0.43	0.02

[a]The interaction coefficient (β) represents the increase or decrease in the effect of high PAH exposure on the log-transformed level of cord blood B[*a*]P–DNA adduct formation in the presence of the SNP compared with the effect of high PAH exposure with the wild-type nucleotide.

Table 3. Functional implications of statistically significant ($P \leq 0.05$) PAH exposure × SNP interactions on cord blood B[*a*]P–DNA adducts

Gene	SNP500Cancer SNP ID	Effect of high PAH exposure on B[*a*]P–DNA adduct formation with the wild-type nucleotide, [e^(β_{PAH})][a] (95% confidence intervals)	Effect of high PAH exposure on B[*a*]P-DNA adduct formation with the SNP, [e^(β_{PAH} + $\beta_{interaction}$)][a] (95% confidence intervals)	Suggested SNP function under conditions of high PAH exposure
Maternal *CYP1A1*	rs2198843	0.75 (0.56, 0.99)	1.32 (1.18, 1.49)	Not protective, increased CYP1A1-mediated DNA adduct formation
Maternal *GSTT2*	rs2719	1.59 (1.28, 1.98)	1.15 (1.00, 1.32)	Protective, clearance of B[*a*]P metabolites prior to adduct formation
Newborn *CYP1A1*	rs2198843	0.87 (0.66, 1.13)	1.29 (1.15, 1.46)	Not protective, increased CYP1A1-mediated DNA adduct formation
Newborn *CYP1B1*	rs10012	0.78 (0.56, 1.15)	1.20 (1.17, 1.50)	Not protective, increased CYP1B1-mediated DNA adduct formation
	rs2617266	0.80 (0.55, 1.09)	1.33 (1.08, 1.34)	Not protective, increased CYP1B1-mediated DNA adduct formation

[a]Fold change of adducts formed with high PAH exposure compared to adducts formed with low PAH exposure.

For those SNPs found to be involved with significant PAH exposure × SNP interactions, we speculate on their roles under high PAH exposure conditions (Table 3). For additional detail, we have provided Supplementary Figure 1, available at *Carcinogenesis* Online, depicting the chromosomal location of the SNPs involved in the significant haplotype interactions we observed. We conducted a thorough literature search on other studies evaluating the role of these SNPs in cancer and related metabolic pathways, and when information was available, we included it in a summary table, as shown in Supplementary Table 1, available at *Carcinogenesis* Online. These studies did not offer consistent conclusions on the role of one of the *CYP1B1* SNPs, rs10012, but we found that the scientific literature supported our speculation about the biological implications of the other SNPs under high PAH exposure conditions. Thus, the interactions identified in our study support the hypothesis that genetic variation can contribute to susceptibility and potential cancer risk from prenatal PAH exposures.

A limitation of our study was due to our inability to incorporate some known roles of PAH on enzyme level and activity in our model. PAH are known inducers of *CYP* enzymes, including *CYP1A1* and *CYP1B1* (22–25). At higher exposures, there may be higher baseline levels of these enzymes due to PAH induction. Here, we report that the *CYP1A1* and *CYP1B1* SNPs are associated with increased cord B[*a*]P–DNA adduct levels under high PAH exposure conditions. Some component of the increased adduct level may be attributable to PAH-mediated induction of either or both of these genes, in addition to the role of the SNPs in modifying the adduct level. Our inability to address PAH-mediated enzyme induction in our model likely results in our underestimating the magnitude of the biologic effect of the *CYP1A1* and *CYP1B1* SNPs. Additionally, it is possible that at high PAH exposure levels, some genetic effects are not captured by our analyses due to the effect of saturation on relevant metabolic pathways.

We published two previous studies evaluating the interactions between maternal PAH exposure and maternal and newborn genetic polymorphisms on cord B[*a*]P–DNA adducts; one of these studies was done in our New York City (NYC)-based cohort (19) and one was done in both our NYC and Poland-based cohorts (20). Interestingly, mean dietary PAH exposure was over 10-fold less in the Polish study participants than in our NYC cohort of African-American and Dominican study participants (19). The two *CYP1B1* SNPs specified in this study were also both part of a significant *CYP1B1* haplotype interaction with maternal PAH exposure on cord blood adducts in African-American study participants (19). Wang *et al.* (20) did not find that these *CYP1B1* SNPs significantly interacted with maternal PAH exposure on cord blood adducts, but the study was limited by a smaller sample size. The *CYP1A1* and *GSTT2* SNPs specified here were evaluated in these previous two studies, but neither significantly interacted with maternal PAH exposure on cord adducts in either the NYC or Polish cohorts (19,20). In our present Polish cohort study, we identified two maternal and three newborn genes that significantly interacted with high PAH exposure on cord B[*a*]P–DNA adduct levels. We previously reported in our NYC cohort study that three maternal and two newborn genes in African-Americans significantly interacted with high PAH exposure on cord B[*a*]P–DNA adducts and that one maternal and one newborn gene in Dominicans were involved in significant interactions (19). This suggests that there is a greater genetic contribution on adduct level in both Polish individuals and African-Americans compared with Dominicans.

This type of analysis is important in the context of understanding the risks to susceptible subpopulations from the carcinogenic effects of B[*a*]P and related PAH. This study suggests that both maternal and fetal genetic variation in plausible candidate genes play a role in B[*a*]P–DNA adduct formation in the developing fetus. Exploring the functional impact of these genetic changes in a laboratory-based experimental design will be key in confirming a mechanism for SNP role in B[*a*]P–DNA adduction. Taken together, the findings from population-based studies like ours and the findings from laboratory-based research have the potential to identify specific at-risk populations who are most susceptible to the formation of the procarcinogenic adducts resulting from PAH exposure.

Supplementary material

Supplementary Figure 1 and Table 1 can be found at http://carcin.oxfordjournals.org/

Funding

The study received funding from the National Institute for Environmental Health Sciences (NIEHS) and the U.S. Environmental Protection Agency (US EPA): NIEHS/EPA P01ES09600/R82702701, NIEHS/EPA P01ES09600/RD832141, NIEHS/EPA P01ES09600/RD834509, NIEHS R01ES10165, NIEHS R01ES015282, NIEHS R01ES08977, NIEHS training grant T32CA009529, the Herbert Irving Comprehensive Cancer Center Core grant (5P30CA3696), and an Anonymous Foundation.

Acknowledgements

This is part of an ongoing comparative longitudinal investigation on the health impact of prenatal exposure to outdoor/indoor air pollution in infants and children being conducted in New York City and Krakow. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the US EPA. Further, the US EPA does not endorse the purchase of any commercial products or services mentioned in the publication.
Conflict of Interest Statement: None declared.

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