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Prostate cancer risk from occupational exposure to polycyclic aromatic hydrocarbons interacting with the *GSTP1 Ile105Val* polymorphism

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Abstract

Condensed Abstract—Men who carry the *GSTP1 Val*^{105} variant who are exposed at high levels to occupational PAH are at increased risk for prostate cancer. This increased risk is more pronounced in men under age 60 or with a family history of prostate cancer.

Background—Variation in the glutathione S-transferase (*GSTP1*) gene and occupational polycyclic aromatic hydrocarbons (PAH) exposure are putative prostate cancer risk factors. An *Ile/Val* polymorphism in codon 105 of *GSTP1* affects its enzymatic activity toward PAH detoxification, a possible mechanism in prostate carcinogenesis.

Methods—To determine whether the *GSTP1 Ile105Val* polymorphism modifies prostate cancer risk associated with occupational PAH exposure, we studied 637 prostate cancer cases and 244 controls of White and African-American race from the Henry Ford Health System in Detroit, Michigan. Occupational exposure to PAH from wood, petroleum, coal or other sources through respiratory and cutaneous routes was retrospectively assessed by expert review of job histories. The association of occupational PAH exposure and *GSTP1 Ile105Val* polymorphism with prostate cancer was tested in multiple logistic regression models adjusting for potential confounders. Cases were over sampled compared with controls to evaluate gene-environment interaction with the statistically efficient case-only analytic approach.

Results—Neither carriage of the *GSTP1 Val*^{105} variant allele nor occupational PAH exposure was significantly associated with prostate cancer. However, case-only analyses revealed that carriage of the *GSTP1 Val*^{105} variant allele was associated with increasing levels of occupational respiratory PAH exposures from any source and from petroleum (trend test p-value = 0.01 for both). The *GSTP1 Val*^{105} allele was observed most frequently in cases in the highest quartile of occupational respiratory PAH exposures from petroleum (OR=1.74; 95% CI = 1.11–2.72) or from any source (OR=1.85; 95% CI = 1.19–2.89). The gene-environment risk estimate in the highest PAH petroleum exposure quartile was greatest in men under age 60 (OR=4.52; 95% CI = 1.96–10.41) or with a positive family history of prostate cancer (OR=3.02; 95% CI = 1.15–7.92).

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Conclusions—Our results suggest men who carry the *GSTP1 Val*^{105} variant and are exposed at high levels to occupational PAH have increased risk for prostate cancer. This increased risk is more pronounced in men under age 60 or with a family history of prostate cancer.

Keywords

glutathione S-transferase pi; case-control studies; DNA damage; logistic models

Introduction

Prostate cancer is a multifactorial disease that likely involves both environmental and genetic factors. Collectively, most putative environmental and genetic risk factors have not shown a consistent association with prostate cancer risk and little is known about the interaction between these factors [1]. Prostate cancer risk varies most prominently with age, ethnicity, family history, and diet [1]. A strong family history indicative of a highly penetrant prostate cancer gene is believed to account for only 5–10% of cases, but a larger percentage of prostate cancers may be due to common polymorphisms in genes giving rise to a low penetrance risk of disease [2–4]. The effect of polymorphisms in metabolic or DNA repair pathways on disease risk may be dependent upon the exposures that are part of these pathways [5–7].

Polycyclic aromatic hydrocarbons (PAH) are a potential environmental risk factor for prostate cancer. PAH are ubiquitous environmental contaminants that result from incomplete combustion processes and are known carcinogens [8]. PAH are thought to exert their carcinogenic properties through their ability to form PAH-DNA adducts [9–11]. Both case-control [12] and cohort [13] studies have found that most jobs associated with occupational PAH exposure have the potential for prostate cancer. Associations between prostate cancer and specific occupational PAH exposure sources have also been reported [14,15]. In addition, we have recently shown that PAH-DNA adducts form in the prostate, and vary in level according to cellular histology [16].

Most PAH require metabolic activation by phase I enzymes (e.g., cytochrome P450 1A1 and 1B1) to form mutagens, such as benzo[a]pyrene diol epoxide (BPDE). Phase II enzymes (e.g., glutathione S-transferases (GSTs) and N-acetyltransferases) mediate the conjugation of water-soluble moieties, such as glutathione, which are responsible for detoxification of these reactive metabolites [17]. GSTP1 is involved in the inactivation of cigarette smoke carcinogens, such as BPDE, and other toxic constituents, such as acrolein [18], and GSTP1 is expressed in normal prostate cells [19]. An A to G transition at nucleotide 313 in exon 5 of the *GSTP1* gene, which replaces isoleucine (*Ile*) at codon 105 with valine (*Val*) within the active site of the enzyme, is associated with reduced enzymatic activity for certain substrates and altered thermostability [20,21]. While some studies have found an association between prostate cancer and the codon 105 variant *Val* allele of *GSTP1* (*Val*^{105}) [22–24], others have failed to find an association [25–28]. Moreover, a recent meta-analysis of prostate cancer association studies involving the *GSTP1 Ile105Val* polymorphism calculated an overall odds ratio of 1.05 for the *GSTP1 Val*^{105} allele [29].

The aim of the current study was to elucidate the joint role of the *GSTP1 Ile105Val* polymorphism and occupational exposures to PAH in prostate cancer. In a case-control study of prostate cancer, in which cases were over sampled for the purpose of using a case-only analytic approach to more efficiently detect gene-environment interaction, we tested the hypothesis that the *GSTP1* gene and occupational PAH exposure interact to increase prostate cancer risk.

Materials and Methods

Study Population

The study population consisted of men who were patients in the Henry Ford Health System (HFHS), which provides medical care to between 20 and 30 percent of the metropolitan Detroit population. Eligible cases and controls used the HFHS for primary care, lived in the study area at time of recruitment, had no other serious medical problems that would preclude participation, and had no previous history of prostate cancer. Potential cases were identified by HFHS pathology reports that gave a diagnosis of primary adenocarcinoma of the prostate. A stratified random sample of potential controls based on race (Caucasian or African-American) and five-year age group was drawn from the HFHS patient database such that the final enrolled sample would be approximately 3 cases:1 control. The over sampling of cases compared with controls was done because the primary objective of the study was to evaluate gene-environment interaction using a statistically more efficient case-only analytic approach [30]. Under this analytic approach, the case sample, in which the association between gene and environment combinations are assessed, serves as the primary analytic sample, whereas the control sample (which is optional) only serves the secondary purpose of evaluating the robustness of the results of the primary analysis by testing the validity of the independence assumption between gene and environment in controls. Therefore, statistical efficiency is based solely on the size of the case sample.

Cases and controls recruited for study were sent a study introduction letter, which was followed by a phone call from a study interviewer. Those who agreed to participate were asked to complete a two-part interviewer-administered risk factor questionnaire (the first part was conducted over the phone and the second part was done in person), and donate a blood sample for DNA analysis and prostate specific antigen (PSA) testing in controls. All study protocols were approved by the Henry Ford Hospital Institutional Review Board.

Between July 1, 2001 and December 31, 2004 we attempted to enroll 863 men who had been diagnosed with prostate cancer within the last two years and 668 agreed to participate (77%). Of the 381 potential controls we were able to contact, 258 (68%) agreed to participate. During the course of enrollment, eight cases and one control were found ineligible and 23 cases and 13 controls did not complete the study protocol, resulting in final study participation percentages of 75% (637/855) for cases and 64% (244/380) for controls. We exceeded our original study goal of 440 cases to facilitate analyses of study subsets, which, for this study, were defined by age, race, family history of disease, type of disease (i.e., aggressive or not) and selected non-occupational sources of PAH exposures (i.e., smoking and diet).

Data Collection

Medical chart abstraction included history of previous cancers, prostate cancer screening history five years prior to diagnosis (for cases) or enrollment (for controls), and PSA at diagnosis and tumor stage and grade for cases. Data collected from telephone interviews included demographic characteristics, lifestyle information, and family history of prostate cancer. Age was analyzed as a continuous variable and also dichotomized as being diagnosed (or enrolled for controls) before or after the age of 60. Race was self described and for our study sample fell into two categories, white or African American. A positive family history of prostate cancer was defined as having a father or full brother with a history of prostate cancer. Aggressive disease was defined as having a Gleason grade of 7 or greater or a tumor stage of 2C or greater.

Data collected on non-occupational sources of PAH exposures included cigarette smoking and dietary PAH intake. Cigarette smoking exposure was analyzed as both an ever/never variable,

with ever smoking defined as ever having smoked 100 or more cigarettes, and as pack years of smoking, defined as average packs of cigarettes smoked per day times number of years smoked. Dietary PAH intake was a summation of two measures: 1) PAH in foodstuffs based on responses to the SELECT food frequency questionnaire [31] and a corresponding database of grams of PAH per food item [32].; and 2) responses to meat preparation questions that allowed a calculation of grams of PAH intake based on consumption of overcooked meats [33].

The face-to-face interview was administered by research interviewers trained by industrial hygienists. Lifetime occupational histories from age 18 onward for jobs held greater than 6 months were recorded. Occupational data collected included job title, company of employment, duration of employment, work environment, and tasks performed. Job descriptions were open ended and highly detailed and interviewers were trained to use probing techniques that would elicit information pertinent to making exposure assessments. For a select group of jobs, job-specific modules adapted from a previous occupational study [34] were used by interviewers so that structured questions tailored to the job in question could be administered.

Industrial Hygiene (IH) Exposure Assessment

The job history data of all subjects were reviewed by one of two industrial hygienists (L.E and J.R.) using a semi-quantitative retrospective exposure assessment methodology previously described [35,36]. For each job, an IH assessed the probability of an occupational PAH exposure that came from petroleum, coal, wood, or another source. For each potential PAH exposure, the IH then assessed the years the exposure likely started and ended, the percent of work time per year the exposure likely occurred, the route of exposure (respiratory, cutaneous, or both), and the frequency of the exposure during the working day. For respiratory exposures, the IH also made an assessment of the relative intensity of exposure (low, medium or high).

Genotyping

All DNA samples were extracted from whole blood collected in EDTA tubes using the commercially available PureGene kit (Gentra Systems, Minneapolis, MN). Each DNA specimen was quantified using spectrophotometric analysis. Genotyping was performed using the Invader ® assay with reagents developed by Third Wave Technologies, Inc [37]. Each plate contained the following controls: *GSTP1* codon 105 *Ile/Ile* homozygous, *Ile/Val* heterozygous, *Val/Val* homozygous and a no target blank. Of the 881 samples, 37 yielded equivocal or unacceptable results and needed to be repeated. Among these, 10 failed repeat attempts at Invader and were genotyped using a PCR RFLP assay previously described [23,38]. For quality control purposes, 5 samples were analyzed by Invader and RFLP and 5 samples were analyzed by two separate Invader assays with the same results obtained in all cases.

Statistical Analyses

To estimate cumulative lifetime occupational PAH exposure, a semi-quantitative exposure index was calculated for each study subject based on his job-specific IH exposure assessment. For an individual that had n jobs with a positive PAH exposure, the exposure calculation for the ith job was a product term that included the total years exposed, the percent of the working year the exposure occurred (p), the frequency of the exposure during a typical working day (f) and a scalar term, k, for respiratory exposures based on their intensity level (low, medium or high). To calculate a lifetime cumulative exposure index for each specific type of PAH exposure, the product term described below was first summed over the three possible respiratory exposure levels for each job and then over all n jobs, i.e.,

$$\sum_{i=1}^{n}\sum_{j=1}^{3} k_{ij} f_{ij} p_{ij} (Y_E - Y_I)_{ij}$$

In this formulation, Y_I and Y_E are the years the exposure was initiated and ended, and for each job f_{ij} is the exposure frequency for *i*th job at the *j*th respiratory exposure intensity level and k_j is scaled at 1, 2 and 3 based on PAH respiratory exposures coded as low, medium or high. For the cutaneous PAH exposure calculation, which was done separately from the respiratory exposure calculation, the first summation was omitted as well as the scaler term, *k*, for exposure intensity. For both respiratory and cutaneous exposure calculations, f_i was coded from 1 to 5 which represented exposure frequencies of less than 30 minutes per day, 30 minutes to 2.5 hours, 2.5 to 5 hours, 5 to 8 hours and greater than 8 hours per day, respectively. This exposure calculation was done separately for PAH exposures from petroleum, wood, coal and other sources, where "other" was defined as PAH that were present in pyrolysis products such as plastic, paint, rubber, food or other organic compounds. We also calculated an overall cumulative PAH exposure index for occupational exposures to any PAH source for cutaneous and respiratory PAH exposures separately. This calculation was based on a summation of all four specific PAH sources described above with no adjustment made to the weights for intensity of respiratory exposure across the different PAH sources. Because of the difficulty in ascertaining relative intensities and doses between cutaneous and respiratory PAH exposures, no attempt was made to combine occupational PAH exposures that occurred via the two different routes.

A reliability study was performed to evaluate the reproducibility of the industrial hygienist PAH exposure assessment. The reliability study used a test-retest design [39], in which 56 study subjects from the entire study sample were randomly selected for independent exposure assessment by both study industrial hygienists. Comparisons of the two independent exposure assessments were done with intra-class correlation analyses that provide an estimate of test-retest reliability [40]. Measures of cumulative lifetime occupational PAH exposure that were tested included mean exposure level, ever exposed and quartile level of exposure (for PAH exposures from petroleum and any source).

Differences between cases and controls in categorical variables were compared using a chi-squared test. Hardy-Weinberg equilibrium of genotypic frequencies in race subsets of cases and controls was also tested using a chi-squared test. Odds ratios (ORs) and 95 percent confidence intervals were calculated using standard non-conditional logistic regression. For case-control comparison of exposure indices that were non-normally distributed, a Wilcoxon rank sum test was used. Quartiles for PAH exposure indices were based on the distributions observed in the control population. Gene-environment interactions were tested in the case sample using logistic regression models that had the genotype as the dependent variable and the exposure as the independent variable. To ensure the interaction odds ratios (IORs) in case-only analyses were equivalent to IORs in case-control analyses (i.e., the estimate of disease risk for individuals who have both the exposure and "at risk" genotype compared with unexposed individuals who do not carry the risk genotype), the gene-environment independence assumption in controls was verified [30]. A p value of 0.05 or less was considered statistically significant.

Results

Case-Control Comparability

The demographic and clinical characteristics of the study population are shown in Table 1. As expected, cases and controls were not significantly different on the frequency-matched factors of age and race. Cases had a higher frequency of a positive family history of prostate cancer

(20.9 vs. 13.3%; p=0.006) and higher PSA levels (10.9 ± 46.6 vs. 1.7 ± 2.4; p<0.0001). The majority of cases (66%) had prostatectomies and therefore could be pathologically staged; the remaining cases had clinical stages and biopsy-based grades assigned. Most cases were stage 2B (33.8%) with only 13.2 percent of cases stage 3A or higher. Most cases had Gleason grade 6 or lower (43.8%) with Gleason grade 7 the predominant histologic grade (39.9%).

In terms of non-occupational sources of PAH exposure assessed, cigarette smoking history had a skewed case/control distribution (p=0.0003) with cases having a lower percentage of current cigarette smokers compared with controls (11.8% vs. 22.1%), but a similar percentage of never smokers (34.4% vs. 33.6%). When we reclassified former smokers as current smokers if they had reported quitting smoking within the last five years prior to diagnosis (cases) or study enrollment (controls), the case/control differential in percent of current smokers was much less pronounced (19.6% in cases vs. 25.0% in controls) and the difference in case/control smoking histories was no longer statistically significant (p=0.19). Furthermore, the mean pack years exposure to cigarette smoking for cases (22.3 ± 29.1) and controls (24.0 ± 29.0) was not significantly different (p=0.48). Cases had a marginally higher intake level of PAH from diet sources compared with controls (159.6 ng/day ± 80.4 vs. 156.4 ng/day ± 90.1; p=0.29).

Risk Associated with Occupational PAH Exposure

The majority of cases and controls had occupational exposures to PAH from petroleum sources as well as from any source (table 2). In models adjusted for age, race, PSA, pack years of smoking and dietary PAH intake, the respiratory PAH exposure with the highest OR was coal (OR=1.29; 95% CI = 0.73–2.30). For cutaneous PAH exposures, the occupational exposures of cases and controls were similar. ORs were less than one for four of the five exposure sources (coal was the only exception), with the OR for cutaneous PAH exposure from petroleum the lowest (OR=0.74; 95% CI =0.48–1.13). For the occupational PAH exposures from petroleum and any source, in which different levels of exposure could be modeled, we also estimated ORs for quartiles of exposure levels. In both cases, the ORs were flat across the increasing quartiles of exposure levels with the OR for the highest quartile of PAH exposures from petroleum (OR=1.06; 95% CI =0.70–1.60) and any source (OR=1.11; 95% CI =0.73–1.68) only slightly elevated and both not significantly different from unity. We found no significant case/control differences in the mean exposure indices of all five types of occupational PAH exposures for both respiratory and cutaneous routes with respiratory occupational PAH exposure from coal showing the strongest association; cases had a 1.5-fold higher mean exposure index compared with controls (5.6 vs. 3.4; p=0.06).

Risk Associated with GSTP1 Ile105Val Polymorphism

The *GSTP1 Val*^{105} variant allele frequency was similar in cases (62.5%) compared with controls (66.4%) of controls. The genotypic proportions in both cases and controls were in Hardy-Weinberg equilibrium and similar across both ethnic groups. In multivariate models that adjusted for age and PSA, odds ratios for the *GSTP1* codon 105 *Val* genotypes were slightly elevated in African Americans, but less than one in Caucasians (table 3). In all subjects, prostate cancer cases were slightly less likely to carry one or more copies of the *GSTP1* codon 105 *Val* allele (OR=0.86; 95% CI =0.65–1.14).

GSTP1-Occupational PAH Exposure Interactions

To maximize statistical power, we tested for potential gene-environment interaction in only cases (Table 4) using the presence or absence of the *GSTP1 Val*^{105} variant as the dependent dichotomous variable in logistic regression models that tested for an association with occupational PAH exposure. However, we first verified that carriage of the *GSTP1 Val*^{105} variant and occupational PAH exposure were independent in controls. Differences in mean occupational PAH exposure indices across *GSTP1* codon 105 genotypes were not statistically

significant and overall the variation across genotypes appeared to be random and unlikely due to any underlying biologic association between genotype and exposure. Therefore, in our case-only models the OR for the exposure variable estimates the risk for prostate cancer among those who have both the "at risk" genotype and environmental exposure (i.e., the gene-environment interaction OR). For respiratory PAH exposures, elevated interaction odds ratios (IORs) were observed for PAH exposure from petroleum (IOR=1.40; 95% CI = 1.02–1.94), other sources (IOR=1.47; 95% CI = 1.03–2.09) and any source (IOR=1.31; 95% CI = 0.95–1.81). For cutaneous exposures, only PAH exposures from other sources had an OR that was markedly different from unity (IOR=1.73; 95% CI = 0.90–3.33).

To discern whether GSTP1 effects were uniform across exposure levels, we tested whether cases with *GSTP1 Val*^{105} genotypes were more likely to have respiratory PAH exposures from petroleum or any source in the 2nd, 3rd and 4th quartiles of exposure compared with the 1st quartile (table 5). For respiratory PAH exposures from petroleum or any source, gene-environment risk estimates for PAH exposures in the 2nd and 3rd quartiles were only slightly elevated, but significant increased risk estimates were observed for PAH exposures in the highest quartile. The highest interaction odds ratio (IOR) was observed for the association between the *GSTP1* codon 105 *Val/Val* genotype and the 4th quartile of respiratory PAH exposure from any source (IOR=2.05; 95% CI = 1.03–4.10). In the comparison of the combined *GSTP1 Val* genotypes with *GSTP1* codon 105 *Ile/Ile* homozygotes, the trend of increasing risk across higher PAH exposure quartiles was statistically significant both for PAH exposures from petroleum and any source (p_{trend}=0.01 for both).

Three-way Interactions

We next conducted analyses to test for potential three-way interactions between selected variables and the gene-environment (GE) combination of *GSTP1* codon 105 *Val* genotypes and occupational PAH exposure (table 6). Since respiratory PAH exposures from petroleum made up on average 81% of PAH exposures from any source, we limited further analyses to the former. The associations between PAH exposures from petroleum and carriage of the *GSTP1 Val*^{105} allele were stronger in white cases and cases without aggressive disease. Of the two parameters that defined aggressive disease, stage and grade, we found that it was only grade that affected this difference with the GE association patterns in cases with low and high stage tumors almost identical. Stratified analyses by age showed that the linear occupational PAH exposure – *GSTP1* genotype relationship in cases remained statistically significant only in men under age 60 who had increasing IORs in each successively higher level of PAH exposure with those in the highest PAH exposure quartile having an odds ratio greater than four (IOR=4.52; 95% CI = 1.96–10.41). When stratifying on non-occupational sources of PAH exposure, such as diet or cigarette smoking, the dose response relationship observed in the full case sample was limited primarily to the case subsets with higher non-occupational PAH exposures. In men with a prostate cancer family history, markedly higher IORs were observed for all three of the higher quartiles of PAH exposure from petroleum. Of the six possible three-way interactions examined, only differences in the gene-exposure risk estimates between age groups were statistically significant (p=0.009).

Inter-rater Reliability of Occupational PAH Exposure Assessment

The results from our inter-rater reliability study showed that the means for any of the ten cumulative occupational PAH exposure indices used in this study did not differ significantly between the two raters. However, intra-class correlations for mean occupational PAH exposure levels between the two raters did vary, with a high of 53.1% for cutaneous petroleum exposure to a low of close to zero percent for cutaneous exposures from coal and other sources. It is important to note that these two exposures were relative rare (10 percent or lower prevalence in controls), which would suggest that mean exposure is not the optimal parameter for

measuring reliability. This was also the case for cutaneous PAH exposure from wood sources where intra-class correlations could not be calculated because neither of the industrial hygienist reviewers scored any of the 56 subjects in the reliability study positive for this exposure. In assessing intra-class correlations for dichotomous measures of exposure, reliability scores were highest for the two most prevalent exposures, respiratory PAH exposures from petroleum (ICC=76.3%) and any source (ICC=66.4%). Intra-class correlations for the quartiled measures of these two exposure indices were both at 90 percent.

Discussion

In our study of the combined effect of occupational PAH exposure and variation in the GSTP1 *Ile105Val* polymorphism on prostate cancer risk, in prostate cancer cases carriage of the *GSTP1 Val*^{105} allele was significantly increased in those at the highest quartile of PAH exposure. A possible "threshold effect" of PAH exposure on cancer risk has been observed previously in breast cancer [41], and if such an effect is restricted to a genetically defined subgroup this could explain previous inconsistent findings with regard to both *GSTP1* and PAH exposure as risk factors for prostate cancer. Furthermore, in cases with an earlier age of disease onset (< 60 years) or who were smokers or had a family history of prostate cancer, the association between the *GSTP1 Val*^{105} variant and respiratory occupational PAH exposure from petroleum was increased. It could be posited that men diagnosed at a younger age or with a family history of prostate cancer are more likely to have additional genetic modifiers of disease risk. Other non-occupational sources of PAH exposures appeared to modify interactions between occupational exposure to PAH from petroleum and the *GSTP1 Val*^{105} variant, but these were not statistically significant. These secondary exposure modifying effects may be due to a higher background body burden of PAH from the non-occupational PAH exposure source, which leads to an increased susceptibility to the effects of occupational PAH exposure compared with non-exposed counterparts.

The workplace may be an important source of PAH exposure in prostate cancer. A large case-control study found that most of the jobs associated with prostate cancer had the potential for occupational PAH exposure [12]. In three separate studies that examined specific occupational exposures, two found modest associations between selected PAH sources and prostate cancer [14,15], while the third found no link between PAH-related exposures and prostate cancer [42]. It is important to note that the two studies that found some associations between PAH exposures and prostate cancer used the expert review method utilized in the present study, whereas the negative study only used self-reported data.

PAH normally occur in the environment as complex mixtures of many different compounds with varying mutagenic and carcinogenic potency [8]. Based on the position of the epoxide ring, PAH diol epoxides can be classified either as bay region or fjord region [43]. GSTP1 demonstrates appreciable activity toward both bay- and fjord-region diol epoxides, but shows a preference for the *anti*-diastereomers [44], which are more carcinogenic [45]. *GSTP1* variants at codon 105 also have variable catalytic efficiencies toward PAH, which vary by the isomeric class of the molecule [46,47]. Since the mix of PAH stereoisomers depends upon the environmental source, the impact of *GSTP1* variants on PAH detoxification will likely not be uniform across different sources of PAH exposure. This may explain why the gene-environment association between *GSTP1 Val*^{105} and occupational PAH exposures from petroleum sources were significant in our study while those from wood or coal were not. Interestingly, several studies have shown that *GSTP1* variants are associated with an increase in biomarkers of DNA damage when subject to high PAH-exposure environments [48,49].

The current study has several strengths that increase the generalizability and validity of its results. Cases and controls were drawn from a large health system that is representative of the

larger population that the system serves. Race-specific genotype frequencies were in Hardy-Weinberg equilibrium, which further supports the lack of selection bias in sampling of cases and controls. Occupational histories did not involve any leading questions about specific exposures, but rather were focused upon detailed descriptions of the work environment and daily job tasks and expert reviewers were blinded to case-control status. Occupational exposure assessment by expert review is considered to have reasonable validity [50] and superior to other common methods of retrospective occupational exposure assessment, such as self-report or job exposure matrices [51]. Occupational PAH exposure assessment was based on only one reviewer. While in our study inter-rater reliability for mean exposure levels was low, the semi-quantitative measure of exposure quartiles used for the two exposures on which the main findings of our study were based, respiratory PAH exposures from petroleum and any source, had a reliability of 90 percent. While limitations of the case-only analytic approach have been noted by others [52,53], in our study we verified the independence between genotype and exposure in a set of controls age and race frequency matched to study cases. Post hoc power analyses using the case-only analytic approach showed good to excellent power for evaluation of gene-environment effects in the entire sample as well as in smaller case subsets. For example, based on the observed frequency of the *GSTP1 Val*^{105} variant and the additive effect it appeared to have, assuming nominal marginal genetic and environmental effects for a dichotomous environmental exposure of a prevalence of 50 percent (e.g., high/low exposure groups for PAH exposure to any source), we had over 90 percent power to detect an iOR of 1.5 in the whole sample and over 85 percent power to detect an iOR of 2.5 in a quarter of the case sample. Even for three-way interactions, assuming the third factor was evenly distributed across cases, our sample afforded the ability to detect iOR for the third factor of 2.1 or greater with 80 percent statistical power. Our study lacked a measure of biologically effective dose, but we have demonstrated in a previous study of a subset of cases drawn from this same study population that PAH-DNA adducts are detectable in the prostate epithelial cells of cases [16].

The results of our study are part of a continuing trend that demonstrates the importance of considering both genes and/or exposures in the context of cancer risk. For instance, recent prostate cancer case-control studies have shown a gene by smoking interaction for variants in the *GSTM1* [5], *GSTT1* [6] and *GSTP1* [7] genes. Effects of variation of *GSTP1* on prostate cancer risk may also be enhanced when considering other conjugation genes, such as *GSTM1* and *GSTT1*, in tandem [22]. In summary, we have detected an association between carriage of the *GSTP1 Val*^{105} allele and high levels of respiratory occupational PAH exposures from petroleum and any source in prostate cancer cases. This association suggests these genetic and environmental factors interact on a multiplicative scale to increase prostate cancer risk. Our results highlight the importance of examining polymorphisms in genes that are involved in conjugation of reactive metabolites derived from PAH exposures. Targeting genetic subsets in exposed populations may shed more light on the effects of PAH and other potential carcinogens. Alternatively, the study of highly exposed groups may help better explain the biologic effects of genetic variation in *GSTP1* and other similar genes involved in metabolic or DNA repair pathways.

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Table 1

Characteristics of Study Population

Characteristic	Cases (n=637) n (%)	Controls (n=244) n (%)	P value
Race:			0.92
African American	274 (43.0)	104 (42.7)	
White	363 (57.0)	140 (57.4)	
Age:			0.39
<60	228 (35.8)	76 (31.2)	
60–69	323 (50.7)	130 (53.3)	
70+	86 (13.5)	38 (15.6)	
Family History:[a]			0.006
Positive	132 (20.9)	30 (13.3)	
Negative	499 (79.1)	196 (86.7)	
PSA Level:[b]			<0.0001
<4	108 (17.0)	223 (91.4)	
4–10	424 (66.6)	17 (7.0)	
>10	105 (16.5)	4 (1.6)	
Smoking Status:			0.0003
Never	219 (34.4)	82 (33.6)	
Former	343 (53.9)	108 (44.3)	
Current	75 (11.8)	54 (22.1)	

[a] 6 cases and 18 controls had missing family history data

[b] PSA was measured at time of diagnosis in cases and at time of enrollment in controls

Table 2

Association between Lifetime Cumulative Occupational PAH Exposure and Prostate Cancer after Adjusting for Age, Race, Packyears Smoking, Dietary PAH Intake and PSA

PAH Exposure Route: Source	Percent Ever Exposed		OR (95% CI)[a]	P value
	Cases (n=637)	Controls (n=244)		
Respiratory:				
Petroleum	85.2	86.1	1.12 (0.73–1.73)[b]	0.61
Coal	19.2	13.9	1.29 (0.73–2.30)[c]	0.39
Wood	6.0	6.6	0.86 (0.36–2.07)[c]	0.74
Other	31.4	37.7	0.79 (0.51–1.23)[c]	0.30
Any	87.9	88.9	1.17 (0.76–1.81)[b]	0.47
Cutaneous:				
Petroleum	71.6	75.0	0.74 (0.48–1.13)[b]	0.16
Coal	8.5	7.4	1.48 (0.68–3.20)[c]	0.32
Wood	2.2	2.5	0.97 (0.24–3.87)[c]	0.97
Other	7.7	10.7	0.77 (0.37–1.60)[c]	0.48
Any	74.3	77.5	0.76 (0.50–1.17)[b]	0.22

[a] Odds Ratio (95% confidence interval)

[b] Odds Ratio for percent above median PAH exposure level in controls

[c] Odds Ratio for ever/never exposure

Table 3

Association between *GSTP1 ile105val* Genotype Frequencies and Prostate Cancer

***GSTP1 ile105val* Genotype**	**Cases n (%)**	**Controls n (%)**	**Odds Ratio[a] (95% confidence interval)**	**P value**
African Americans:				
ile/ile	82 (29.9)	29 (27.9)	1.00 (reference)	---
ile/val	146 (53.3)	59 (56.7)	1.11 (0.49–2.49)	0.80
val/val	46 (16.8)	16 (15.4)	1.30 (0.43–3.94)	0.65
Total	274 (100.0)	104 (100.0)		
Caucasians:				
ile/ile	157 (43.3)	53 (37.9)	1.00 (reference)	---
ile/val	164 (45.2)	70 (50.0)	0.54 (0.31–0.96)	0.03
val/val	42 (11.6)	17 (12.1)	0.79 (0.34–1.85)	0.58
Total	363 (100.0)	140 (100.0)		
All Subjects:				
ile/ile	239 (37.5)	82 (33.6)	1.00 (reference)	---
ile/val	310 (48.7)	129 (52.9)	0.67 (0.43–1.07)	0.09
val/val	88 (13.8)	33 (13.5)	0.91 (0.47–1.78)	0.79
Total	637 (100.0)	244 (100.0)		

[a] Odds ratios adjusted for age, PSA and race (for all subjects)

Table 4

Interaction Modeling of Carriage of the *GSTP1 Val*^{105} Allele and Occupational PAH Exposure in Prostate Cancer Cases (n=637).

PAH Exposure Route: Source	IOR[a]	95% confidence interval	P value
Respiratory:			
Petroleum	1.40	(1.02 – 1.94) [b]	0.04
Coal	0.99	(0.66 – 1.49) [c]	0.96
Wood	0.82	(0.42 – 1.59) [c]	0.55
Other	1.47	(1.03 – 2.09) [c]	0.03
Any Source	1.31	(0.95 – 1.81) [b]	0.10
Cutaneous:			
Petroleum	0.97	(0.71 – 1.35) [b]	0.88
Coal	0.94	(0.53 – 1.66) [c]	0.83
Wood	0.59	(0.21 – 1.71) [c]	0.33
Other	1.73	(0.90 – 3.33) [c]	0.10
Any Source	0.99	(0.72 – 1.37) [b]	0.96

[a] IOR = Interaction Odds Ratio = PAH exposure x carriage of 1 or more *GSTP1* codon 105 *val* allele

[b] Odds Ratio for percent above median PAH exposure level in controls

[c] Odds Ratio for ever/never exposure

Table 5

Interaction Modeling of Carriage of the *GSTP1 Val*^{105} Allele and Lifetime Cumulative Occupational PAH Exposure Levels from Petroleum and Any Source in Prostate Cancer Cases.

PAH Respiratory Exposure Level[a]	*GSTP1* 105 *ile/val* vs. *ile/ile* (n=549) IOR[b]	95% Confidence Interval	P	*GSTP1* 105 *val/val* vs. *ile/ile* (n=327) IOR[b]	95% Confidence Interval	P	*GSTP1* 105 *val/val* and *val/ile* vs. *ile/ile* (n=637) IOR[b]	95% Confidence Interval	P
Petroleum:									
2nd Quartile	1.06	(0.65 – 1.72)	0.82	0.97	(0.46 – 2.07)	0.94	1.04	(0.65 – 1.66)	0.87
3rd Quartile	1.11	(0.70 – 1.77)	0.66	1.39	(0.70 – 2.74)	0.34	1.17	(0.75 – 1.82)	0.49
4th Quartile	1.70	(1.07 – 2.72)	0.03	1.89	(0.96 – 3.71)	0.07	1.74	(1.11 – 2.72)	0.02
Trend Odds Ratio	1.18	(1.02 – 1.36)	0.03	1.25	(1.01 – 1.56)	0.04	1.19	(1.04 – 1.37)	0.01
Any Source:									
2nd Quartile	1.16	(0.71 – 1.90)	0.55	1.24	(0.58 – 2.67)	0.58	1.18	(0.74 – 1.88)	0.50
3rd Quartile	0.94	(0.58 – 1.50)	0.78	1.53	(0.77 – 3.05)	0.23	1.05	(0.68 – 1.63)	0.83
4th Quartile	1.81	(1.14 – 2.87)	0.01	2.05	(1.03 – 4.10)	0.04	1.85	(1.19 – 2.89)	0.006
Trend Odds Ratio	1.17	(1.01 – 1.36)	0.03	1.27	(1.02 – 1.58)	0.03	1.19	(1.04 – 1.37)	0.01

[a] 1st quartile is referent group

[b] IOR = interaction odds ratio

Table 6

Three-Way Interaction Modeling of the GSTP1 *Val*[105] Variant Genotype, Lifetime Cumulative Occupational PAH Exposure Levels from Petroleum and Other Selected Variables in Prostate Cancer Cases

	Variable Present			Variable Absent			
3rd Variable: PAH Exposure Level[a]	**IOR[b]**	**95% confidence interval**	**P value**	**IOR[b]**	**95% confidence interval**	**P value**	**P value[c]**
Under Age 60:		(n=228)			(n=409)		
2nd Quartile	1.84	(0.83 – 4.06)	0.13	0.77	(0.43 – 1.38)	0.39	
3rd Quartile	2.08	(1.02 – 4.23)	0.04	0.87	(0.49 – 1.54)	0.63	
4th Quartile	4.52	(1.96 – 10.41)	0.0004	1.11	(0.65 – 1.91)	0.71	
Trend Odds Ratio	1.57	(1.22 – 2.02)	0.0005	1.04	(0.88 – 1.24)	0.63	0.009
African-American:		(n=274)			(n=363)		
2nd Quartile	0.66	(0.28 – 1.53)	0.33	1.08	(0.60 – 1.94)	0.80	
3rd Quartile	0.69	(0.31 – 1.54)	0.37	1.21	(0.68 – 2.15)	0.51	
4th Quartile	1.09	(0.48 – 2.51)	0.83	1.81	(1.04 – 3.16)	0.04	
Trend Odds Ratio	1.06	(0.84 – 1.36)	0.61	1.20	(1.01 – 1.43)	0.04	0.43
Ever Smoker:		(n=419)			(n=218)		
2nd Quartile	0.96	(0.54 – 1.72)	0.90	1.39	(0.60 – 3.18)	0.44	
3rd Quartile	1.72	(1.00 – 2.98)	0.05	0.58	(0.27 – 1.24)	0.16	
4th Quartile	1.98	(1.14 – 3.44)	0.02	1.54	(0.70 – 3.38)	0.29	
Trend Odds Ratio	1.30	(1.09 – 1.55)	0.004	1.05	(0.82 – 1.33)	0.71	0.16
High PAH diet: [d]		(n=340)			(n=297)		
2nd Quartile	0.96	(0.51 – 1.81)	0.89	1.14	(0.58 – 2.24)	0.72	
3rd Quartile	1.41	(0.76 – 2.62)	0.28	0.98	(0.52 – 1.84)	0.94	
4th Quartile	2.00	(1.09 – 3.68)	0.03	1.46	(0.75 – 2.82)	0.27	
Trend Odds Ratio	1.27	(1.05 – 1.54)	0.01	1.10	(0.89 – 1.35)	0.37	0.31
Family History:[e]		(n=132)			(n=499)		
2nd Quartile	2.52	(0.86 – 7.37)	0.09	0.82	(0.49 – 1.38)	0.45	
3rd Quartile	2.38	(0.89 – 6.35)	0.08	0.98	(0.59 – 1.60)	0.92	
4th Quartile	3.02	(1.15 – 7.92)	0.02	1.50	(0.90 – 2.50)	0.12	
Trend Odds Ratio	1.41	(1.03 – 1.92)	0.03	1.14	(0.97 – 1.34)	0.10	0.24
Aggressive Disease:[f]		(n=398)			(n=239)		
2nd Quartile	0.86	(0.44 – 1.66)	0.64	1.25	(0.65 – 2.43)	0.50	
3rd Quartile	1.26	(0.69 – 2.30)	0.46	1.11	(0.57 – 2.15)	0.76	
4th Quartile	1.37	(0.76 – 2.48)	0.30	2.37	(1.18 – 4.74)	0.01	
Trend Odds Ratio	1.14	(0.94 – 1.37)	0.19	1.27	(1.02 – 1.57)	0.03	0.45

[a] 1st quartile is referent group

[b] IOR = interaction odds ratio

[c] P value for difference between strata

[d] based on median dietary intake in controls

[e] 6 cases had missing family history data

[f] Aggressive disease defined as Gleason grade 7 or T stage 2C or higher