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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

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 $p = 0.01$ 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). *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; Wood; Petroleum; Coal; Cigarette smoking; Polycyclic aromatic hydrocarbons (PAH); Exposure assessment; Gene-environment risk; PAH-DNA adducts; DNA repair pathways; Hardy–Weinberg equilibrium; Genotyping; Enzymatic activity; Polymorphism; Ethnicity; Family history; Diet

1. 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

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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 prostate cancer have the potential for occupational PAH exposure. 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.

2. Materials and methods

2.1. 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% 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 5-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 2 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, 8 cases and 1 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).