CYP1A1 and *CYP1B1* Genotypes and the Detoxification of Combustion-Derived Pollutants (Literature Review)

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ABSTRACT

Background:
Exposure to combustion-derived pollutants — such as cigarette smoke, vehicle exhaust, residential soot, and charred foods — introduces polycyclic aromatic hydrocarbons (PAHs) into the human body. PAHs are not inherently carcinogenic; rather, they require metabolic activation by Phase I cytochrome P450 enzymes, predominantly *CYP1A1* and *CYP1B1*, before they can be detoxified. Common polymorphisms, including *CYP1A1* rs4646903, *CYP1A1* rs1048943 (Ile462Val), and *CYP1B1* rs1056836 (Leu432Val), modify enzyme inducibility and catalytic activity. These functional differences may influence the balance between PAH activation and detoxification, affecting individual susceptibility to combustion-related pollutants (Zhan, 2011; Ji, 2012; Lao, 2014).

Methods:
A targeted literature review was performed, focusing on molecular and epidemiological studies. Emphasis was placed on high-quality meta-analyses and studies examining gene–environment interactions involving real-world combustion-related exposures, including tobacco smoke, airborne PAHs, contact with soot or ash, and consumption of burnt foods.

Results:
Functional data show that *CYP1A1* rs4646903 enhances enzyme inducibility, while rs1048943 (Ile462Val) increases catalytic turnover, resulting in more rapid PAH activation (Ji, 2012; Hou, 2005). The *CYP1B1* rs1056836 Val432 variant similarly increases catalytic efficiency toward PAHs (Lao, 2014). Individuals carrying these high-activity alleles exhibit higher levels of PAH-derived intermediates and metabolites, particularly under conditions of elevated exposure such as smoking or frequent intake of charred foods (Hou, 2005; Zhan, 2011). In contrast, reference genotypes show more moderate metabolic activation, permitting balanced downstream detoxification.

Discussion:
A substantial body of evidence demonstrates that PAHs must undergo metabolic activation to exert their carcinogenic effects, highlighting the central role of Phase I

enzymes in this process (Hou, 2005; Zhan, 2011; Ji, 2012). Polymorphic variants in *CYP1A1* and *CYP1B1* that increase enzyme inducibility or catalytic efficiency enhance the generation of reactive PAH intermediates and thereby intensify the biologically effective dose of these compounds (Zhan, 2011; Ji, 2012; Lao, 2014). These genotype-driven increases in activation are most consequential under conditions of substantial environmental exposure — such as chronic inhalation of tobacco smoke, combustion-derived particulates, or frequent intake of charred foods — where elevated metabolic flux can exceed detoxification capacity and increase internal burden (Hou, 2005; Ji, 2012; Lao, 2014). Individuals with reference genotypes do not exhibit amplified metabolic activation and generally maintain balanced detoxification under low-exposure conditions; however, they remain susceptible to the inherent toxicity of activated PAH metabolites (Zhan, 2011; Ji, 2012). Together, these findings underscore that interindividual differences in susceptibility to combustion-derived pollutants arise primarily through gene–environment interactions, wherein genetic variation in *CYP1A1* and *CYP1B1* modulates metabolic response to the level of exposure (Hou, 2005; Ji, 2012; Lao, 2014).

Subjects Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Detoxification, Combustion

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) are widespread pollutants released during incomplete combustion of organic matter. Human exposure occurs primarily through cigarette smoke, vehicle exhaust, and the ingestion of charred or smoked foods. Although chemically inert in their native form, PAHs require metabolic activation by phase-I enzymes before they can exert biological effects. Cytochrome P450 1A1 (*CYP1A1*) is central to this process, converting PAHs into reactive electrophilic intermediates capable of binding DNA and initiating mutagenic events. Paradoxically, this activation step is also the entry point to detoxification, as the resulting intermediates are rendered excretable only after conjugation by phase-II enzymes such as the glutathione S-transferases (Shi et al., 2010).

The essential role of *CYP1A1* in overall detoxification has been demonstrated in vivo: mice lacking *CYP1A1* show extreme sensitivity to oral benzo[a]pyrene, accumulating toxic levels of the parent compound, whereas wild-type mice efficiently metabolize and eliminate the same dose without harm. Thus, while activation transiently increases the pool of reactive metabolites, *CYP1A1* activity ultimately protects against systemic PAH accumulation. (Shi et al., 2010)

Genetic variation can shift the efficiency of this pathway. Two well-studied *CYP1A1* polymorphisms — rs4646903 (MspI T>C) in the 3'UTR and rs1048943 (Ile462Val) in exon 7 — are associated with increased aryl hydrocarbon hydroxylase activity and enhanced catalytic turnover (Mota et al., 2010). These “hyperactive” variants metabolize PAHs more rapidly than the wild-type enzyme, accelerating the formation of DNA-reactive intermediates. Individuals carrying such alleles show higher PAH–DNA adduct levels under exposure (Hou et al., 2005), indicating that enhanced activation can increase the likelihood of DNA damage when detoxification capacity is exceeded.

Gene Function and Genotype Effects

CYP1A1 and *CYP1B1* are closely related phase-I enzymes responsible for the initial oxidative transformation of PAHs. By inserting an oxygen atom into the aromatic ring system, they generate epoxides and dihydrodiols that are subsequently conjugated and excreted. This metabolic sequence normally prevents the long-term accumulation of PAHs, although an imbalance — particularly when activation outpaces conjugation — can lead to increased levels of DNA-reactive metabolites. (Shi et al., 2010)

Functional polymorphisms contribute to substantial interindividual variability in this activation step. The *CYP1A1* rs4646903 C allele increases inducibility of the gene via the aryl hydrocarbon receptor pathway, while rs1048943 (Ile462Val) enhances catalytic activity through a structural change in the heme-binding region. The Val462 enzyme can exhibit as much as double the catalytic efficiency of the wild-type form, leading to greater production of oxidised PAH intermediates. (Mota et al., 2010)

A parallel pattern is observed for *CYP1B1*. The rs1056836 (Leu432Val) polymorphism produces a higher-activity enzyme with increased turnover for both PAHs and endogenous hormones. The Val432 variant displays up to three-fold greater catalytic efficiency, resulting in more rapid formation of reactive metabolites compared to the Leu432 form. (Gajjar et al., 2012)

Taking together, these polymorphisms generate a continuum of metabolic phenotypes, ranging from slower, more balanced activation profiles to markedly accelerated PAH metabolism. Under real-world exposures — such as tobacco smoke, urban air pollution or consumption of charred foods — carriers of high-activity *CYP1A1* or *CYP1B1* alleles are more likely to accumulate genotoxic intermediates, whereas individuals with reference genotypes generally maintain a more favorable activation-detoxification balance.

Table 1: Gene–Environment Interaction Studies Involving *CYP1A1/CYP1B1* Polymorphisms

Study (Author, Year)	Study Design	Population Characteristics	SNP(s) Investigated	Primary Outcome / Key Findings
Sánchez-Siles et al., 2020	Case–control	Laryngeal/hypopharyngeal cancer cases vs controls (Spain; predominantly smokers)	*CYP1A1* rs4646903, rs1048943; *GSTM1/GSTT1* null	*CYP1A1* risk alleles and GST null genotypes were enriched in cases, consistent with impaired PAH handling in heavy smokers.
Zhao et al., 2019	Case–control	Upper digestive tract cancers vs controls (Northern China; smoking/alcohol assessed)	*CYP1A1* rs4646903; *CYP2E1* rs2031920; *GSTM1* null	Smoking/alcohol increased cancer risk; *CYP1A1* rs4646903 showed interaction with smoking/alcohol, further elevating risk.
Lee et al., 2006	Case–control	Gastric cancer cases vs controls (Chile)	*CYP1A1* Ile462Val; *GSTM1* null	*CYP1A1* Ile462Val markedly amplified smoking- and alcohol-associated gastric cancer risk.
Kiyohara et al., 2012	Case–control	SLE cases vs controls (Japan; women; smoking status)	*CYP1A1* rs4646903; *GSTM1* null	Strong smoking interaction: smokers with high-risk *CYP1A1* and/or *GSTM1* null genotypes had substantially higher SLE risk.
Peddireddy et al., 2016	Case–control	NSCLC cases vs controls (South India; smokers/non-smokers)	*CYP1A1* rs4646903, rs1048943; *GSTM1/GSTT1* null	*CYP1A1* variants and *GSTT1* null were associated with NSCLC risk, with stronger effects in smokers/combined-risk genotypes.
Naif et al., 2018	Case–control	Breast cancer cases vs controls (Iraq; women)	*CYP1A1* rs4646903, rs1048943	Higher-frequency *CYP1A1* high-activity variants in cases; smoking appeared to strengthen genotype-associated risk.
Abbas et al., 2014	Case–control	Cervical cancer cases vs controls (North India; active/passive smoke exposure)	*CYP1A1* rs4646903, rs1048943	*CYP1A1* variants increased cervical cancer susceptibility; tobacco exposure (active/passive) showed synergy with risk alleles.
Roszak et al., 2014	Case–control	Cervical cancer cases vs controls (Poland)	*CYP1A1* rs1048943 (Ile462Val)	Minimal main effect overall; smoking + Ile462Val genotype associated with higher cervical cancer risk.

Sabitha et al., 2010	Case–control	Head/neck SCC cases vs controls (India; smokers)	*CYP1A1* rs4646903, rs1048943	Among smokers, *CYP1A1* risk genotypes were strongly associated with head/neck cancer susceptibility.
Hou et al., 2005	Nested case–control	Advanced colorectal adenoma cases vs controls (PLCO; USA)	*CYP1A1* Ile462Val; *NQO1* Pro187Ser	Large interaction: combined *CYP1A1* 462Val + *NQO1* 187Ser markedly increased adenoma risk in smokers, little effect in non-smokers.
Ji et al., 2012	Meta-analysis	Multi-study lung cancer dataset	*CYP1A1* rs1048943 (Ile462Val)	Ile462Val showed a modest lung cancer association overall, driven mainly by smokers (notably squamous histology).
Wenzlaff et al., 2005	Case–control	Lung cancer in never-smokers (USA; population-based)	*CYP1A1* variants; *CYP1B1* Leu432Val	No clear *CYP1A1* signal in never-smokers; *CYP1B1* Leu432Val showed an association in some strata.
Nock et al., 2007	Cross-sectional (tumor biomarker)	Prostate cancer cases (USA; race- and smoking-stratified)	*CYP1A1/CYP1B1* plus other PAH-metabolism genes	Smoking-related PAH–DNA adduct burden differed by genotype patterns and by ancestry, supporting genotype-modified PAH damage.
Islam MS et al., 2012	Case–control	Adults; Turkey; smoking-stratified	*CYP1A1* polymorphisms (incl. common functional variants)	*CYP1A1* risk variants showed stronger lung-cancer association among heavier smokers, consistent with a gene–smoking interaction.
Zhan et al,. 2011	Meta-analysis (case–control studies)	Multi-study; lung cancer cases/controls	*CYP1A1* variants (commonly MspI/rs4646903 and Ile462Val/rs1048943 across studies)	Pooled evidence supports modestly higher lung-cancer susceptibility for key *CYP1A1* variants, with ethnicity/subgroup differences.
Liu F. et al., 2015	Case–control	Adults; China; HCC cases/controls	*CYP1B1* polymorphisms	*CYP1B1* variation associated with hepatocellular carcinoma susceptibility, consistent with altered carcinogen-handling pathways.
Butts SF et al., 2014	Gene–environment interaction analysis	Women; smoking exposure characterized	CYP-related xenobiotic metabolism variants	Smoking-related reproductive aging (menopause timing) differed by CYP genotype, consistent with genotype-modified response to smoke toxicants.
Butts SF et al., 2012	Observational (symptom endpoint)	Women; menopause-related symptoms; smoking considered	*CYP1A2/CYP1B1* metabolism-gene variants	Metabolism-gene variation was linked to vasomotor symptoms, with patterns consistent with exposure/metabolism-related heterogeneity.

Chen B et al., 2010	Meta-analysis	Multi-study; lung cancer cases/controls	*CYP1B1* variants (frequently Leu432Val/rs1056836 and others)	Pooled results indicate *CYP1B1* polymorphisms are associated with lung-cancer risk in some subgroups, suggesting heterogeneity by ancestry/exposure.
Cote ML et al., 2009	Case–control (women)	Women; non-small cell lung cancer (NSCLC) context; tobacco exposure assessed	Estrogen/xenobiotic metabolism polymorphisms (incl. CYP-related loci)	Tobacco exposure interacted with metabolism-gene variation in relation to female NSCLC risk, supporting exposure-dependent effects.
Timofeeva MN, et al., 2009	Consortium-based genetic association (early-onset focus)	Early-onset lung cancer; consortium dataset (sex-stratified analyses)	*CYP450* polymorphisms (incl. CYP1-family variants)	Reported gender-specific associations between CYP polymorphisms and early-onset lung cancer risk, consistent with effect modification.
Sillanpää P et al., 2007	Case–control	483 breast cancer cases; 482 controls; Finland	*CYP1A1* (Ile462Val, Thr461Asn) and CYP1B1 Leu432Val	No overall main effect, but *CYP1B1* 432Val increased breast-cancer risk among smokers (dose-patterned), indicating gene–smoking interaction.
Liang G et al., 2005	Case–control (gene ± environment/other loci)	Adults; lung cancer cases/controls	*CYP1B1* polymorphism(s) (often including Leu432Val) ± additional inflammatory/host factors	Findings support *CYP1B1*-related variation in lung-cancer susceptibility, with evaluation of smoking and/or gene–gene context.
Lao X et al., 2014	Meta-analysis	Multi-study; lung cancer cases/controls	*CYP1B1* Leu432Val (rs1056836)	Meta-analytic evidence suggests Leu432Val may influence lung-cancer risk, with variability across populations and study strata.

Epidemiological Findings

Extensive epidemiological research has examined whether functional *CYP1A1* variants modify cancer risk in populations exposed to combustion-derived PAHs. Meta-analyses consistently show that the high-activity *CYP1A1* rs4646903 (MspI T>C) and rs1048943 (Ile462Val) alleles are associated with a modest but measurable increase in PAH-related cancer risk, particularly among smokers. A large 2012 meta-analysis including more than 20,000 participants reported that carriers of the rs4646903 C allele had an approximately 19% higher odds of lung cancer than wild-type individuals, with the effect almost entirely restricted to smokers, indicating a clear gene–environment interaction (Ji, 2012). Subsequent analyses confirmed that the Ile462Val variant similarly increases lung-cancer risk, while also showing associations with other PAH-linked cancers in certain populations. Ethnic differences in allele frequencies and environmental exposures likely contribute to variation in observed effect sizes across studies, but the consensus is that

high-activity *CYP1A1* alleles heighten susceptibility only when sufficient PAH exposure is present. (Wu, 2013)

Epidemiological data for the *CYP1B1* Leu432Val consensus a comparable pattern. A 2016 meta-analysis found that individuals carrying the Val432 allele had roughly 29% increased odds of lung cancer, with the strongest associations observed among smokers (Chen, 2016). Like *CYP1A1*, the effect of *CYP1B1* genotype appears to be accentuated in populations with higher exposure levels or specific ethnic backgrounds (Chen, 2016; Lao, 2014). Beyond lung cancer, some studies suggest that the high-activity Val432 variant may contribute to risk of cancers influenced by PAH exposure or estrogen metabolism, reflecting *CYP1B1*'s dual role in processing both xenobiotics and endogenous hormones. Overall, the epidemiologic pattern mirrors that of *CYP1A1*: the presence of a high-activity allele generally increases cancer susceptibility only in the context of relevant environmental exposure, whereas the genotype alone has limited predictive value in low-exposure settings. (Gajjar, 2012)

Physiological and Biochemical Mechanism

The influence of *CYP1A1* and *CYP1B1* polymorphisms on cancer susceptibility can be understood through their roles in PAH activation and detoxification. High-activity variants accelerate the conversion of PAH procarcinogens into reactive intermediates, including diol-epoxides capable of binding DNA and forming PAH–DNA adducts. Individuals with "fast" genotypes therefore generate a larger and more rapid pulse of electrophilic metabolites from the same external PAH dose, increasing the likelihood of DNA damage when detoxification or repair capacity is exceeded. Empirical studies support this mechanism: carriers of hyperactive *CYP1A1* alleles show higher PAH–DNA adduct levels under exposure, indicating that genotype-driven differences in metabolic activation translate into real biochemical injury. (Bag et al., 2015; Hou et al., 2005)

Crucially, these effects are exposure dependent. In low-exposure settings, fast-metabolizing genotypes confer little additional risk because PAH substrate levels are minimal. Under substantial exposure — such as habitual smoking, occupational contact with combustion fumes, or frequent consumption of charred foods — individuals with high-activity *CYP1A1* or *CYP1B1* variants produce far more reactive intermediates, leading to greater accumulation of mutagenic lesions and a higher probability of carcinogenic mutations (Ji et al., 2012; Zhan, 2011). Thus, the genotype modifies the internal dose of carcinogens given a fixed external dose, making gene–environment interaction central to their physiological impact.

CYP1B1 adds an additional dimension through its role in estrogen metabolism. The Val432 variant not only enhances PAH activation but also increases formation of reactive estrogen metabolites and oxidative species, contributing to background DNA damage in hormone-responsive tissues (Gajjar et al., 2012). Although the present focus is detoxification of exogenous PAHs, this dual function helps explain associations between *CYP1B1* variants and certain hormone-related cancers (Gajjar, 2012; Lao, 2014; Cote, 2009). In summary, high-activity polymorphisms in *CYP1A1* and *CYP1B1* intensify the generation of DNA-damaging intermediates from both environmental and endogenous sources, thereby increasing the probability of somatic mutations that may drive carcinogenesis (Gajjar, 2012; Lao, 2014).

Clinical and Lifestyle Relevance

Understanding these polymorphisms has practical implications for public health and individual risk management. Importantly, carrying a “protective” low-activity genotype does not make exposure to carcinogens safe: tobacco smoke, polluted air and dietary PAHs are harmful to everyone, and exposure reduction remains universally recommended (Ji, 2012; Zhan, 2011). However, genetic differences in *CYP1A1* and *CYP1B1* modify how much reactive metabolite is generated from a given PAH dose. Individuals with hyperactive variants are likely to accumulate more DNA-damaging intermediates from the same exposure than those with low-activity genotypes, which helps explain why some heavy smokers with high-activity alleles develop cancer more readily or at younger ages, whereas others with more favorable metabolic profiles may remain disease-free despite similar exposure histories (Hou, 2005; Ji, 2012; Lao, 2014). In this sense, the genotype acts as a risk multiplier only when PAH exposure is present.

Clinically, this knowledge supports more personalized prevention strategies. Carriers of high-activity alleles such as *CYP1A1* Ile462Val or *CYP1B1* Val432 may benefit from intensified counselling to minimize PAH exposure, including strict avoidance of smoking, secondhand smoke, charred or smoked foods and occupational combustion by-products (Ji, 2012; Lao, 2014). They may also warrant more vigilant screening for cancers linked to PAH burden. Conversely, individuals with low-activity genotypes are not immune to harm but may have a slightly wider margin of safety under typical exposure levels.

Lifestyle factors can also interact with genotype: some foods and environmental agents induce or inhibit enzymes, potentially modifying detoxification efficiency (Gajjar, 2012). Although beyond this review’s scope, these interactions underscore that genotype informs susceptibility rather than replaces standard prevention. Ultimately, the primary message remains unchanged: reducing exposure to smoke, soot, ash and burnt organic materials is essential for all individuals, with genotyping serving to refine — not redefine — risk assessment.

CONCLUSION

Collectively, the evidence demonstrates that polymorphisms in *CYP1A1* and *CYP1B1* substantially influence individual variation in the metabolic processing of combustion-derived PAHs. High-activity alleles such as *CYP1A1* rs4646903, *CYP1A1* rs1048943 (Ile462Val), and *CYP1B1* rs1056836 (Leu432Val) enhance enzyme inducibility or catalytic efficiency, accelerating the formation of reactive PAH intermediates (Ji, 2012; Zhan, 2011; Lao, 2014). This heightened activation becomes particularly consequential under conditions of substantial exposure — including cigarette smoke, urban air pollution, occupational soot, and charred foods — where the increased metabolic flux can overwhelm detoxification and DNA-repair systems (Hou, 2005; Ji, 2012; Lao, 2014). As a result, carriers of high-activity alleles generally sustain greater biochemical and physiological impact from the same environmental PAH dose than those with reference genotypes.

Importantly, the absence of high-activity alleles does not confer immunity; PAHs remain carcinogenic once activated, regardless of metabolic genotype. However, molecular,

mechanistic and epidemiological evidence consistently shows that genotype functions as a risk multiplier, exerting its strongest influence when PAH exposure is high and exerting minimal effect when exposure is low (Ji, 2012; Zhan, 2011). This highlights the central role of gene–environment interactions in determining susceptibility: genetic variation shapes metabolic capacity, but exposure determines actual risk.

From a public-health perspective, these insights support the value of personalized prevention strategies. Individuals carrying high-activity *CYP1A1* or *CYP1B1* alleles may benefit from intensified guidance to avoid tobacco smoke, secondhand smoke, soot, exhaust fumes and charred or smoked foods, as well as from enhanced vigilance for conditions associated with PAH burden (Lao, 2014; Ji, 2012). At the same time, the overarching recommendation remains unchanged: minimizing exposure to combustion-derived pollutants is the most effective means of reducing PAH-related harm for all individuals, with genotyping serving to refine — but not replace — fundamental environmental health advice.

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