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## Genetic polymorphisms in glutathione S-transferases (GSTs) and cytochrome P450s (CYPs), tobacco smoking, and risk of non-Hodgkin lymphoma

Briseis A. Kilfoy<sup>1,2</sup>, Tongzhang Zheng<sup>1</sup>, Qing Lan<sup>2</sup>, Xuesong Han<sup>1</sup>, Qin Qin<sup>3</sup>, Nathaniel Rothman<sup>2</sup>, Theodore Holford<sup>1</sup>, and Yawei Zhang<sup>1</sup>

<sup>1</sup> School of Epidemiology and Public Health, Yale University, New Haven, CT 06520, USA

<sup>2</sup> Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

<sup>3</sup> Center for Toxicology and Environmental Health, University of Southern Maine. Portland, Maine, USA

### Abstract

We investigated variation in GSTs and CYPs and smoking in a population-based case-control study of NHL including 1,115 women. Although risk of NHL was not altered by variant polymorphisms in GSTs or CYPs, it was significantly changed for DLBCL when considered in conjunction with smoking behavior, though only in non-smokers. An increased risk of DLBCL in non-smokers was associated with the variant G allele for *GSTP1* (OR=1.6, 95%CI: 1.0–2.3) and *CYP1A1* (OR=2.4; 95%CI: 1.0–5.7), but a decreased risk for the variant G allele for *CYP1B1* (OR=0.6, 95%CI: 0.4–1.0). Our results confer support investigation of the gene-environment interaction in a larger study population of DLBCL.

### Keywords

non-Hodgkin lymphoma; GSTs; CYPs; smoking

## INTRODUCTION

Tobacco smoke contains carcinogens such as polycyclic aromatic hydrocarbons (PAHs), aldehydes, benzo[alpha]pyrene, ethylene oxide, 4-aminobiphenyl, and nitrosamines which are metabolically activated through xenobiotic metabolism by phase I and II enzymes, including cytochrome P450s (CYPs) and glutathione-S-transferases (GSTs). CYPs act by first adding a functional group making the compounds in tobacco smoke more electrophilic, and GSTs detoxify a broad array of chemical in tobacco smoke by conjugating them with glutathione (1). CYP and GST activity is important in detoxification reactions because electrophiles are potentially toxic species that can bind to nucleophiles, such as proteins and nucleic acids, and can cause cellular damage and genetic mutations. Polymorphisms in genes that code various types of CYPs and GSTs manifest as decreased or lack of enzyme activity (2), prompting the hypothesis that allelic variants may be associated with an impaired detoxification capacity and subsequently an overall increased susceptibility to cancer.

The investigation of genetic variation of CYPs and GSTs in relation to NHL risk has been limited to date (3–9). Differential susceptibility to NHL according to metabolic activity could provide important evidence supporting the role of carcinogenic compounds found in tobacco smoke or its metabolites in the etiology of NHL. We therefore investigated NHL risk in general and by subtype in relation to genetic variation in CYPs and GSTs and exposure to cigarette smoke in a population-based case-control study in Connecticut women.

## RESULTS

The association between smoking and NHL in this genotyped population was consistent with the original report (10). Briefly, of the 597 controls, 52.8% reported ever smoking and 55.6% of the 518 cases reported ever smoking (Table 1). Women who smoked for 15 pack-years or more experienced a 30% increased risk of NHL overall. When stratified by NHL subtypes, a significantly increased risk was observed for follicular lymphoma among women who had smoked for 25 years or longer (OR=1.6, 95%CI: 1.0–2.5) or who had smoked for 15 pack-years or more (OR=1.6, 95%CI: 1.0–2.4). No association was observed between smoking behavior and risk of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), marginal zone (MZ) lymphoma, or T cell lymphoma (data not shown).

When we looked at polymorphisms in GSTs and CYPs and risk of NHL by smoking status (Table 2), we found that the variant C allele of *CYP1A2* was associated with an increased risk of NHL overall (OR=1.3, 95%CI: 1.0–1.7) among smokers. In the subtype analyses, we found an increased risk of DLBCL among non-smokers with the *GSTP1* variant G allele (OR=1.6, 95%CI: 1.0–2.3) as well as the *CYP1A1* variant G allele (OR=2.4; 95%CI: 1.0–5.7). However, a decreased risk of DLBCL was observed among non-smokers with a variant G *CYP1B1* allele of (OR=0.6; 95%CI: 0.4–1.0). No statistically significantly altered risk of follicular lymphoma, of SLL/CLL, or of marginal zone lymphoma was found among either smokers or non-smokers with the genetic variations of interest.

## DISCUSSION

We evaluated SNPs that were drawn from 5 key genes that play a role in the mediation of carcinogen metabolism. Overall, our results presented modest evidence that the potential relationship between NHL and the absence or presence of smoke exposure may be modified by common genetic variation in CYP and GST genes, particularly for DLBCL. However, the limited case numbers, especially for the homozygous variant persons, suggest that these findings should be further pursued in a larger study population.

Prior investigation into the association of smoking and NHL has been inconsistent (11–17). An analysis of pooled case-control studies, including the current study, found that there is a modest increased risk from smoking in individuals with follicular lymphoma (18). However, our study found that genetic variation in GST and CYP genes did not significantly modify the relationship between cigarette smoking and risk of follicular lymphoma. This suggests that the carcinogens in tobacco smoke may overwhelm the metabolic system such that polymorphisms in individual metabolic enzymes do not alter the risk of follicular lymphoma.

The findings between CYP and GST polymorphisms and risk of DLBCL in the non-smoking population are interesting. We did not expect to find the increased risk in non-smokers. However, DLBCL is a molecularly heterogeneous disease with multiple complex chromosomal translocations and genetic abnormalities. Previous research has suggested that immunological and hormonal factors may play an important role in the development of DLBCL (19–22). In fact, the current study has reported a reduced risk of DLBCL for women who had four or more pregnancies (23) as well as for women who reported HRT use (24). Our results

suggest that polymorphisms in genes that are involved in the endogenous hormone metabolic pathway may affect the risk of DLBCL.

The *CYP1A1* gene is associated with variation in estrogen levels (25). *CYP1A1* is involved in estrogen catabolism and the conversion of estrone and estradiol to water-soluble metabolites, thus affecting estrogenic function and potentially impacting rates of hormone related carcinogenesis (25). The finding that genetic variation in *CYP1A1* and an increased risk of DLBCL in non-smokers is biologically plausible as smoking typically lowers estrogen levels, making an observable effect of this mechanism more likely in non-smokers. *CYP1B1* is involved in the activation of benzo[a]pyrene, a chemical found in tobacco smoke, and mutations in *CYP1B1* significantly decrease the enzyme's ability to metabolize such carcinogens. In our study, we found a decreased risk of NHL in non-smokers in those with the variant genotypes. As *CYP1B1* is involved in phase I conjugation, we suspect that the decreased risk is a function of the lower rate of metabolism of carcinogens not necessarily included in tobacco smoke.

The *GSTP1* variant investigated consists of an A-to-G substitution at base pair 313 at codon 105 resulting in an amino acid difference, from isoleucine to valine (26). Previous studies have shown that the activity of the isoleucine 105 variant toward several carcinogenic diol epoxides is lower compared with that of the valine 105 form (27,28). This result was confirmed by the finding that *GSTP1* Val possesses up to fivefold more enzymatic activity than in *GSTP1* Ile/Val or Ile/Ile (29,30). In our population, the increased risk associated with *GSTP1* Val/Val was observed in the non-smokers. Although it is possible that the non-smokers are exposed to PAHs from sources not measured in this study, the increased risk of DLBCL in non-smokers suggests that the role of increased enzymatic activity on potentially harmful endogenous factors may be of interest. Increased enzymatic activity of *GSTP1* Val increases metabolism of estrogens resulting in a reduction of estrogen levels, which may lead to an increased risk of DLBCL.

Our study has several strengths. It is a population-based, case-control study with both incident cases that are histologically confirmed and highly accurate genotyping data. The primary limitation of our study is that the sample size is modest and the number of cases in several histologic subgroups was small. This resulted in reduced power to detect associations for SNPs with low allele frequencies. It was limited to women and may be non-generalizable to the entire population. Information bias, resulting from exposure misclassification is likely to have been non-differential, thus biasing our risk estimates towards the null. The positive findings in our report require replication in larger studies with greater power, which will be particularly valuable if tagged SNPs with full genomic coverage of the most promising candidate genes are used.

In summary, our study suggested that the common genetic variation in the metabolic pathway genes may be associated with the risk of DLBCL and the risk may be modified by cigarette smoking. A detailed, extensive genomic analysis of genes that play a role in the metabolic pathway is warranted in future studies. Further, these findings require replication in larger studies and ultimately in pooled analyses.

## METHODS

The study population has previously been described in detail elsewhere (16,24,31). Briefly, from 1996 to 2000, all histologically confirmed incident female NHL cases aged 21–84 years old in Connecticut, alive at the time of interview and without a previous diagnosis of cancer except for non-melanoma skin cancer, were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA). The study was approved by the Institutional Review Board at Yale University, the Connecticut Department of Public Health, and the

National Cancer Institute. Written, informed consent was obtained from each subject and participation was voluntary.

We selected five single nucleotide polymorphisms (SNPs) for genotyping in the following genes: *GSTM3* (rs1799735), *GSTP1* (rs1695), *CYP1A1* (rs1048943), *CYP1A2* (rs762551), and *CYP1B1* (rs1056836). These genes were selected given their role in tobacco smoke metabolism. DNA was extracted from blood or buccal cell samples using phenol chloroform extraction. Genotyping was carried out by real-time PCR on an ABI 7900HT sequence detection system as described on the SNP500 website (<http://www.snp500cancer.nci.nih.gov>). Duplicate samples from 100 study subjects and 40 replicate samples from each of two blood donors were interspersed throughout the plates used for genotype analysis. The concordance rates for quality control samples were 99–100% for all assays. We observed no significant departure from Hardy-Weinberg equilibrium in the control population for any of the SNPs analyzed.

Unconditional logistic regression models were used to estimate the ORs and the 95% CIs for associations between cigarette smoking, polymorphisms in GSTs and CYPs and risk of NHL, adjusting for age and race. Adjustment for other potential confounding variables such as education, DNA source, and alcohol use, did not result in material changes of the observed associations. Gene dosage effects were evaluated by assessing the linear trend of the genotypes. Analyses were also conducted for five major histological subtypes of NHL according to the World Health Organization (WHO) classification. All tests were two-sided with significance level of 0.05 using SAS 8.2 (SAS Institute Inc., Cary, NC).

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Table 1

Cigarette smoking and risk of NHL and NHL subtypes<sup>†</sup>

Smoking	NHL Overall			DLBCL		FL	
	Controls	Cases	OR <sup>‡</sup> (95%CI)	Cases	OR <sup>‡</sup> (95% CI)	Cases	OR <sup>‡</sup> (95% CI)
Never	282	230	1	70	1	50	1
Ever	315	288	1.1(0.9-1.4)	91	1.1(0.8-1.6)	69	1.2(0.8-1.8)
<b>Duration</b>							
<25	151	122	0.9(0.7-1.3)	44	1.0(0.7-1.6)	24	0.8(0.4-1.3)
25+	164	166	1.2(0.9-1.6)	47	1.2(0.8-1.9)	<b>45</b>	<b>1.6(1.0-2.5)</b>
<b>Pack-Years</b>							
<15	145	108	0.9(0.6-1.2)	37	0.9(0.6-1.4)	21	0.7(0.4-1.3)
15+	170	180	<b>1.3(1.0-1.7)</b>	54	1.3(0.9-2.0)	48	<b>1.6(1.0-2.4)</b>

<sup>†</sup> DLBCL=Diffuse large B-cell lymphoma; FL=follicular lymphoma

<sup>‡</sup> Adjusted for age, race, and family history of NHL



Table 2

Polymorphisms of GSTs and CYPs and risk of NHL and NHL subtypes<sup>†</sup> among non-smokers and smokers

SNP	Overall		Non-smokers Overall		Smokers Overall		DLBCL		DLBCL Non-smokers		DLBCL Smokers		FL		FL Non-Smokers		FL Smoker	
	Controls	Cases	OR <sup>‡</sup> (95%CI)	Controls	Cases	OR <sup>‡</sup> (95%CI)	Controls	Cases	OR <sup>‡</sup> (95%CI)	Controls	Cases	OR <sup>‡</sup> (95%CI)	Controls	Cases	OR <sup>‡</sup> (95%CI)	Controls	Cases	OR <sup>‡</sup> (95%CI)
<b>GSTM3 rs1799735</b>	321	144	1	179	144	1	193	105	1	43	1	62	79	1	37	1	42	1
++	372	159	1.1 (0.8-1.4)	71	59	1.1 (0.7-1.6)	88	42	0.9 (0.6-1.4)	19	1	23	27	0.8 (0.5-1.3)	8	1	19	1.1 (0.6-1.8)
+ - or - -																		0.1746
P-interaction									0.8347									
<b>GSTP1 rs1695</b>	230	187	1	109	77	1	121	51	1	22	1	29	43	1	15	1	28	1
AA	302	271	1.1 (0.9-1.5)	140	124	1.3 (0.9-1.8)	162	96	1.5 (1.0-2.2)	40	1.6 (1.0-2.3)	56	62	1.3 (0.9-1.8)	29	1.5 (0.9-2.4)	33	1.0 (0.6-1.5)
AG or GG																		0.2121
P-interaction									0.4177									
<b>CYP1A1 rs1048943</b>	487	418	1	232	181	1	255	129	1	51	1	78	98	1	40	1	58	1
AA	39	33	1.0 (0.6-1.6)	16	18	1.3 (0.7-2.6)	23	15	1.5 (0.8-2.8)	9	2.4 (1.0-5.7)	6	6	0.8 (0.3-2.1)	4	1.5 (0.5-4.6)	2	0.8 (0.3-2.2)
AG or GG																		0.1379
P-interaction									0.1355									
<b>CYP1A2 rs762551</b>	267	211	1	124	98	1	143	72	1	33	1	39	50	1	23	1	27	1
AA	267	245	1.2 (0.9-1.5)	126	104	1.0 (0.8-1.4)	141	74	1.1 (0.7-1.6)	28	1.0 (0.6-1.6)	46	55	1.2 (0.9-1.8)	22	1.0 (0.6-1.7)	33	1.3 (0.9-2.0)
AC or CC																		0.7182
P-interaction									0.5496									
<b>CYP1B1 rs1056836</b>	194	170	1	89	79	1	105	62	1	27	1	35	33	1	13	1	20	1
CC	326	274	1.0 (0.7-1.3)	153	118	0.8 (0.6-1.1)	173	77	0.8 (0.5-1.1)	31	0.6 (0.4-1.0)	46	70	1.1 (0.8-1.5)	31	1.1 (0.7-1.7)	39	1.2 (0.8-1.7)
CG or GG																		0.746
P-interaction									0.4508									

<sup>†</sup> DLBCL=Diffuse large B-cell lymphoma; FL=follicular lymphoma;

<sup>‡</sup> Adjusted for age, race, and family history of NHL

\* The first p-value is when genotype is used as an ordinal variable; the second p-value is when genotype is used as a categorical variable