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# Genetic variation in *N*-acetyltransferases 1 (NAT1) and 2 (NAT2), cigarette smoking, and risk of non-Hodgkin lymphoma

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## Abstract

Cigarette smoke contains many carcinogens that are metabolically activated through xenobiotic metabolism by phase I and II enzymes, including *N*-acetyltransferases 1 and 2 (NAT1 and NAT2). We investigated non-Hodgkin lymphoma (NHL) risk in general and by subtype in relation to NAT1 and NAT2 genotypes and cigarette smoking in a population-based case-control study in Connecticut. We found a 2-fold increased risk of T-cell lymphoma among those possessing the *NAT1*10* haplotype compared to those with other NAT1 haplotypes; including an OR of 2.2 (95%CI: 1.1–4.5) for those heterozygous for *NAT1*10* and an OR of 2.0 (95% CI: 1.0–2.4) for those heterozygous or homozygous for *NAT1*10* genotypes. Rapid acetylator NAT2 phenotype increased the risk of both T-cell lymphoma (OR=3.2; 95% CI: 1.1–9.5) and marginal zone lymphoma (OR=3.0; 95% CI: 1.0–8.7). When NAT1 and NAT2 genotypes were stratified by smoking status, an increased risk of NHL overall was observed in ever (OR=1.5; 95% CI: 1.1–2.1) and current (OR=1.7; 95% CI: 1.2–2.4) smokers without the NAT1*10 haplotype. No association between history of cigarette smoking and risk of NHL overall was observed with *NAT1*10* haplotype or NAT2 genotype.

### Keywords

non-Hodgkin lymphoma; NAT1; NAT2; smoking; single nucleotide polymorphisms

## Introduction

There have been consistent reports of increases in the incidence and mortality due to non-Hodgkin lymphoma (NHL) during the past decades (1–6). The etiology of NHL, however, remains unclear with few known risk factors (i.e., severe immunosuppression resulting from

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diseases, treatments, and viral infections) (7–10). Tobacco products contain several carcinogenic compounds hypothesized to increase NHL risk (11). Although smoking has been associated with several hematopoietic cancers (12–20), previous results in the literature have been conflicting for NHL in general, suggesting the association may be NHL subtype specific, and in most studies any observed effect has been relatively weak (21–30).

Xenobiotic-metabolizing enzymes catalyze both the activation and/or deactivation of carcinogenic chemicals found in tobacco products (31,32). Many enzymes are genetically polymorphic and are responsible for inter-individual variation in metabolism. This variation may result in different patterns of susceptibility to the effects of smoking on cancer outcomes. *N*-acetyltransferase 1 and 2 (NAT1 and NAT2) exhibit genetic polymorphisms that are common in most populations. We therefore investigated NHL risk in general and by subtype in relation to genetic variation in NAT1/ and NAT2 and smoking status in a population-based case-control study of females in Connecticut, USA.

## Methods

The study population has previously been described in detail elsewhere (27,33,34). 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). Of 832 eligible cases, 601 (72%) completed in-person interviews. Controls were frequency matched to cases on age (within 5-year groups) and were recruited using random digit dialing (RDD) methods for those aged <65 years, or randomly selected from the files provided by the Centers for Medicare and Medicaid Service (CMS) for those aged ≥65 years. The participation rate was 69% for RDD controls and 47% for CMS controls. 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. About 75% of the interviewed subjects provided blood samples (76.7% of cases and 74.6% of controls), and about 10% of the study subjects (11.0% of cases and 10.4% of controls) provided buccal cell samples.

DNA was extracted from blood or buccal cell samples using phenol–chloroform extraction. Genotyping was conducted at the National Cancer Institute Core Genotyping Facility (Advanced Technology Center, Gaithersburg, Maryland, USA) using validated assays on the Taqman (Applied Biosystems, Foster City, California, USA) or MGB Eclipse (Epoch Biosciences, Bothell, Washington, USA) platforms. Sequence data and assay conditions available at: http://snp500cancer.nci.nih.gov (35). We selected four single nucleotide polymorphisms (SNPs) in NAT1 and six SNPs in NAT2 for genotyping (Table 1). All 10 SNPs were genotyped in blood-based DNA samples because DNA samples from buccal cell were insufficient for this analysis, yielding a population of 461 cases and 535 controls. Because of incomplete genotyping for some SNPs due to insufficient DNA, the most likely NAT alleles could not be determined for 8 cases and 7 controls for NAT1, and 5 cases and 2 controls for NAT2, yielding a final population of 453 cases and 528 controls for analyses of NAT1 genotypes, and 456 cases and 533 controls for analyses of NAT2 genotypes.

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 ($P>0.05$). Demographic characteristics (age, race, and education) for cases and

controls did not differ significantly for individuals with undetermined NAT1 and NAT2 alleles compared with those with known NAT1 and NAT2 alleles.

Unconditional logistic regression models were used to estimate the odds ratio (OR) and the 95% confidence interval for associations between cigarette smoking, genetic polymorphisms in NAT1s and NAT2s and risk of NHL, adjusting for age (continuous) and race (white and non-white), and family history. Adjustment for other potential confounding variables such as education, and alcohol use, did not result in material changes of the observed associations, thus they were not included in the final model. Analyses were also conducted for five major histological subtypes of NHL according to the World Health Organization (WHO) classification: Diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone lymphoma, and T-cell lymphoma. All tests were two-sided with significance level of 0.05. All analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NC).

## Results

The association between smoking and NHL in this genotyped population was consistent with the original report (27). Briefly, of the 535 controls, 53.1% reported ever smoking and 55.7% of the 461 cases reported ever smoking (OR=1.1; 95%CI: 0.8–1.4) (Table 2). Of these, 200 cases and 209 controls were former smokers (OR=1.2; 95%CI: 0.9–1.5) and the remaining 57 cases and 75 controls were current smokers (OR=0.9; 95%CI 0.6–1.4). No significant variation in risk between cases and controls was observed by race or alcohol use (Table 2).

No association was observed between *NAT1*10* genotypes and NHL overall (Table 3). However, the subtype analyses presented a 2.2-fold significantly increased risk of T-cell lymphoma among those heterozygous for the *NAT1*10* haplotype (OR=2.2; 95%CI: 1.1–4.5) as well as a 2.0-fold increased risk among those with heterozygous or homozygous *NAT1*10* genotypes (OR=2.0; 95%CI: 1.0–4.2). A decreased risk of DLBCL (OR = 0.6; 95% CI: 0.4–1.0) and an increased risk of T-cell lymphoma (OR = 2.3; 95%CI: 1.0–5.3) was associated with the *NAT1*10* haplotype (data not shown).

NAT2 acetylation phenotypes were not associated with the risk of NHL overall (Table 4). A three-fold increased risk of marginal zone lymphoma (OR=3.0, 95%CI: 1.0–8.7) and T-cell lymphoma (OR=3.2, 95%CI: 1.1–9.5) was observed for those with a rapid NAT2 phenotype compared with the slow NAT2 phenotype.

When the associations with smoking were stratified by NAT1 genotypes and NAT2 phenotypes (Table 5), a significant increase in risk of NHL overall (OR=1.5, 95%CI: 1.1–2.1) was observed for ever smokers without *NAT1*10* alleles. This increased risk was also observed among current smokers (OR=1.7, 95%CI: 1.2–2.4). The increased risk in smokers without a *NAT*10* genotype was also observed for DLBCL (OR=1.7, 95%CI: 1.1–2.6) and T-cell lymphoma (OR=3.8, 95%CI: 1.0–14.1) (data not shown). However, no significant alteration in risk was observed for the NAT2 phenotype by smoking status.

When the above analyses were restricted to non-Hispanic Caucasians, changes in the results were not material (data not shown).

## Discussion

Our results present modest evidence that acetylation rate modifies the risk of NHL for specific subtypes and that the *NAT1*10* genotype is an “at-risk” allele. Additionally, our results suggest that the relationship between NHL and smoking status may be modified by common genetic variation in NAT1 but not NAT2.

The role of *N*-acetyltransferases as important metabolic enzymes is well established in the literature. However, to date, only four studies (30,36–38) have evaluated the relationship of NAT1 and NAT2 polymorphisms with NHL risk. The studies by Lemos and Kerridge both reported no association of NHL with the NAT1 or NAT2 slow acetylation genotypes. However, the more recent studies by Chiu (36) and Morton (30), both found that the NAT1*10 genotype was associated with an increased risk of NHL (only in women in the Chiu et al. study). Although we didn't find an association for NHL overall, we did identify a significantly increased risk for T-cell lymphoma and a decreased risk of DLBCL for the *NAT1*10* genotype.

Neither Chiu nor Morton found an association between the NAT2 slow genotype and overall NHL risk in either sex. However, we found a significantly increased risk for marginal zone and T-cell lymphoma with rapid NAT2 acetylation phenotypes. Morton et al. noted an increased risk for NAT2 rapid acetylators for the marginal zone and follicular subtypes.

The biologic role of the enzymes suggests that gene-environment analyses may be a more informative pursuit as their physiological impact is dependent on the presence of chemicals for metabolism. We found an association between risk of NHL, as well as for those with DLBCL and T-cell lymphoma, for those without a *NAT*10* genotype and smoking status. We did not, however, identify a modified association between NHL and NAT2 phenotypes by smoking status. Morton et al. found that the risk of NHL associated with current cigarette smoking was observed among NAT2 intermediate and rapid acetylators. They suggested that the variation in acetylation capacity and differential susceptibility to NHL indirectly supports the role of carcinogenic aromatic and/or heterocyclic amines in the etiology of NHL.

Previous studies have suggested that women with the slow acetylation phenotypes for NAT2 may be more adversely affected by tobacco smoking (39–41) but the data have been inconsistent (42–43). Our results indicate that the NAT1 rapid genotype (without *NAT*10* alleles) increases the risk of NHL in smokers relative to the risk observed in non-smokers, indicating that NAT2 activation (via O-acetylation) is more important than deactivation. This point is strengthened by the results from Morton (30) which demonstrated a more than 2-fold in increased risk of NHL in smokers with the rapid NAT2 phenotype.

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. Further, the response rate in our study is moderate and could potentially result in biased risk estimates if willingness to participate in our study was associated with genotype frequency. However, a recent report observed that subject participation status was unrelated to genotype frequencies for a wide spectrum of genes (44). 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.

In summary, our study suggest that the risk associated with NHL overall appears to be modified by cigarette smoking for those with *NAT1*10* haplotype. 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.

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**Table 1**

NAT1 and NAT2 polymorphisms selected for genotyping

| SNP rs# | Nucleotide change | Amino acid change |
|---|---|---|
| **NAT1** | | |
| rs1057126 | Ex3-177A>T | |
| rs15561 | Ex3-170A>C | |
| rs4987076 | Ex3+451G>A | V149I |
| rs4986782 | Ex3+566G>A | R187Q |
| **NAT2** | | |
| rs1208 | Ex2-367G>A | K268R |
| rs1799931 | Ex2-313G>A | G286E |
| rs1041983 | Ex2+288C>T | Y94Y |
| rs1801280 | Ex2+347T>C | I114T |
| rs1799929 | Ex2+487C>T | L161L |
| rs1799930 | Ex2-580G>A | R197Q |

## Table 2

Distribution of selected characteristics in the study population

| | Cases (n=461) | Controls (n=535) | OR (95%CI) |
|---|---|---|---|
| **Age** | | | |
| ≤45 | 56 | 74 | 1.0 |
| 46–55 | 93 | 96 | 1.3 (0.8–2.0) |
| 56–65 | 102 | 102 | 1.3 (0.8–2.1) |
| 66–75 | 133 | 156 | 1.1 (0.7–1.7) |
| 75+ | 77 | 107 | 1.0 (0.6–1.5) |
| **Race** | | | |
| White | 444 | 504 | 1.0 |
| Black | 13 | 14 | 1.1 (0.5–2.3) |
| Other | 4 | 11 | 0.4 (0.1–1.3) |
| **Family History** | | | |
| No | 454 | 533 | 1.0 |
| Yes | 9 | 2 | 5.3 (1.1–24.7) |
| **Smoking** | | | |
| Never | 204 | 251 | 1.0 |
| Ever | 257 | 284 | 1.1(0.8–1.4) |
| Former | 200 | 209 | 1.2 (0.9–1.5) |
| Current | 57 | 75 | 0.9 (0.6–1.4) |
| **Alcohol Consumption** | | | |
| No | 165 | 172 | 1.0 |
| Yes | 296 | 363 | 0.9 (0.7–1.1) |
| **Subtypes** | | | |
| DLBCL | 147 | | |
| Follicular | 106 | | |
| CLL/SLL | 54 | | |
| Marginal | 31 | | |
| T-cell | 33 | | |

[†]DLBCL=Diffuse large B-cell lymphoma; SLL/CLL=small lymphocytic lymphoma/chronic lymphocytic leukemia;

**Table 3**

Association between NAT1*10 and risk of NHL and NHL Subtypes

| | No NAT1*10 alleles | | Heterozygous for NAT1*10 | | NAT1*10/*10 | | Heterozygous for NAT1*10 or NAT1*10/*10 | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **OR (95%CI)** | **n** | **OR (95%CI)** | **n** | **OR (95%CI)** | **n** | **OR (95%CI)** |
| Controls | 328 | | 172 | | 22 | | 194 | |
| All NHL | 289 | 1.0 | 145 | 1.0 (0.7–1.3) | 19 | 1.1 (0.6–2.0) | 164 | 1.0 (0.7–1.3) |
| **Subtype** | | | | | | | | |
| DBCL | 104 | 1.0 | 36 | 0.7 (0.4–1.0) | 4 | 0.6 (0.2–1.9) | 40 | 0.7 (0.4–1.0) |
| Follicular | 69 | 1.0 | 33 | 0.9 (0.6–1.5) | 4 | 1.0 (0.3–3.1) | 37 | 0.9 (0.6–1.4) |
| SLL/CLL | 32 | 1.0 | 20 | 1.2 (0.7–2.2) | 2 | 1.0 (0.2–4.3) | 22 | 1.2 (0.7–2.1) |
| Marginal | 19 | 1.0 | 10 | 1.0 (0.4–2.2) | 1 | 0.9 (0.1–6.8) | 11 | 1.0 (0.4–2.1) |
| T-Cell | 15 | 1.0 | 17 | **2.2 (1.1–4.5)** | 1 | 1.0 (0.1–8.0) | 18 | **2.0 (1.0–4.2)** |

[†]DLBCL=Diffuse large B-cell lymphoma; SLL/CLL=small lymphocytic lymphoma/chronic lymphocytic leukemia;

[‡]Odds Ratio (OR) [95% confidence interval (CI)] adjusted for age, race, and family history of NHL

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**Table 4**

Association between NAT2 phenotypes and risk of NHL and NHL subtypes

| | Slow | | Intermediate | | Rapid | | Intermediate/Rapid | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **OR (95%CI)** | **n** | **OR (95%CI)** | **n** | **OR (95%CI)** | **n** | **OR (95%CI)** |
| Controls | 315 | | 189 | | 29 | | 218 | |
| All NHL | 257 | 1.0 | 166 | 1.1 (0.8–1.4) | 33 | 1.4( 0.8– 2.4) | 199 | 1.1 (0.9–1.5) |
| **Subtype** | | | | | | | | |
| DBCL | 88 | 1.0 | 48 | 0.9 (0.6–1.3) | 10 | 1.2 (0.6–2.7) | 58 | 0.9 (0.6–1.4) |
| Follicular | 58 | 1.0 | 41 | 1.2 (0.7–1.8) | 6 | 1.1 (0.4–2.9) | 47 | 1.2 (0.8–1.8) |
| SLL/CLL | 30 | 1.0 | 21 | 1.2 (0.7–2.1) | 3 | 1.1 (0.3–3.9) | 24 | 1.2 (0.7–2.1) |
| Marginal | 20 | 1.0 | 6 | 0.5 (0.2–1.3) | 5 | **3.0 (1.0–8.7)** | 11 | 0.8 (0.4–1.8) |
| T-Cell | 17 | 1.0 | 11 | 1.1 (0.5– 2.4) | 5 | **3.2( 1.1– 9.5)** | 16 | 1.4 (0.7–2.8) |

† DLBCL=Diffuse large B-cell lymphoma; SLL/CLL=small lymphocytic lymphoma/chronic lymphocytic leukemia;

‡ Odds Ratio (OR) [95% confidence interval (CI)] adjusted for age, race, and family history of NHL

**Table 5**

Association between history of cigarette smoking and risk of NHL overall by NAT1*10 genotype and NAT2 phenotype

| | No NAT1*10 alleles | | | NAT1*10/any | | |
|---|---|---|---|---|---|---|
| | **controls** | **cases** | **OR 95% CI** | **controls** | **cases** | **OR 95% CI** |
| **Non-smokers** | 164 | 113 | 1.0 | 85 | 84 | 1.0 |
| **Ever smokers** | 162 | 168 | **1.5 (1.1–2.1)** | 117 | 88 | 0.7 (0.5–1.1) |
| **Current smokers** | 120 | 137 | **1.7 (1.2–2.4)** | 85 | 62 | 0.7(0.4–1.1) |
| **Former smokers** | 42 | 31 | 1.0(0.6–1.8) | 32 | 26 | 0.8(0.4–1.5) |
| | **NAT2 Slow** | | | **NAT2 Intermediate/Rapid** | | |
| | controls | cases | OR 95% CI | controls | cases | OR 95% CI |
| **Non-smokers** | 150 | 115 | 1.0 | 99 | 86 | 1.0 |
| **Ever smokers** | 165 | 142 | 1.1 (0.8–1.6) | 119 | 113 | 1.0 (0.7–1.5) |
| **Current smokers** | 122 | 110 | 1.2 (0.8–1.7) | 87 | 89 | 1.2 (0.8–1.7) |
| **Former smokers** | 43 | 32 | 1.0 (0.6–1.7) | 32 | 24 | 0.8 (0.4–1.5) |

‡Odds Ratio (OR) [95% confidence interval (CI)] adjusted for age, race, and family history of NHL