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Smoking, variation in *N*-acetyltransferase 1 (*NAT1*) and 2 (*NAT2*), and risk of non-Hodgkin lymphoma: a pooled analysis within the InterLymph consortium

Todd M. Gibson,
Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 7090, Bethesda, MD 20892, USA

Cancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA

Karin E. Smedby,
Unit of Clinical Epidemiology, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden

Christine F. Skibola,
Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA, USA

David W. Hein,
Department of Pharmacology and Toxicology and James Graham Brown Cancer Center, School of Medicine, University of Louisville, Louisville, KY, USA

Susan L. Slager,
Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN, USA

Silvia de Sanjosé,
Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d'Oncologia, IDIBELL, Barcelona, Spain

CIBER Epidemiologia y Salud Pública, Madrid, Spain

Claire M. Vajdic,
Adult Cancer Program, University of New South Wales, Sydney, NSW, Australia

Lowy Cancer Research Center, Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia

Yawei Zhang,
Yale School of Public Health, Yale University, New Haven, CT, USA

Brian C.-H. Chiu,
Department of Health Studies, University of Chicago, Chicago, IL, USA

Sophia S. Wang,
Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute and the City of Hope, Duarte, CA, USA

Correspondence to: Todd M. Gibson, gibsontm@mail.nih.gov.

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Henrik Hjalgrim,
Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

Alexandra Nieters,
Centre of Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany

Paige M. Bracci,
Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, CA, USA

Anne Kricker,
School of Public Health, University of Sydney, Sydney, NSW, Australia

Tongzhang Zheng,
Yale School of Public Health, Yale University, New Haven, CT, USA

Carol Kolar,
The Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE, USA

James R. Cerhan,
Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN, USA

Hatef Darabi,
Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

Nikolaus Becker,
Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany

Lucia Conde,
Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA, USA

Theodore R. Holford,
Yale School of Public Health, Yale University, New Haven, CT, USA

Dennis D. Weisenburger,
Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, USA

Anneclaire J. De Roos,
Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA, USA

Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Katja Butterbach,
Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany

Jacques Riby,
Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA, USA

Wendy Cozen,
Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Yolanda Benavente,
Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d'Oncologia, IDIBELL, Barcelona, Spain

Casey Palmers,
Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA, USA

Elizabeth A. Holly,
Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, CA, USA

Joshua N. Sampson,
Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 7090, Bethesda, MD 20892, USA

Nathaniel Rothman,
Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 7090, Bethesda, MD 20892, USA

Bruce K. Armstrong, and
School of Public Health, University of Sydney, Sydney, NSW, Australia

Lindsay M. Morton
Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 7090, Bethesda, MD 20892, USA

Todd M. Gibson: gibsontm@mail.nih.gov

Abstract

Purpose—Studies of smoking and risk of non-Hodgkin lymphoma (NHL) have yielded inconsistent results, possibly due to subtype heterogeneity and/or genetic variation impacting the metabolism of tobacco-derived carcinogens, including substrates of the *N*-acetyltransferase enzymes *NAT1* and *NAT2*.

Methods—We conducted a pooled analysis of 5,026 NHL cases and 4,630 controls from seven case–control studies in the international lymphoma epidemiology consortium to examine associations between smoking, variation in the *N*-acetyltransferase genes *NAT1* and *NAT2*, and risk of NHL subtypes. Smoking data were harmonized across studies, and genetic variants in *NAT1* and *NAT2* were used to infer acetylation phenotype of the NAT1 and NAT2 enzymes, respectively. Pooled odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for risk of NHL and subtypes were calculated using joint fixed effects unconditional logistic regression models.

Results—Current smoking was associated with a significant 30 % increased risk of follicular lymphoma (n = 1,176) but not NHL overall or other NHL subtypes. The association was similar among *NAT2* slow (OR 1.36; 95 % CI 1.07–1.75) and intermediate/rapid (OR 1.27; 95 % CI 0.95–1.69) acetylators ($p_{\text{interaction}}$ = 0.82) and also did not differ by *NAT1*10* allelotype. Neither *NAT2* phenotype nor *NAT1*10* allelotype was associated with risk of NHL overall or NHL subtypes.

Conclusion—The current findings provide further evidence for a modest association between current smoking and follicular lymphoma risk and suggest that this association may not be influenced by variation in the *N*-acetyltransferase enzymes.

Keywords

Non-Hodgkin lymphoma; Gene environment interaction; Cigarette smoking; *N*-acetyltransferase; Follicular lymphoma

Introduction

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of malignant neoplasms that arise from lymphoid tissues at various stages of differentiation. Other than the importance of immune dysregulation and certain infections, the etiology of NHL is not well understood [1]. Numerous studies examining the role of tobacco smoking in NHL risk have yielded inconsistent results, although these studies were generally underpowered to investigate NHL subtype-specific associations [2]. Previously, a large pooled analysis in the international lymphoma epidemiology consortium (InterLymph) found that current smokers had a statistically significant 30 % increased risk of follicular lymphoma compared with never smokers [3], while a multicenter case–control study in Europe did not find a significant association [4]. Given this potential modest subtype-specific association, further evidence is needed to elucidate a possible role for smoking in risk of follicular lymphoma and other NHL subtypes.

Cigarettes contain numerous carcinogenic compounds, many of which are activated or deactivated by xenobiotic-metabolizing enzymes [5]. The *N*-acetyltransferase enzymes, NAT1 and NAT2, metabolize aromatic and heterocyclic amines and can lead to detoxification or activation of tobacco-derived carcinogens [6]. The activity of these enzymes can vary between individuals, and the relative activity can be predicted via determination of genotypes for specific single nucleotide polymorphisms (SNPs) in the *NAT1* and *NAT2* genes. These genetic variations with known functional consequences for NAT1 or NAT2 activity have been demonstrated conclusively to modify risk for bladder cancer, particularly among cigarette smokers [7], indicating a mechanistic role for aromatic or heterocyclic amines such as those found in cigarettes. Differing susceptibility due to genetic variation in metabolic enzymes such as the *N*-acetyltransferases could account for the inconsistent associations observed between smoking and NHL risk. The few previous studies that have examined the combined effects of *NAT1* or *NAT2* genetic variants and smoking on risk of NHL have not had sufficient sample size to investigate NHL subtypes [8–10].

We conducted a pooled analysis in seven case–control studies from the InterLymph consortium to examine associations between smoking, *NAT1* or *NAT2* variability, and risk of NHL and NHL subtypes. These new analyses included more than 3,700 NHL cases and 3,400 controls that were not examined in the earlier InterLymph smoking analysis [3]. Furthermore, an interaction between smoking and *NAT* variability on risk of NHL or NHL subtypes would support a mechanistic role for components of cigarette smoke in lymphoma carcinogenesis.

Materials and methods

Study population

Seven case–control studies with available data on cigarette smoking status and *NAT1* or *NAT2* genotypes were identified through the InterLymph consortium. The seven studies included four from the United States (Nebraska [10], National Cancer Institute-Surveillance Epidemiology End Results (NCI-SEER) [11], Yale University/Connecticut (Yale) [12], and University of California at San Francisco (UCSF2) [13]), two from Europe (Scandinavian Lymphoma Etiology (SCALE) [14], and EpiLymph [15]), and one from Australia (New South Wales [16]). Genotype data for *NAT1* were available for four studies (New South Wales, Nebraska, NCI-SEER, Yale), whereas *NAT2* data were available for six studies (all but New South Wales). Methodological details of the individual studies have been published previously [10–16] and are summarized in Table 1. Analyses were restricted to non-

Hispanic white participants. Each participating study obtained informed consent from participants and approval from local human subjects committees.

Exposure assessment

Each study obtained detailed information on smoking behaviors, demographics, and potential confounders via in-person or telephone interviews. Each then provided original, individual-level de-identified data to a central data-coordinating center for harmonization of variables according to pre-specified rules. Smoking status was classified as never (never smoked more than 100 cigarettes or never smoked regularly for more than 6 months), former (quit at least 12 months before cancer diagnosis for cases or interview for controls), or current (currently smoking or quit in the prior 12 months). Other smoking variables harmonized from individual study data included frequency, duration, total pack-years, age at start of smoking, and years since quitting for former smokers. Potential confounders included age (<50, 50–59, 60–69, 70+), sex, socioeconomic status (low, medium, and high based on education for all studies except New South Wales, which grouped a deprivation indicator from census data into tertiles), and history of alcohol consumption (drinker, non-drinker, missing; not available for UCSF2 and SCALE).

Genotyping and phenotype assignment

Genotype data were collected for four *NAT1* (rs15561, rs1057126, rs4987076, and rs13249533) and six *NAT2* (rs1208, rs1041983, rs1799929, rs1799930, rs1799931, and rs1801280) SNPs. Specific *NAT1* and *NAT2* SNPs were selected to infer *NAT1* allelotype (**3*, **4*, **10*, **11*, **11A*, **11B,* or **14A*) and *NAT2* acetylation activity (phenotype: slow, intermediate, or rapid acetylation), as described previously [9, 17, 18]. Genotyping was conducted by the individual studies and utilized Taqman (New South Wales [19], NCI-SEER [9], Yale [8], UCSF2 [20]), Illumina GoldenGate (Epilymph [21]), Sequenom (SCALE [22]), or PCR–RFLP (Nebraska [10]) methodology. Not all SCALE participants had sufficient genotype data for accurate phenotype inference, so we included only the 72 % of participants with *NAT2* phenotype inferred with high confidence based on sufficient genotype data. No participants in the UCSF2 study had sufficient data on the six SNP panel to infer *NAT2* phenotype. We thus included the 43 % of UCSF2 participants who had data from a genomewide association study [20] for the tag SNP rs1495741, which has been shown to predict *NAT2* phenotype with high accuracy in populations of European descent [23]. Only non-Hispanic white participants were included in the analyses, and the distribution of inferred *NAT2* phenotypes for UCSF2 was similar to that observed for the other studies (Table 2). For both SCALE and UCSF2, distributions of smoking variables and potential confounders among controls were similar between included participants and those excluded due to insufficient genotype data (not shown).

Case ascertainment and classification

Cases of incident, histologically confirmed NHL (excluding plasma cell neoplasms) were identified, and NHL subtypes were grouped according to the World Health Organization (WHO) classification [24] using InterLymph Pathology Working Group guidelines [25].

Statistical methods

Pooled odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were computed as estimates of relative risk of NHL in joint fixed effects unconditional logistic regression models, with NHL subtypes analyzed using polytomous models. Heterogeneity by study was investigated to determine suitability of the fixed effects models. For both pooled and study-specific estimates, multivariable models included age group and sex, as these were matching factors for most studies. All models included adjustment for study center using the 16

centers within the seven participating studies. Additional adjustment for socioeconomic status or alcohol consumption did not alter risk estimates. Wald χ^2 tests with a multiplicative interaction term between the factor of interest and study were employed with all models to test for heterogeneity by study or study center. Likelihood ratio tests yielded similar results in all analyses. We first separately examined main effects of smoking status and *NAT1* or *NAT2* variation on risk of NHL and NHL subtypes. Investigation of *NAT1* compared participants having one or two copies of the *NAT1*10* allele with those having no copies of the *NAT1*10* allele, as has been done in previous studies of *NAT1* variation and cancer risk [8, 9]. Evidence suggests that the *NAT1*10* and *NAT1*11* allelotypes are associated with increased NAT1 acetylation activity, so we also examined *NAT1* phenotypes inferred from the presence (rapid or intermediate acetylation) or absence (slow acetylation) of these alleles [26]. *NAT2* comparisons were based on phenotypes assigned from genotype data as described [18]. We then investigated the associations between smoking status and NHL and its subtypes, stratified by *NAT2* phenotype or *NAT1* allelotype. Statistical interaction was assessed as a multiplicative cross-product term for smoking status and *NAT1* allelotype or *NAT2* phenotype in multivariable models. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

In a pooled analysis of original data for 5,026 NHL cases and 4,630 controls from seven case–control studies (Table 2), current cigarette smoking was associated with a significantly increased risk of follicular lymphoma (n = 1,176; OR 1.34; 95 % CI 1.12–1.59 compared to never smoking) but not NHL overall or any other NHL subtype (Table 3). Notably, the association remained (OR 1.30; 95 % CI 1.06–1.60) when the analysis was restricted to the four studies (Nebraska, Epilymph, SCALE, and UCSF2; n = 3,752 NHL cases with 796 follicular lymphoma cases; 3,400 controls) that were not included in the previous InterLymph smoking analysis [3]. Former smoking was not associated with follicular lymphoma risk. Among current smokers, risk was increased for those with greater intensity (≥10 vs. <10 cigarettes/day: OR 1.61, 95 % CI 1.09–2.40), duration (>15 vs. ≤15 years: OR 3.55, 95 % CI 1.80–6.98), or pack-years (≥10 vs. <10 pack-years: OR 2.01; 95 % CI 1.26–3.19) of exposure, although there was not a significant linear dose-response.

We were able to infer *NAT2* phenotypes for 4,421 NHL cases (968 follicular lymphoma cases) and 4,095 controls, and *NAT1* allelotypes for 1,528 NHL cases (455 follicular lymphoma cases) and 1,586 controls. Among the subgroups with available *NAT2* or *NAT1* data, associations between current smoking and risk of follicular lymphoma, NHL, and other NHL subtypes were similar to those observed in the entire study population (data not shown). Inferred *NAT2* phenotype was not associated with follicular lymphoma risk (Table 4), and stratification by *NAT2* phenotype revealed similar positive associations between current smoking and follicular lymphoma risk among slow (OR 1.36; 95 % CI 1.07–1.75) and intermediate and rapid (OR 1.27; 95 % CI 0.95–1.69) acetylators ($p_{\text{interaction}}$ = 0.82). Similarly, neither the presence of the *NAT1*10* allele (Table 4) nor the inferred rapid *NAT1* phenotype (data not shown) had a significant impact on the smoking-follicular lymphoma association ($p_{\text{interaction}}$ = 0.32 and 0.84, respectively).

Analyses of associations between smoking and overall NHL risk were null in the pooled data (Table 3) and in the individual studies (Tables S1 and S2). Similarly, neither *NAT2* phenotype nor *NAT1*10* allelotype was associated with risk of NHL overall or NHL subtypes. There were also no significant associations with individual *NAT2* or *NAT1* SNPs, although there was a suggestive inverse association between having minor alleles for rs1799930 and risk of follicular lymphoma (OR 0.95; 95 % CI 0.89–1.01, assuming an additive model). Stratified analyses investigated whether *NAT2* phenotype or *NAT1*10*

allelotype would affect the null associations between current smoking and risk of NHL or subtypes, but results were generally similar among different *NAT2* phenotypes or *NAT1* allelotypes (Table S3). However, a significant interaction based on a small number of cases (<15 per stratum) was observed between *NAT1*10* allelotype and ever smoking for mantle cell lymphoma (OR 1.29; CI 0.60–2.78 for no *NAT1*10* alleles; OR 0.34; CI 0.12–0.92 for at least one *NAT1*10* allele; $p_{\text{interaction}} = 0.03$). No significant heterogeneity of results by study was found for any of the pooled analyses.

Discussion

In this pooled analysis of 9,656 participants from seven NHL case–control studies in the United States, Europe, and Australia, current smoking was associated with a significantly increased risk of follicular lymphoma. This result confirms the association identified in a previous InterLymph smoking pooled analysis [3], with 796 (68 %) of the 1,176 follicular lymphoma cases in this study having not been included in the previous study. Although we did not observe a strong linear dose-response with intensity or duration of exposure, categorical analyses demonstrated increased follicular lymphoma risk among heavier smokers and individuals who smoked for a longer period. In addition, our study showed that the association between smoking and follicular lymphoma was not significantly modified by acetylation status, as measured by *NAT2* phenotype or *NAT1*10* allelotype. This finding suggests that NAT1 or NAT2 substrates in cigarette smoke are not prominently involved in follicular lymphoma carcinogenesis, but enzyme activity was not measured directly and some role for these substrates remains possible. Genetic variations in other carcinogen-metabolizing pathways could play a role as well. The cytochrome P-450 (CYP) enzymes have been associated with risk of smoking-related cancers [27], although studies of *CYP* variation and NHL risk have not generally yielded strong associations [28–32].

While case–control studies support a positive association between current smoking and follicular lymphoma, results from prospective cohort studies have been mixed [33–37]. Some studies observed positive associations [34, 36], but two large cohort studies reported an inverse association with current smoking based on 257 and 161 follicular lymphoma cases [33, 37]. The authors of these studies suggest the observed protective associations are implausible and likely due to confounding or chance, but the observations remain unexplained. Strong dose–response associations have generally not been observed for case–control or cohort studies. One study reported a stronger association between smoking and NHL risk when women with exposure to passive smoking were excluded from the reference category [34]. The associations we observed for follicular lymphoma may be attenuated by exposure of never smokers to passive smoking, but data on passive smoke exposure were not available.

In contrast to some previous reports based on much smaller samples [8, 9], we did not observe any associations between *NAT2* inferred phenotypes or *NAT1* allelotypes and risk of NHL or NHL subtypes. Pooling of data from multiple studies yielded 8,516 participants for *NAT2* analyses and 3,114 participants for *NAT1* analyses, with no indication of significant heterogeneity across studies. These pooled results, representing the largest examination of *NAT1* and *NAT2* genetic variability and NHL risk yet reported, do not support an association between inferred *NAT1* allelotype or *NAT2* phenotype and risk of NHL or subtypes. The inferred rapid acetylation phenotype was relatively rare (6 % of cases), and misclassification of phenotype is possible when inferred from genotypes [38], so further study may be warranted.

This large pooled analysis enabled examination of associations between smoking and NHL subtypes stratified by *NAT1* or *NAT*2 status that was not possible in individual studies.

However, even with pooling the power for stratified examinations of rare subtypes was low. We report an interaction between *NAT1*10* allelotype and ever smoking for risk of mantle cell lymphoma, but given the small number of cases and large number of comparisons, this finding may be attributed to chance. The use of original data allowed for harmonization of exposures across studies, and a central coordinating center facilitated accurate pooling and harmonization. Classification of NHL subtypes may be a source of variability, which we addressed by using a single group of pathologists and epidemiologists to review the subtype classifications. Given the lack of association observed for all other subtypes, any misclassification of follicular lymphomas would be expected to attenuate the observed association with current smoking. Genotyping platforms varied across studies, and we excluded some participants from the UCSF2 and SCALE studies due to insufficient genotype data, but genotype methodology and availability were unlikely to be associated with smoking and thus were unlikely to introduce bias. *NAT2* phenotypes were inferred for UCSF2 participants using the tag SNP rs1495741; the distribution of the resulting phenotypes was similar to that in the other studies, and UCSF2 results were not materially different from those of the pooled analyses.

The current findings provide further evidence supporting a modest association between current smoking and follicular lymphoma risk, and they suggest that this association may not be strongly influenced by established variation in the *N*-acetyltransferase genes. Further research is warranted to fully understand the association between smoking and follicular lymphoma, particularly given the lack of linear dose–response associations and inconsistent reports in prospective cohort studies [33–37].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Methods and characteristics of the individual studies included in the InterLymph pooled analysis of smoking, *NAT1/2* genetic variation, and NHL risk

Study name	Location	Years	Age (years)	Matching variables	Cases		Controls			Genotyping platform
					n^a	Participation rate^b (%)	n^a	Participation rate^b (%)	Source	
New South Wales (NSW)	New South Wales, Australian Capital Territory, Australia	2000–2002	20–74	Age, sex, state or territory	485	85	434	61	Random selection from electoral rolls	Taqman
Nebraska	Nebraska	1999–2002	20–75	Age, sex	317	74	417	78	RDD	PCR–RFLP
NCI-SEER	Detroit, MI, USA; Iowa; Los Angeles, CA, USA; Seattle, WA, USA	1998–2001	20–74	Age, sex, study site	360	76	306	52	<65 years: RDD; ≥65 years: random selection from CMMS files	Taqman
Epilymph Studies	Spain	1998–2003	17–96	Age, sex, region	254	82	305	96	Hospital-based^c	Illumina GoldenGate
	Germany	1999–2002	18–82	Age, sex, region	389	87	513	44	Random selection from population registries	Illumina GoldenGate
	Ireland	1998–2004	19–85	Age, sex, region	76	90	98	75	Hospital-based^c	Illumina GoldenGate
	Czech Republic	2001–2003	19–82	Age, sex, region	157	90	227	60	Hospital-based^c	Illumina GoldenGate
	France	2000–2003	18–82	Age, sex, region	120	91	143	74	Hospital-based^c	Illumina GoldenGate
	Italy (Sardinia)	1998–2004	25–81	Age, sex, region	85	93	110	66	Random selection from population registries	Illumina GoldenGate
Yale	New Haven, CT, USA	1995–2001	21–84	Age	429	72	490	RDD: 69 CMMS: 47	<65 years: RDD; ≥65 years: random selection from CMMS files	Taqman
SCALE	Denmark, Sweden	1999–2002	18–74	Age, sex, country	1,849	81	1,027	71	Random selection from population registries	Sequenom
UCSF2	San Francisco, CA, USA	2001–2006	20–84	Age, sex, region	505	70	560	68	<65 years: RDD; ≥65 years: random selection from CMMS files	Taqman

RDD random digit dialing, *CMMS* Centers for Medicare and Medicaid Services

[a] Participants with data on smoking status and either *NAT1* or *NAT2* genotype were included

[b] Participation rate (%) in the overall case-control study

[c] Patients admitted to hospital for infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic, or respiratory conditions

Table 2

Distribution of selected variables among cases and controls in the InterLymph smoking and *NAT1* or *NAT2* pooled analyses and individual studies

	Pooled		New South Wales		Nebraska		NCI-SEER		Epilymph		Yale		SCALE		UCSF-2	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Total (*n*)	5,026	4,630	485	434	317	417	360	306	1,081	1,396	429	490	1,849	1,027	505	560
Age (%)																
<50	20	23	24	21	27	24	27	18	24	32	19	19	16	20	14	14
50–59	26	22	31	29	19	25	24	21	21	19	21	18	31	25	25	22
60–69	32	31	30	34	30	29	30	37	32	27	25	22	35	37	30	32
70+	22	24	15	17	25	22	19	24	23	22	35	41	18	17	32	32
Female (%)	48	51	41	42	45	47	47	47	45	45	100	100	41	47	44	43
Education/SES (%)																
Less than HS	37	34	33	34	42	43	41	36	49	43	40	36	34	25	17	19
High school (HS)	33	37	34	36	30	27	29	28	38	44	34	30	34	42	25	29
More than HS	29	29	33	30	28	30	30	36	13	14	25	33	32	31	57	52
Smoking (%)																
Never	45	45	44	46	52	51	46	44	47	45	43	46	44	41	44	45
Former	36	35	41	41	35	32	34	40	31	31	44	40	36	34	42	43
Current	18	19	15	13	14	17	19	16	22	24	13	13	20	25	13	12
NAT2 phenotype (%)[a]																
Slow	57	58	–	–	59	58	52	60	58	59	57	61	56	53	61	60
Intermediate	37	37	–	–	36	37	45	35	37	36	36	34	37	41	34	34
Rapid	6	5	–	–	6	5	4	5	5	6	7	5	7	5	4	6
NAT1 allelotype (%)[b]																
**Any/*any*[c]	65	66	65	64	71	68	65	71	–	–	63	62	–	–	–	–
**Any/*10*	31	31	32	32	26	28	31	26	–	–	33	35	–	–	–	–
**any*10/*10*	4	4	4	4	3	4	5	3	–	–	4	4	–	–	–	–
Subtype[d] (% cases)																
Follicular	22	–	37	–	32	–	27	–	17	–	24	–	19	–	32	–
DLBCL	30	–	32	–	27	–	35	–	33	–	32	–	25	–	37	–
CLL/SLL	23	–	3	–	7	–	10	–	27	–	10	–	25	–	30	–

	Pooled		New South Wales		Nebraska		NCI-SEER		Epilymph		Yale		SCALE		UCSF-2	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
MCL	4	–	4	–	4	–	3	–	4	–	2	–	5	–	0	–
MZL	6	–	10	–	10	–	6	–	10	–	7	–	4	–	<1	–
Peripheral T cell	3	–	2	–	3	–	2	–	4	–	3	–	4	–	<1	–
MF/SS	2	–	1	–	2	–	2	–	2	–	2	–	2	–	<1	–
Other	11	–	12	–	16	–	15	–	2	–	20	–	16	–	<1	–

New South Wales, Nebraska (316 cases, 416 controls), NCI-SEER (300 cases, 258 controls), and Yale (427 cases, 478 controls) contributed to the *NAT1* analyses

Nebraska (317 cases, 417 controls), NCI-SEER (262 cases, 225 controls), Yale (407 cases, 470 controls), Epilymph, SCALE, and UCSF2 contributed to the *NAT2* analyses

NCI-SEER National Cancer Institute-Surveillance Epidemiology End Results, *SCALE* Scandinavian lymphoma epidemiology, *UCSF* University of California at San Francisco

[a] Among participants with *NAT2* genotype data

[b] Among participants with *NAT1* genotype data

[c] *NAT1* allelotype inferred as *NAT1*10* or *NAT1*any* (**any* includes **3, *4, *11, *11A, *14B*) based on genotype data for four *NAT1* SNPs

[d] Subtype abbreviations: *DLBCL* diffuse large B cell lymphoma, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *MCL* mantle cell lymphoma, *MZL* marginal zone lymphoma, *MF/SS* mycosis fungoides/sezary syndrome

Table 3

Multivariable odds ratios and 95 % confidence intervals for the associations between smoking and risk of NHL and NHL subtypes in the pooled InterLymph data set

	Non-Hodgkin Lymphoma		Follicular Lymphoma		DLBCL[b]		CLL/SLL[b]		MZL[b]		MCL[b]		PTCL[b]		MF/SS[b]	
	Cases/controls	**OR[a] (95 % CI)**	**Cases**	**OR**	**Cases**	**OR**	**Cases**	**OR**	**Cases**	**OR**	**Cases**	**OR**	**Cases**	**OR**	**Cases**	**OR**
Smoking status																
Never	2,278/2,082	1.00	521	1.00	705	1.00	469	1.00	142	1.00	75	1.00	66	1.00	32	1.00
Current	922/893	0.99 (0.89–1.11)	278	1.34 (1.12–1.59)	248	0.86 (0.73–1.02)	161	0.82 (0.67–1.01)	60	1.11 (0.80–1.53)	40	1.18 (0.78–1.77)	35	1.14 (0.74–1.74)	14	0.82 (0.43–1.57)
Former	1,826/1,655	1.01 (0.92–1.11)	377	0.94 (0.81–1.09)	558	1.01 (0.89–1.15)	390	0.97 (0.82–1.13)	110	1.07 (0.82–1.39)	80	1.16 (0.83–1.62)	57	1.22 (0.84–1.77)	34	1.39 (0.84–2.30)
$p_{\text{homogeneity by study}}$		0.70		0.59		0.85		0.62		0.90		0.67		0.86		0.58

[a] Adjusted for age, sex and study center

[b] Subtype abbreviations: *DLBCL* diffuse large B cell lymphoma, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *MZL* marginal zone lymphoma, *MCL* mantle cell lymphoma, *PTCL* peripheral T cell lymphoma, *MF/SS* mycosis fungoides/sezary syndrome

Table 4

Associations of *NAT2* phenotype and *NAT1* allelotype and risk of follicular lymphoma in the pooled study populations and associations of smoking status with risk of follicular lymphoma stratified by *NAT2* phenotype and by *NAT1* allelotype

	Follicular lymphoma	
	Cases/controls	**OR (95 % CI)**
NAT2 phenotype[a,b]		
Slow	543/2,366	1.00
Intermediate	371/1,507	1.06 (0.91–1.23)
Rapid	54/222	1.08 (0.79–1.48)
Rapid/int	425/1,729	1.06 (0.92–1.23)
NAT2 slow		
Never smoking	246/1,056	1.00
Former smoking	159/840	0.86 (0.69–1.08)
Current smoking	138/470	1.36 (1.07–1.75)
NAT2 intermediate/rapid		
Never smoking	182/780	1.00
Former smoking	148/605	1.07 (0.83–1.38)
Current smoking	95/344	1.27 (0.95–1.69)
$p_{interaction}$		0.82
NAT1 allelotype[c]		
**Any/*any*	295/1,040	1.00
**Any/*10*	139/484	1.00 (0.79–1.26)
**10/*10*	21/62	1.14 (0.68–1.92)
At least one **10*	160/546	1.02 (0.81–1.27)
*NAT1*any/*any*		
Never smoking	141/495	1.00
Former smoking	98/383	0.95 (0.71–1.28)
Current smoking	56/162	1.11 (0.77–1.61)
At least one *NAT1*10 allele*		
Never smoking	0/246	1.00
Former smoking	54/225	0.82 (0.54–1.24)
Current smoking	36/75	1.53 (0.93–2.51)
$p_{interaction}$		0.32

[a] *NAT2* phenotype inferred as slow, intermediate, or rapid acetylation based on genotype data for six *NAT2* SNPs

[b] *NAT2* phenotype inferred based on genotype data for tag SNP rs1495741 for UCSF2 participants

[c] *NAT1* allelotype inferred as *NAT1*10* or *NAT1*any* (**any* includes **3,*4,*11,*11A,*14A*) based on genotype data for four *NAT1* SNPs