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Occupational solvent exposure, genetic variation in immune genes, and the risk for non-Hodgkin lymphoma

Qian Deng^{a,c}, Tongzhang Zheng^c, Qing Lan^d, Yajia Lan^a, Theodore Holford^c, Yingtai Chen^b, Min Dai^b, Brian Leaderer^c, Peter Boyle^f, Stephen J. Chanock^{d,e}, Nathaniel Rothman^c, and Yawei Zhang^c

^aDepartment of Occupational and Environmental Health, West China School of Public Health, Sichuan University, Chengdu, Sichuan

^bCancer Institute/Hospital, Chinese Academy of Medical Sciences, Beijing, China

^cDepartment of Epidemiology and Public Health, Yale University School of Public Health, New Haven, Connecticut

^dDepartment of Health and Human Services, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville

^eCore Genotyping Facility, Advanced Technology Center, National Cancer Institute, NIH, DHHS, Gaithersburg, Maryland, USA

^fInternational Prevention Research Institute, Lyon, France

Abstract

Solvent exposure has been inconsistently linked to the risk for non-Hodgkin lymphoma (NHL). The aim of this study was to determine whether the association is modified by genetic variation in immune genes. A population-based case-control study involving 601 incident cases of NHL and 717 controls was carried out in 1996–2000 among women from Connecticut. Thirty single nucleotide polymorphisms in 17 immune genes were examined in relation to the associations between exposure to various solvents and the risk for NHL. The study found that polymorphism in interleukin 10 (*IL10*; rs1800890) modified the association between occupational exposure to organic solvents and the risk for diffuse large B-cell lymphoma ($P_{\text{for interaction}}=0.0058$). The results remained statistically significant after adjustment for false discovery rate. Compared with women who were never occupationally exposed to any organic solvents, women who were exposed to organic solvents at least once had a significantly increased risk for diffuse large B-cell lymphoma if they carried the *IL10*(rs1800890) TT genotype (odds ratio=3.31, 95% confidence interval: 1.80–6.08), but not if they carried the AT/AA genotype (odds ratio=1.14, 95% confidence interval: 0.72–1.79). No significant interactions were observed for other immune gene single nucleotide polymorphisms and various solvents in relation to NHL overall and its major subtypes. The study provided preliminary evidence supporting a role of immune gene variations in modifying the association between occupational solvent exposure and the risk for NHL.

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Correspondence to Yawei Zhang, MD, PhD, Yale University School of Public Health, 60 College Street LEPH 440, New Haven, CT 06520, USA Tel: +1 203 785 6210; fax: +1 203 737 6023; yawei.zhang@yale.edu.

Conflicts of interest

There are no conflicts of interest.

Keywords

immune genes; non-Hodgkin lymphoma; occupational exposure; single nucleotide polymorphism; solvents

Introduction

Organic solvents are a group of solvents that have carbon in their structure and have been used in many industrial settings. As a substantial increase in mortality due to non-Hodgkin lymphoma (NHL) was first observed among men with potential exposure to solvents (Vianna and Polan, 1979), numerous efforts have been made to explore the association between occupational exposure to solvents and the risk for NHL (Smith and Lickiss, 1980; Cartwright *et al.*, 1988; Wong and Raabe, 2000; Rego *et al.*, 2002; Kato *et al.*, 2005; Zhao *et al.*, 2005; Mandel *et al.*, 2006; Wang *et al.*, 2009; Purdue *et al.*, 2011). Although some studies have reported an increased risk for NHL associated with organic solvents (Cartwright *et al.*, 1988; Rego *et al.*, 2002; Kato *et al.*, 2005), such as benzene (Smith and Lickiss, 1980; Zhao *et al.*, 2005), trichloroethylene (Purdue *et al.*, 2011), carbon tetrachloride, and formaldehyde (Wang *et al.*, 2009), other studies did not support the associations (Wong and Raabe, 2000; Mandel *et al.*, 2006; Seidler *et al.*, 2007; Tranah *et al.*, 2009; Alexander and Wagner, 2010). A meta-analysis including 26 cohorts of petroleum workers exposed to benzene (Wong and Raabe, 2000) and a metaanalysis including 14 cohort and four case-control studies on workers exposed to trichloroethylene (Mandel *et al.*, 2006) did not observe an increased risk for NHL. The inconsistent results from previous studies could be because of the potential misclassification of exposure to solvents. In addition, genetic susceptibility in different populations may have also contributed toward the conflicting results (Barry *et al.*, 2010).

NHL is a heterogeneous group of diseases arising from the immune system. The only established risk factor for NHL is immune dysregulation resulting from various medical conditions, medication use, and infections (La Vecchia *et al.*, 1992; Muller *et al.*, 2005). Genetic variations in immune genes have been reported to be associated with the risk for NHL (Lan *et al.*, 2006; Purdue *et al.*, 2007; Colt *et al.*, 2009). For example, interleukin 10 (*IL10*) and tumor necrosis factor (*TNF*) are genes coding for immunoregulatory cytokines that are key mediators of inflammation, apoptosis, and Th1/Th2 balance, and function as autocrine growth factors in lymphoid tumors (Khatri and Caligiuri, 1998; Aggarwal, 2003). A pooled analysis of eight case-control studies suggested that the *TNF*(rs1800629) AA genotype was associated with 25 and 65% increased risks for NHL overall and diffuse large B-cell lymphoma (DLBCL), respectively, compared with those for the GG genotype (Rothman *et al.*, 2006). The study also found that the *IL10*(rs1800890) AA genotype was associated with 19 and 28% increased risks for NHL overall and DLBCL, respectively, compared with those in the TT genotype (Rothman *et al.*, 2006). The association was further confirmed by updated pooled analyses with additional studies (Skibola *et al.*, 2010).

Given the identified role of genetic polymorphisms of immune genes in NHL tumorigenesis and the potential association between occupational exposure to solvents and the risk for NHL, we analyzed data from a population-based case-control study in Connecticut to examine whether the relationship between occupational exposure to solvents and the risk for NHL varies according to polymorphisms in a number of immune genes.

Methods

Study population

A detailed description of the study population has been published elsewhere (Zhang *et al.*, 2004; Wang *et al.*, 2009). Briefly, NHL cases were histologically confirmed incident cases (International Classification of Diseases for Oncology, 2nd edition, codes M-9590-9642, 9690-9701, 9740-9750) that were diagnosed between 1996 and 2000; the patients were aged between 21 and 84 years without a history of any cancers, except nonmelanoma skin cancer, were female residents of Connecticut, and were alive at the time of interview. A total of 601 of 832 patients identified with incident NHL (72%) completed in-person interviews. All NHL cases were histologically confirmed by study pathologists and were classified according to the 2001 World Health Organization classification (Jaffe and Vardiman, 2001).

Population-based controls were recruited through random digit dialing for women aged younger than 65 years and through Centers for Medicare and Medicaid services (CMMS) files for those aged 65 years or older, with participation rates of 69 and 47%, respectively. A total of 717 controls completed in-person interviews. Patients and controls were frequency matched by age within 5-year groups. Of the 601 patients and 717 controls, 518 patients and 597 controls donated blood or buccal-cell samples. The study was approved by the Institutional Review Boards at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute.

Interview

Exposure assessment of solvents has been described previously (Wang *et al.*, 2009). Briefly, a standardized, structured questionnaire was administered to study participants to collect information on employment history including job/industry titles and employment dates. These self-reported jobs and industries were coded on the basis of the 1980 Standard Occupational Classification Manual (US Department of Commerce, 1980) and the 1987 Standard Industrial Classification Manual (Office of Management and Budget, 1987) and then linked to a generic job-exposure matrix developed by the National Cancer Institute's industrial hygienists to assess solvent exposures (Dosemeci *et al.*, 1994). The job-exposure matrix included the probability and intensity of exposure (ordinal categories) for each job and industry for any organic solvent, any chlorinated solvent, benzene, formaldehyde, and a number of individual chlorinated solvents, including chloroform, carbon tetrachloride, dichloromethane, dichloroethane, methyl chloride, and trichloroethylene.

Genotyping

Phenol–chloroform extraction was used to isolate DNA from the blood and buccal-cell samples. Genotyping was carried out at the National Cancer Institute's Core Genotyping Facility (<http://cgf.nci.nih.gov>). All TaqMan assays (Applied Biosystems, Foster City, California, USA) for this study were optimized on the ABI 7900HT detection system with 100% concordance with sequence analysis of 102 individuals as listed on the SNP500Cancer website (<http://snp500cancer.nci.nih.gov>). A total of 39 single nucleotide polymorphisms (SNPs) in 20 Th1/Th2 immune genes were selected for genotyping on the basis of the following criteria: minor allele frequencies more than 5%, laboratory evidence of function, or previous association with human disease studies. Because of the limited amount of DNA available from participants who provided only buccal cells, we first genotyped participants who provided a blood sample. If there was suggestive evidence, or if we had a relatively high suspicion that a given SNP was associated with a risk for NHL, genotype analysis would include participants who provided only buccal-cell samples.

Duplicate samples from 100 study participants and 40 replicate samples from each of two blood donors were interspersed throughout the plates used for genotype analysis. As reported previously, the concordance rates for quality control samples were between 99 and 100% for all assays. The genotype frequencies for four SNPs (rs1059293, rs231775, rs2243250, and rs2070874) analyzed using a χ^2 -test ($P < 0.05$) were not consistent with Hardy–Weinberg equilibrium among non-Hispanic white controls and were excluded from the final analysis. Another five SNPs (rs2069822, rs2069818, rs2069807, rs3024509, and rs361525) with a minor allele frequency less than 10% were also excluded from the final analysis. A total of 30 SNPs in 17 Th1/Th2 genes, *IFNG* (rs1861494, rs2069705), *IFNGR1* (rs3799488), *IFNGR2* (rs9808753), *IL10RA* (rs9610), *IL12A* (rs568408, rs582054), *IL13* (rs20541, rs1800925, rs1295686), *IL15* (rs10833), *IL15RA* (rs2296135), *IL2* (rs2069762), *IL4* (rs2243248, rs2243290, rs2243268), *IL4R* (rs2107356), *IL5* (rs2069812), *IL6* (rs1800795, rs1800797), *IL7R* (rs1494555), *JAK3* (rs3008), *IL10* (rs1800871, rs1800872, rs1800896, rs3024496, rs3024491, rs1800890), and *TNF* (rs1800629, rs1799724), were included in the final analysis.

Statistical analysis

Solvent exposure variables were presented as dichotomous ever/never exposure metrics because of the small cell counts for some solvents within genotype strata. In addition, the numbers with exposure to several individual solvents were low; the final analyses were carried out for any organic solvents, any chlorinated solvents, trichloroethylene, benzene, and formaldehyde. To increase the statistical power, heterozygous and homozygous variant genotypes were combined for all genes. Unconditional logistic regression models were used to determine odds ratios (ORs) and 95% confidence intervals (CIs) for associations between various solvents and the risk for NHL within each genotype stratum adjusted for age (continuous) and race (white/nonwhite). Additional adjustment for a family history of hematopoietic cancers, alcohol consumption, tobacco smoking, education, and medical history of immune-related disease did not markedly alter effect estimates, and thus, these variables were not included in the final models. Statistical significance was defined at the 0.05 level on the basis of two-sided tests. The significance of immune gene–solvent interaction was assessed by including an interaction term in the logistic regression models. The false discovery rate (FDR) method set at 0.2 was used to control for multiple comparisons (Benjamini, 1995). All statistical analyses were performed using the SAS software (version 9.1; SAS Institute Inc., Cary, North Carolina, USA).

Results

As shown in Table 1, genetic polymorphism in *IL15RA* (rs2296135) significantly modified the association between occupational exposure to organic solvents and the risk for NHL overall ($P_{\text{for interaction}} = 0.0195$), whereas *IL10* (rs1800890), *IL15RA* (rs2296135), *IL4* (rs2243248), and *IL10* (rs1800896) significantly modified the association between organic solvents and the risk for DLBCL ($P_{\text{for interaction}} = 0.0058, 0.0275, 0.0262$, and 0.0240 , respectively). After adjustment for FDR, an interaction with the *IL10* (rs1800890) polymorphism in the risk for DLBCL remained statistically significant. Compared with women who were never occupationally exposed to organic solvents, women who were exposed to organic solvents at least once had a significantly increased risk for DLBCL if they carried the *IL10* (rs1800890) TT genotype (OR=3.31, 95% CI: 1.80–6.08), but not if they carried AT/AA genotypes (OR=1.14, 95% CI: 0.72–1.79).

For occupational exposure to chlorinated solvents, a significant interaction with *IL12A* (rs582054) was observed for NHL overall ($P_{\text{for interaction}} = 0.0169$), DLBCL ($P_{\text{for interaction}} = 0.0423$), and follicular lymphoma ($P_{\text{for interaction}} = 0.0201$; Table 1). A significant interaction with *IL7R* (rs1494555) was only observed for NHL overall

($P_{\text{for interaction}}=0.0275$). However, none of the interactions remained statistically significant after adjustment for FDR.

Significant associations among individual solvents (i.e. trichloroethylene, benzene, and formaldehyde), immune gene polymorphisms, and the risk for NHL are presented in Table 2. Compared with women without occupational exposure to trichloroethylene, women who had undergone occupational exposure to trichloroethylene had an increased risk for NHL overall (OR=2.09, 95% CI: 1.28–3.42) and DLBCL (OR=2.66, 95% CI: 1.42–4.96) if the women carried *IL12A* (rs582054) AT/AA genotypes; however, this risk was not observed among women who carried the *IL12A* (rs582054) TT genotype. A significant interaction was observed between exposure to trichloroethylene and *IL12A* (rs582054) for NHL overall and DLBCL ($P_{\text{for interaction}}=0.0090$ and 0.0119 , respectively). After adjustment for FDR, none of these interactions, however, remained statistically significant.

For benzene exposure, significant interactions were observed for *IL10* (1800890) for DLBCL ($P_{\text{for interaction}}=0.0415$); *IL12A* (rs582054) for NHL overall ($P_{\text{for interaction}}=0.0201$) and follicular lymphoma ($P_{\text{for interaction}}=0.0468$); *TNF* (rs1800629) for follicular lymphoma ($P_{\text{for interaction}}=0.0206$); and *IL15* (rs10833) for follicular lymphoma ($P_{\text{for interaction}}=0.0406$). However, none of these interactions remained statistically significant after adjustment for FDR.

Significant interactions were also observed between occupational exposure to formaldehyde and polymorphisms in *IL6* (rs1800795, rs1800797) and *IL10* (rs1800890) for DLBCL ($P_{\text{for interaction}}=0.0279$, 0.0311 , and 0.0373 , respectively). Significant interactions were observed between exposure to formaldehyde and *IL6* (rs1800795, rs1800797) polymorphisms for follicular lymphoma risk ($P_{\text{for interaction}}=0.028$). Again, none of the interactions remained statistically significant after adjustment for FDR.

Nonsignificant interactions were observed for other immune gene polymorphisms and various solvents in relation to NHL overall and its major subtypes (data are not shown but are available directly from the corresponding author).

Discussion

For the first time, we examined the potential interactions between occupational exposure to solvents and genetic variations in 17 immune genes. Our analysis suggested that *IL10* (rs1800890), which has previously been found to be associated with the risk for NHL in several studies (Lan *et al.*, 2006; Rothman *et al.*, 2006; Skibola *et al.*, 2010), modified the association between occupational exposure to an organic solvent and the risk for DLBCL. *IL10* (rs1800890) is located in the distal region of the *IL10* promoter and is believed to be associated with *IL10* expression (Wieczorek *et al.*, 2008). The *IL10* (rs1800890) T allele results in high *IL10* production (Gibson *et al.*, 2001). High *IL10* expression can hinder the inflammatory response by inducing apoptosis in mast cells and macrophages as an immunoregulatory cytokine of T cells (Bailey *et al.*, 2006). Thus, the immunosuppressive property of *IL10* could increase susceptibility to tumorigenicity (Hori *et al.*, 2003). A cohort study reported that high serum levels of *IL10* were associated with an increased risk for B-cell NHL among individuals with acquired immunodeficiency syndrome (Breen *et al.*, 2003). A high serum level of *IL10* was also found to be associated with a poor prognosis of DLBCL (Lech-Maranda *et al.*, 2004).

However, it has been suggested that an immunologic mechanism could be involved in lymphomagenesis from solvents (Vineis *et al.*, 2007). Occupational benzene exposure has been found to impair the immune system and may contribute to the process of carcinogenesis (Brandao *et al.*, 2005). Occupational exposure to solvents (i.e. hydrocarbons

and toluene) has been reported to result in abnormal values of lymphocyte subpopulations and impaired lymphocyte functions (Lange *et al.*, 1973; Zeman *et al.*, 1990). We speculated that the impaired immune system resulting from the *IL10*(rs1800890) T allele could be more susceptible to occupational solvent exposures and act synergistically with solvents in lymphomagenesis.

The major strengths of the study include the population-based study design and histologically confirmed incident NHL cases, which minimized potential misclassification of disease. Solvent exposure was assessed by linking generic job-exposure matrixes with self-reported occupational histories; thus, possible exposure misclassification was unavoidable. Because we used dichotomous solvent variables in the current study, the effect of misclassification was expected to be attenuated. We examined a total of 30 SNPs, which increased the likelihood of false-positive findings. Therefore, we used the FDR approach to control for multiple comparisons (Hochberg, 1990). Although the study had a relatively large sample size, the power was limited for NHL subtypes. Finally, the study included only women; the findings may not be generalizable to men.

Conclusion

Our study provided preliminary evidence supporting the role of immune gene variation in modulating the association between occupational solvent exposure and the risk for NHL. A possible role of *IL10* with organic solvents warrants further investigation in larger populations.

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Table 1

Associations between occupational exposure to organic solvents and chlorinated solvents, polymorphisms in immune genes, and the risk for non-Hodgkin lymphoma

SNPs	NHL overall						B-cell lymphoma									
	Nonexposed			Exposed			Diffuse large B-cell lymphoma			Follicular lymphoma						
	Co	Ca	OR ^a	Co	Ca	OR ^a (95% CI)	Ca	OR ^a	Exposed	Ca	OR ^a (95% CI)	Ca	OR ^a	Nonexposed	Exposed	
Organic solvents																
IL15RA_02 (rs2296135)																
GG	87	72	1.0	64	41	0.74 (0.45, 1.24)	22	1.0	14	0.82 (0.39, 1.75)	12	1.0	12	1.29 (0.53, 3.12)		
GT or TT	240	182	1.0	140	160	1.56 (1.16, 2.11)	49	1.0	62	2.29 (1.48, 3.53)	48	1.0	31	1.16 (0.70, 1.92)		
<i>P</i> _{for interaction}						0.0195					0.0275				0.7745	
IL4_02 (rs2243248)																
TT	315	226	1.0	193	185	1.35 (1.04, 1.77)	59	1.0	70	1.97 (1.33, 2.91)	58	1.0	39	1.10 (0.70, 1.73)		
GT or GG	38	51	1.0	32	31	0.81 (0.42, 1.58)	18	1.0	9	0.67 (0.25, 1.78)	8	1.0	5	0.87 (0.25, 3.05)		
<i>P</i> _{for interaction}						0.1023					0.0262				0.7771	
IL10_03 (rs1800896)																
AA	116	72	1.0	68	65	1.61 (1.02, 2.54)	14	1.0	26	3.42 (1.66, 3.07)	19	1.0	12	1.25 (0.56, 2.79)		
AG or GG	243	210	1.0	160	163	1.17 (0.88, 1.56)	64	1.0	56	1.31 (0.87, 1.99)	49	1.0	38	1.14 (0.71, 1.83)		
<i>P</i> _{for interaction}						0.2404					0.0240				0.9238	
IL10_17 (rs1800890)																
TT	158	98	1.0	103	90	1.45 (0.99, 2.13)	19	1.0	39	3.31 (1.80, 6.08)	25	1.0	15	0.97 (0.48, 1.95)		
AT or AA	206	185	1.0	130	137	1.18 (0.86, 1.61)	59	1.0	43	1.14 (0.72, 1.79)	44	1.0	34	1.23 (0.74, 2.04)		
<i>P</i> _{for interaction}						0.4094					0.0058				0.5767	
Chlorinated solvents																
IL12A_07 (rs582054)																
TT	120	101	1.0	51	35	0.83 (0.50, 1.39)	32	1.0	12	0.95 (0.45, 2.00)	25	1.0	5	0.52 (0.19, 1.47)		
AT or AA	280	211	1.0	83	110	1.88 (1.33, 2.65)	63	1.0	40	2.29 (1.42, 3.70)	48	1.0	27	2.02 (1.18, 3.49)		
<i>P</i> _{for interaction}						0.0169					0.0423				0.0201	
IL7R_01 (rs1494555)																
AA	179	152	1.0	66	53	0.98 (0.64, 1.50)	47	1.0	20	1.24 (0.67, 2.28)	38	1.0	14	1.06 (0.53, 2.11)		

SNPs	NHL overall						B-cell lymphoma							
	Nonexposed			Exposed			Diffuse large B-cell lymphoma			Follicular lymphoma				
							Nonexposed			Nonexposed				
	Co	Ca	OR ^a	Co	Ca	OR ^a (95% CI)	Ca	OR ^a	Ca	OR ^a (95% CI)	Ca	OR ^a (95% CI)		
AG or GG	220	158	1.0	67	89	1.93 (1.32, 2.84)	46	1.0	31	2.32 (1.35, 3.98)	35	1.0	17	1.73 (0.90, 3.32)
<i>P</i> _{for interaction}	0.0275						0.1544						0.3480	

Ca, cases; CI, confidence interval; Co, controls; NHL, non-Hodgkin lymphoma; OR, odds ratio; SNPs, single nucleotide polymorphisms.

^a Adjusted for age and race.

Table 2

Associations between occupational exposure to trichloroethylene, benzene, and formaldehyde, polymorphisms in immune genes, and the risk for non-Hodgkin lymphoma

SNPs	NHL overall						B-cell lymphoma							
	Nonexposed			Exposed			Diffuse large B-cell lymphoma			Follicular lymphoma				
	Nonexposed			Exposed			Nonexposed			Nonexposed				
	Co	Ca	OR ^a	Co	Ca	OR ^a (95% CI)	Ca	OR ^a	Ca	OR ^a (95% CI)	Ca	OR ^a	Ca	OR ^a (95% CI)
Trichloroethylene														
IL12A_07 (rs582054)														
TT	145	122	1.0	26	14	0.70 (0.34, 1.42)	40	1.0	4	0.59 (0.19, 1.85)	26	1.0	4	0.82 (0.25, 2.72)
AT or AA	332	270	1.0	31	51	2.09 (1.28, 3.42)	82	1.0	21	2.66 (1.42, 4.96)	65	1.0	10	1.71 (0.78, 3.77)
P _{for interaction}	0.0090						0.0119			0.3498				
Benzene														
IL12A_07(rs582054)														
TT	133	115	1.0	38	21	0.62 (0.34, 1.12)	35	1.0	9	0.87 (0.38, 1.99)	27	1.0	3	0.35 (0.10, 1.25)
AT or AA	309	254	1.0	54	67	1.46 (0.98, 2.17)	79	1.0	24	1.76 (1.02, 3.04)	59	1.0	16	1.51 (0.80, 2.83)
P _{for interaction}	0.0201						0.1786			0.0468				
IL15_02(rs10833)														
CC	199	172	1.0	37	29	0.90 (0.53, 1.53)	51	1.0	13	1.41 (0.69, 2.86)	40	1.0	3	0.36 (0.11, 1.24)
CT or TT	244	197	1.0	55	59	1.31 (0.86, 1.98)	63	1.0	20	1.39 (0.77, 2.50)	46	1.0	16	1.55 (0.81, 2.98)
P _{for interaction}	0.2460						0.9211			0.0406				
IL10_17 (rs1800890)														
TT	219	148	1.0	42	40	1.39 (0.86, 2.25)	41	1.0	17	2.13 (1.11, 4.12)	30	1.0	10	1.66 (0.75, 3.69)
AT or AA	270	262	1.0	66	60	0.93 (0.63, 1.37)	84	1.0	18	0.87 (0.49, 1.56)	63	1.0	15	0.94 (0.50, 1.76)
P _{for interaction}	0.2104						0.0415			0.2753				
TNF_02 (rs1800629)														
GG	359	286	1.0	71	74	1.30 (0.91, 1.87)	84	1.0	22	1.31 (0.77, 2.25)	65	1.0	22	1.66 (0.95, 2.89)
AG or AA	128	126	1.0	37	27	0.67 (0.38, 1.18)	41	1.0	13	1.07 (0.51, 2.23)	29	1.0	3	0.32 (0.09, 1.13)
P _{for interaction}	0.0762						0.7017			0.0206				
Formaldehyde														
IL6_01 (rs1800795)														

NHL overall										B-cell lymphoma										
SNPs	Nonexposed					Exposed					Diffuse large B-cell lymphoma				Follicular lymphoma					
	Co		Ca		OR ^a	Co		Ca		OR ^a (95% CI)	Nonexposed		Exposed		Nonexposed		Exposed			
	Co	Ca	OR ^a	Co	Ca	OR ^a	Co	Ca	OR ^a	Co	Ca	OR ^a	Co	Ca	OR ^a	Co	Ca	OR ^a (95% CI)		
GG	180	145	1.0	61	66	1.43 (0.94, 2.19)	27	1.0	30	3.64 (1.97, 6.71)	43	1.0	8	0.54 (0.23, 1.25)						
CG or CC	249	189	1.0	100	110	1.43 (1.03, 2.00)	61	1.0	40	1.56 (0.98, 2.48)	38	1.0	30	1.79 (1.04, 3.07)						
<i>P</i> _{for interaction}	0.9810										0.0279								0.0280	
IL6_04 (rs1800797)																				
GG	173	145	1.0	60	67	1.39 (0.91, 2.13)	24	1.0	30	3.97 (2.12, 7.45)	42	1.0	8	0.53 (0.23, 1.24)						
AG or AA	243	175	1.0	95	106	1.52 (1.08, 2.14)	59	1.0	41	1.67 (1.04, 2.66)	36	1.0	26	1.67 (0.95, 2.95)						
<i>P</i> _{for interaction}	0.7575										0.0311								0.0345	
IL10_17 (rs1800890)																				
TT	182	118	1.0	79	70	1.40 (0.94, 2.08)	23	1.0	35	3.69 (2.03, 6.69)	29	1.0	11	0.91 (0.43, 1.93)						
AT or AA	251	214	1.0	85	108	1.49 (1.06, 2.10)	65	1.0	37	1.64 (1.02, 2.64)	52	1.0	26	1.45 (0.84, 2.48)						
<i>P</i> _{for interaction}	0.7915										0.0373								0.3319	

Ca, cases; CI, confidence interval; Co, controls; NHL, non-Hodgkin lymphoma; OR, odds ratio; SNPs, single nucleotide polymorphisms.

^a Adjusted for age and race.