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Occupational Solvent Exposure, Genetic Variation of DNA Repair Genes, and Risk of Non-Hodgkin Lymphoma

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Abstract

Objective—To test the hypothesis that genetic variations in DNA repair genes may modify the association between occupational exposure to solvents and the risk of non-Hodgkin lymphoma (NHL).

Methods—A population-based case-control study was conducted in Connecticut women including 518 histologically confirmed incident NHL cases and 597 controls. Unconditional logistic regression models were used to estimate odds ratios (OR) and effect modification from the 30 SNPs in 16 DNA repair genes of the association between solvent exposure and risk of NHL overall and subtypes.

Results—SNPs in *MGMT*(rs12917) and *NBS1*(rs1805794) significantly modified the association between exposure to chlorinated solvents and NHL risk ($P_{forinteraction} = 0.0003$ and 0.0048 respectively). After stratified by major NHL histological subtypes, *MGMT*(rs12917) modified the association between chlorinated solvents and risk of diffuse large B-cell lymphoma ($P_{forinteraction} = 0.0027$) and follicular lymphoma ($P_{forinteraction} = 0.0024$). A significant interaction was also observed between occupational exposure to benzene and *BRCA2*(rs144848) for NHL overall ($P_{forinteraction} = 0.0042$).

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Conclusions—Our study results suggest that genetic variations in DNA repair genes modify the association between occupational exposure to solvents and risk of NHL.

Keywords

Non-Hodgkin Lymphoma; Occupational Exposure; Solvents; Single Nucleotide Polymorphism; DNA Repair Genes

Introduction

Non-Hodgkin lymphoma (NHL) is the fifth most common cancer among men and women in the United States [1]. The etiology of NHL remains largely unknown with the only established risk factor being immune dysregulation [2]. Occupational exposure to solvents has been suggested as a risk factor for NHL; however, results from epidemiological studies have been inconsistent [3–11]. One of the potential explanations for the observed conflicting results is variation in genetic susceptibility among study populations. Our recent study suggested that genetic variation in metabolic pathway genes may modify the association between solvent exposure and risk of NHL [12].

To further explore whether genetic variation in other biological pathways modify the solvent-NHL association, we selected DNA repair as a target pathway due to a recent finding that occupational exposure to solvents could increase DNA damage and decrease repair capacity [13]. In addition, genetic polymorphisms in DNA repair genes have also been linked to the risk of NHL [14–17]. Here, we analyzed data from a population-based case-control study in Connecticut women to test the hypothesis that genetic polymorphisms in DNA repair pathway genes modify the association between occupational exposure to solvents and risk of NHL.

Methods

Study population

A detailed description of the study population has been published elsewhere [11, 12]. In brief, incident female NHL cases were identified in 1996–2000 through the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource, a component of the Connecticut Tumor Registry. Eligible cases included female residents of Connecticut diagnosed with NHL (ICD-O, M-9590-9642, 9690-9701, 9740-9750), who were aged between 21 and 84 years at the time of diagnosis, had no previous diagnosis of cancer (except non-melanoma skin cancer), and were alive at the time of the interview. A total of 601 NHL cases (72% of all eligible cases) agreed to participate in this study. All NHL cases were histologically confirmed by study pathologists and were classified according to the 2001 World Health Organization classification [18].

Population-based controls were recruited using random digit dialing (RDD) methods for women younger than 65 years or using random selection from the Centers for Medicare and Medicaid Services (CMMS) for women 65 years or older. The participation rate was 69% for RDD controls and 47% for CMMS controls. The controls were frequency matched to cases by age within 5-year groups. A total of 717 qualified controls completed in-person interview. The study was approved by the human investigation committees at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. Of the 601 cases and 717 controls, blood or buccal cell samples were available for 518 cases and 597 controls.

Interview

A standardized, structured questionnaire was employed to collect information on lifetime occupational history and other major suspected risk factors for NHL through in-person interviews. Information on occupational history included job/industry titles and employment dates. These self-reported jobs were coded to standardized occupation and industry classifications according to the 1980 Standard Occupational Classification Manual [19] and the 1987 Standard Industry Classification Manual [20] and linked to a generic job-exposure matrix developed by industrial hygienists at the National Cancer Institute to assess solvent exposures [21, 22]. The assessed exposures included the probability and intensity of exposure for each job and industry for any organic solvents, any chlorinated solvent, benzene, formaldehyde, and a number of individual chlorinated solvents including chloroform, carbon tetrachloride, dichloromethane, dichloroethane, methyl chloride, and trichloroethylene.

Genotyping

DNA was extracted from blood and buccal cell samples using phenol–chloroform extraction [23]. Genotyping was conducted at the National Cancer Institute's Core Genotyping Facility by using real-time polymerase chain reaction on an Applied Biosystems 7900HT sequence detection system (Life Technologies Corporation, Carlsbad, California) [24]. A total of 38 SNPs in 18 DNA repair genes were genotyped. Concordance rates for quality control samples were over 98%. The genotyping frequencies for three SNPs (rs2230009, rs16941, and rs25489) were not consistent with Hardy-Weinberg equilibrium among non-Hispanic white controls using a χ^2 test ($P < .05$) and were excluded from the final analysis. Another 5 SNPs (rs766173, rs1799944, rs1799802, rs1805388, rs3734091) with minor allele frequency less than 10% were also excluded from the final analysis. A total of 30 SNPs in 16 DNA repair genes, *BRCA1* (rs16940, rs799917, rs16942, rs1799966), *BRCA2* (rs144848, rs4986856, rs543304, rs1799955, rs15869), *APEX1* (rs1130409), *ADPRT* (rs1136410), *ERCC1* (rs3212961), *ERCC2* (rs1799793, rs13181), *ERCC5* (rs17655), *MGMT* (rs2308321, rs2308327, rs12917), *NBS1* (rs1805794), *RAD23B* (rs1805329), *XRCC1* (rs25487, rs1799782), *XRCC2* (rs3218536), *XRCC3* (rs861539), *XRCC4* (rs1805377, rs1056503), *WRN* (rs1800391, rs1801195, rs1346044), *XPC* (rs2228001), were included in the final analysis.

Statistical analysis

The exposure variables were presented as dichotomous ever/never exposure metrics because of the small cell counts for some solvents within genotype strata when using multilevel exposure metrics. In addition, numbers of exposure to several individual solvents were small, the final analysis were conducted for any organic solvents, any chlorinated solvents, benzene, and formaldehyde. To increase the statistical power, heterozygous and homozygous variant genotypes were combined for all genes. Unconditional logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations between occupational exposure to solvents and risk of NHL and its subtypes in different genotype strata. Potential confounding variables included in the final models were age (< 50 years, 50–70 years, > 70 years), and race (white, black, other). Adjustments for other variables, such as cigarette smoking, alcohol consumption, and family history did not result in material changes in the observed associations, and these variables were not included in the final models reported here. Significance of gene-solvent interaction was assessed by adding an interaction term in the logistic models. The false discovery rate (FDR) method set at 0.2 was used to control for multiple comparisons [25]. All P values presented are 2-sided, and all analyses were performed using SAS Software Version 9.2 (SAS Institute).

Results

As shown in Table 1, SNPs in *MGMT* (rs12917) and *NBS1* (rs1805794) modified the association between occupational exposure to chlorinated solvents and NHL risk ($P_{\text{forinteraction}} = 0.0003$ and 0.0048 respectively). The results remained statistically significant after adjustment for FDR. Compared to women who had no occupational exposure to chlorinated solvents, exposed women had an increased risk of NHL if they carried the *MGMT* (rs12917) CT/TT genotypes (OR=3.05, 95%CI: 1.76–5.29) or *NBS1* (rs1805794) CG/CC genotypes (OR=2.04, 95%CI: 1.40–2.98), but not among women who carried the *MGMT* (rs12917) CC genotype (OR=1.02, 95%CI: 0.74–1.42) or *NBS1* (rs1805794) GG genotype (OR=0.91, 95%CI: 0.61–1.37). Similar interaction was noted in *MGMT* (rs12917) and diffuse large B-cell lymphoma ($P_{\text{forinteraction}} = 0.0027$) and follicular lymphoma ($P_{\text{forinteraction}} = 0.0024$).

A significant interaction was also observed between occupational exposure to benzene and *BRCA2* (rs144848) for NHL overall ($P_{\text{forinteraction}} = 0.0042$). Compared to women without occupational exposure to benzene, exposed women experienced an increased risk of NHL if they carried the *BRCA2* (rs144848) AA genotype (OR=1.72, 95%CI: 1.11–2.65), but not among women who carried the *BRCA2* (rs144848) AC/CC genotypes (OR=0.66, 95%CI: 0.41–1.08). Although similar associations were also observed for diffuse large B-cell lymphoma and follicular lymphoma, the interactions were not statistically significant after adjustment for FDR ($P_{\text{forinteraction}} = 0.1051$ and 0.0247 respectively). Non-significant associations were presented in supplementary tables 1 to 4.

Discussion

To our knowledge, this is the first study to evaluate interactions between occupational exposure to solvents and genetic variations in DNA repair genes in relation to NHL. We investigated 30 SNPs in 16 DNA repair genes and found that *MGMT* (rs12917) and *NBS1* (rs1805794) modified the association between chlorinated solvents exposure and NHL risk and that *BRCA2* (rs144848) modified the association between benzene exposure and risk of NHL. No interactions were observed for other genes.

MGMT gene encodes a DNA repair protein, O⁶-alkylguanine-DNA alkyltransferase, which repairs O⁶-alkylguanine DNA adducts caused by environmental or therapeutic alkylating agents [26, 27], including chlorinated solvents. *In vitro* and *in vivo* data suggest that *MGMT* protects cells against the mutagenic and carcinogenic effects of alkylating agents [27, 28]. A one to 20-fold interindividual difference in methyltransferase activity has been observed among the cultured human fibroblasts [29]. Genetic polymorphisms of *MGMT* gene may cause variation in *MGMT* activities and result in varying susceptibility to environmental alkylating agents. It is also important to note that the *MGMT* (rs12917) polymorphism may affect the association indirectly, as it is in linkage disequilibrium with 12 other polymorphisms on the *MGMT* gene [30].

NBS1 is a member of the MRE11-RAD50-NBS1 tri-complex involved in DNA double-strand break repair [31, 32]. Mutations in *NBS1* gene cause the disease Nijmegen breakage syndrome (NBS), which has been linked to an increased incidence of lymphoproliferative disorders [33, 34]. The *NBS1* (rs1805794) polymorphism is a non-synonymous mutation causing the change of 185 Glu to Gln, which may possibly change the function of the *NBS1* protein and then influences its repair capacity of DNA damage [35]. A recent study suggested that workers exposed to organic solvents had higher frequency of chromosome aberrations, and the frequency of chromosome aberrations varied by genetic susceptibility of

DNA repair genes [36], consistent with the current study that carriers of a *NBS1* (rs1805794) C minor allele had a higher risk of NHL than women who did not.

Benzene is a well-known human carcinogen. Benzene and its metabolites (i.e., benzene oxide, phenol, hydroquinone, catechol, and benzoquinones) generate different types of DNA lesions including double-strand breaks [37]. *BRCA2* is involved in double-strand break repairs. Although the function of *BRCA2* (rs144848) polymorphism is unclear, the amino acid substitution of asparagine to histidine may alter *BRCA2* structure and function as it falls in a region that interacts with the histone acetyltransferase P/CAF prior to transcriptional activation of other genes [38]. The observed interaction between *BRCA2* (rs144848) and benzene with respect to NHL deserves further investigation.

Several strengths and limitations existed in this study. This was a population-based case-control study with histologically confirmed incident NHL cases which minimized potential disease misclassification. The study had modest sample size, and statistical power was limited, particularly for NHL subtype analysis. As such, chance could not be ruled out for some of the significant findings; however, we adjusted for multiple comparisons using the FDR approach to minimize false positives. The study only included women, so the results may not be generalizable to men.

Use of a generic job-exposure matrix may have led to exposure misclassification. However, any exposure misclassification is likely to be non-differential and limited recall bias in job reporting has been demonstrated in previous studies [39, 40]. We applied the job-exposure matrix blinded to participant disease status to minimize differences between cases and controls [11]. Given our use of dichotomous solvent variables, any exposure misclassification is expected to have attenuated solvent effects.

In summary, our data suggested that variants in DNA repair genes modified association between solvent exposure and risk of NHL overall or its subtypes. Further research should be conducted with larger sample sizes to conduct further stratified analyses and other gene pathways that may modify the association of solvent exposure and NHL risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Associations Between Occupational Exposure to Chlorinated Solvents, Benzene, DNA Repair Genes, and Risk of Non-Hodgkin lymphoma

	Overall						Diffuse large B-cell lymphoma						Follicular lymphoma					
	Non-exposed			Exposed			Non-exposed			Exposed			Non-exposed			Exposed		
	Control	Case	OR*	Control	Case	OR* (95%CI)	Control	Case	OR*	Control	Case	OR* (95%CI)	Control	Case	OR*	Control	Case	OR* (95%CI)
Chlorinated																		
MGMT_06(rs12917)																		
CC	314	255	1.0	110	90	1.02(0.74–1.42)	74	1.0	28	1.13	1.13(0.69–1.86)	60	1.0	18	0.88	0.88(0.49–1.57)		
CT+TT	104	67	1.0	29	58	3.05(1.76–5.29)	22	1.0	24	4.24	4.24(2.03–8.86)	14	1.0	15	4.44	4.44(1.86–10.61)		
<i>P for interaction</i>						0.0048						0.0027						0.0024
NBS1_01(rs1805794)																		
GG	175	167	1.0	70	61	0.91(0.61–1.37)	47	1.0	26	1.45	1.45(0.82–2.55)	36	1.0	10	0.72	0.72(0.33–1.55)		
CG+CC	247	160	1.0	71	89	2.40(1.40–2.98)	52	1.0	26	1.94	1.94(1.11–3.37)	39	1.0	24	2.20	2.20(1.22–3.97)		
<i>P for interaction</i>						0.0048						<i>0.5372</i>						<i>0.0188</i>
Benzene																		
BRCA2_01(rs 144848)																		
AA	257	193	1.0	44	57	1.72(1.11–2.65)	62	1.0	20	1.90	1.90(1.04–3.48)	42	1.0	14	1.90	1.90(0.95–3.79)		
AC+CC	202	193	1.0	52	33	0.66(0.41–1.08)	55	1.0	13	0.89	0.89(0.45–1.76)	47	1.0	6	0.53	0.53(0.21–1.32)		
<i>P for interaction</i>						0.0042						<i>0.1051</i>						<i>0.0247</i>

* Adjusted for age and race.