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Polymorphisms in DNA repair genes and risk of non-Hodgkin lymphoma in a pooled analysis of three studies

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Abstract

Background—Elevated incidence of lymphoma has been observed among carriers of rare high-penetrance mutations in DNA repair genes (e.g., Nijmegen breakage syndrome, Ataxia-telangectasia syndrome, etc.). Common gene variants in DNA repair genes may also influence lymphomagenesis.

Methods—Study subjects were pooled from three population-based case-control studies of non-Hodgkin lymphoma (NHL) in the US and Australia. A total of 1,946 cases and 1,808 controls were analyzed. A total of 319 tag single nucleotide polymorphisms (SNPs) in 27 DNA repair gene regions were genotyped. Unconditional logistic regression models were used to estimate the relative risk of NHL and NHL subtypes in relation to SNPs. Tail-strength statistics were used to test for the association between DNA repair pathways and NHL or NHL subtypes. The statistical significance of the smallest P-trend within each gene region was estimated by permutation-based resampling methods.

Results—Overall, DNA repair genetic polymorphisms were associated with NHL (P = 0.005). Tests for the double strand break repair (P = 0.02) and nucleotide excision repair (P = 0.04) pathways were also significant. Four gene regions were significantly associated with NHL or NHL subtypes at the

[*]MS and IM contributed equally to this work.

0.05 level: *RAD50*, *BLM*, *RAD51*/*FAM82C*, and *ERCC3*/*MAP3K2*. Specifically, *BLM* rs441399 (P_{trend} = 0.004) and *FAM82C* rs2304583 (P_{trend} = 0.001) were associated with follicular lymphoma, and *XRCC4* rs13178127 was associated with NHL overall (P_{trend} = 0.006) significantly. In addition, the *ERCC3* rs4150506 was associated with reduced risk for marginal zone lymphoma (P_{trend} = 0.002).

Conclusion—These results support the hypothesis that common genetic polymorphisms in human DNA repair genes may modify the risk of NHL.

Keywords

non-Hodgkin lymphoma; DNA repair; single nucleotide polymorphism; pooled analysis

Introduction

DNA repair mechanisms are important in maintaining genomic stability and defects in DNA repair can lead to the development of chromosomal aberrations, a hallmark of lymphoma (Palitti, 2004). Several hereditary syndromes, including Ataxia telangiectasia (OMIM 208900), Bloom syndrome (OMIM 210900), and Nijmegan breakage syndrome (OMIM 251260), are characterized by defective DNA repair and high occurrence of lymphoma, indicating the important role of DNA repair in the pathogenesis and development of NHL.

Recent studies have reported associations between certain DNA repair gene single-nucleotide polymorphisms (SNP) and NHL risk (Shen *et al*, 2006;Shen *et al*, 2007;Hill *et al*, 2006). To investigate this question in greater detail, we conducted a pooled investigation of genetic variation in 27 gene regions involved in human DNA repair based on three case-control studies in the US and Australia.

Subjects and methods

Study Populations

Study subjects were pooled from three population-based case-control studies of NHL: a study conducted within the Surveillance Epidemiology and End Results (SEER) registry catchment areas of Iowa, Detroit, Los Angeles and Seattle (NCI-SEER study) (Hill *et al*, 2006), a study conducted among female residents of Connecticut (Shen *et al*, 2006), and a study conducted among residents of New South Wales (NSW) and the Australian Capital Territory, Australia (Shen *et al*, 2007).

The final analytic population consisted of 1,946 cases and 1,808 controls (NCI-SEER, 990 / 828; Connecticut, 436 / 515; NSW, 520 / 465) after a few samples were excluded with completion rates <90% (NCI-SEER, N = 17; Connecticut, N = 2; NSW, N = 3).

The four most common NHL subtypes were also evaluated separately: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), and chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL).

DNA extraction and Genotyping

DNA was extracted from blood clots, buffy coats, or buccal cell samples. Genes were selected based on experimental evidence of functional relevance and findings from previous association studies of lymphoma, related malignancies, and other tumor sites. These genes are involved in different DNA repair pathways (double strand break repair (DSBR), nucleotide excision repair (NER), and base excision repair (BER)).

Tag SNPs for each gene were selected from the designable set of common SNPs (minor allele frequency ≥0.05) genotyped in the HapMap Project (Data Release 20/Phase II, NCBI B35 assembly, dbSNP b125). For each gene, SNPs within the region 20 kb 5′ of the ATG-translation initiation codon and 10kb 3′ of the end of the last exon, which is called gene region, were binned using a binning threshold of $r^2 > 0.80$. Genotyping was performed at the National Cancer Institute Core Genotyping Facility (Gaithersburg, MD) using the Illumina GoldenGate platform. Data for an additional 28 SNPs that had been previously genotyped by TaqMan assay in at least two of the studies and are located within one of the 27 investigated gene regions were also included in the overall analysis. In total, 319 SNPs were analyzed in this report (Supplementary Table 1).

All investigated SNPs had assay completion rates ≥ 98% except *BLM* rs441399, *ERCC2* rs50872 and *NBN* rs7006322 (97% for each), and genotype concordance rates ≥ 99% except *BLM* rs16944894 (96%) in quality control duplicates.

Statistical Methods

The relative risk of NHL and NHL subtypes in relation to SNPs were estimated by calculating odds ratios (OR) and 95% confidence intervals (CI) using polytomous multivariate unconditional logistic regression models, adjusting for age, race/ethnicity, sex and study center. Tests for trend were conducted using an additive model by assigning the ordinal values 0, 1, and 2 to homozygous wild type, heterozygous and homozygous variant genotypes respectively, and by modeling these scores as a continuous variable.

Tail-strength statistics were used to test for the association between pathways and NHL or NHL subtypes. The tail-strength method evaluates the univariate strength of a collection of observed P values (e.g. from a particular pathway) and assesses its statistical significance using a permutation procedure (10,000 permutations) (Taylor & Tibshirani, 2006).

We assessed the statistical significance of the smallest P-trend within each gene region by permutation-based resampling methods (10,000 permutations) that automatically adjust for the number of tag SNPs tested within that gene region and the underlying linkage disequilibrium pattern (Chen *et al*, 2006). Finally, haplotype analysis was carried out among non-Hispanic Caucasian subjects.

Results

Cases and controls were similar with respect to demographic characteristics including sex, age, race, and ethnicity (Supplementary Table 2). Overall, DNA repair genetic polymorphisms were associated with NHL (P = 0.005). Tests of the DSBR (P = 0.02) and NER (P = 0.04) pathways were also statistically significant (Table 1).

Four gene regions were significantly associated with NHL subtypes at the 0.05 level: DLBCL (*RAD50*), FL (*BLM*, *RAD51*/*FAM82C*), and MZL (*ERCC3*/*MAP3K2*) (Table 2).

Genotype frequencies for cases and controls, and main effects of SNPs are presented in Supplementary Table 3. One or more SNPs in *BLM*, *WRN*, *RAD50*, *FAM82C*, *RAD54L*, *XRCC4*, *ERCC3*, *CCDC16*, and *IRGQ* were associated with NHL or NHL subtypes risk at a significance level of 0.005. Five SNPs (*BLM* rs441399, *RAD50* rs2237060, *FAM82C* rs2304583, *ERCC3* rs4150506, and *XRCC4* rs13178127) were particularly noteworthy because their gene regions were significantly associated with NHL or NHL subtypes at the 0.05 level or because of high level of statistical significance and consistent findings across the three studies (Table 3) (Figure 1). Among them, *BLM* rs441399 ($P_{trend} = 0.004$) and *FAM82C* rs2304583 ($P_{trend} = 0.001$) were associated with follicular lymphoma significantly, and

XRCC4 rs13178127 was significantly associated with NHL overall ($P_{trend} = 0.006$). Most of the statistically significant findings were restricted to DLBCL or FL. However, the *ERCC3* rs4150506 was associated with reduced risk for MZL ($P_{trend} = 0.002$).

Haplotype analysis was conducted to examine different subsets in these gene regions. However, it did not provide additional information for a given gene beyond those significant SNPs found in individual SNP analysis. Subgroup analysis in non-Hispanic Caucasians showed similar results (results not shown).

Discussion

We studied 319 SNPs in 27 DNA repair genes and found that a number of genetic polymorphisms were significantly associated with altered risk of NHL or NHL subtypes. Among them, genes repairing DNA double strand breaks are particularly notable. These results support the hypothesis that common genetic polymorphisms in DNA repair genes may modify the risk of NHL.

BLM, the Bloom syndrome gene product, is related to the RecQ subset of DNA helicases and has both DNA-stimulated ATPase and ATP-dependent DNA helicase activities. Mutations in the gene causes Bloom syndrome characteristic of high cancer predisposition including lymphoma. BLM plays a role in both homogenous recombination and nonhomologous end joining (NHEJ) manifested by its interaction with RAD51 and LIG4 (So *et al*, 2004). Two nuclear localization signals (NLS) were found in the C-terminal domain, which is crucial in targeting the BLM protein to the cell nucleus (Kaneko & Kondo, 2004). We found two significant SNPs in this gene and the one in the C-terminal (rs441399) was significantly associated with FL.

The gene region *RAD51*/*FAM82C* was associated with NHL overall and especially for follicular lymphoma. *FAM82C* is a mitochondrial protein with apoptosis-inducing function (Lv *et al*, 2006). RAD51 is involved in the homologous recombination and repair of DNA. This protein also interacts with BRCA1 and BRCA2, which may be important for the cellular response to DNA damage. *RAD51* had been found involved in family breast cancer (Thacker, 2005). The gene *FAM82C* is located physically close to *RAD51*. So the association of *FAM82C* with NHL may be due to functional loci in *RAD51*.

At the center of the NHEJ, XRCC4 forms a complex with the LIG4 (Sibanda *et al*, 2001), and further interacts with the DNA-dependent protein kinase for rejoining breaks. The *XRCC4*/*p53* double knockout mice die early from pro-B cell lymphoma (Gao *et al*, 2000). NHEJ is also critical in the process of V(D)J recombination that generates immunoglobulin and T cell receptor diversity. Errors in the DNA repair genes responsible for ligating the V, D, and J segments are implicated in characteristic chromosomal rearrangements found in some types of NHL. Our findings suggest the XRCC4 and the NHEJ may play a role in the development of NHL.

In summary, we found that variants in genes that play an important role in several DNA repair pathways were associated with risk of NHL. These findings suggest that common genetic polymorphisms in DNA repair genes may be important susceptibility factors for NHL. Identification of the key DNA repair genes that play a role in lymphomagenesis may ultimately help to identify particular exposures or general classes of exposures. Recent genome-wide scan studies of lymphoma identified several loci that were associated with FL and CLL/SLL (Skibola *et al*, 2009;Di Bernardo *et al*, 2008). Our findings need to be replicated in other studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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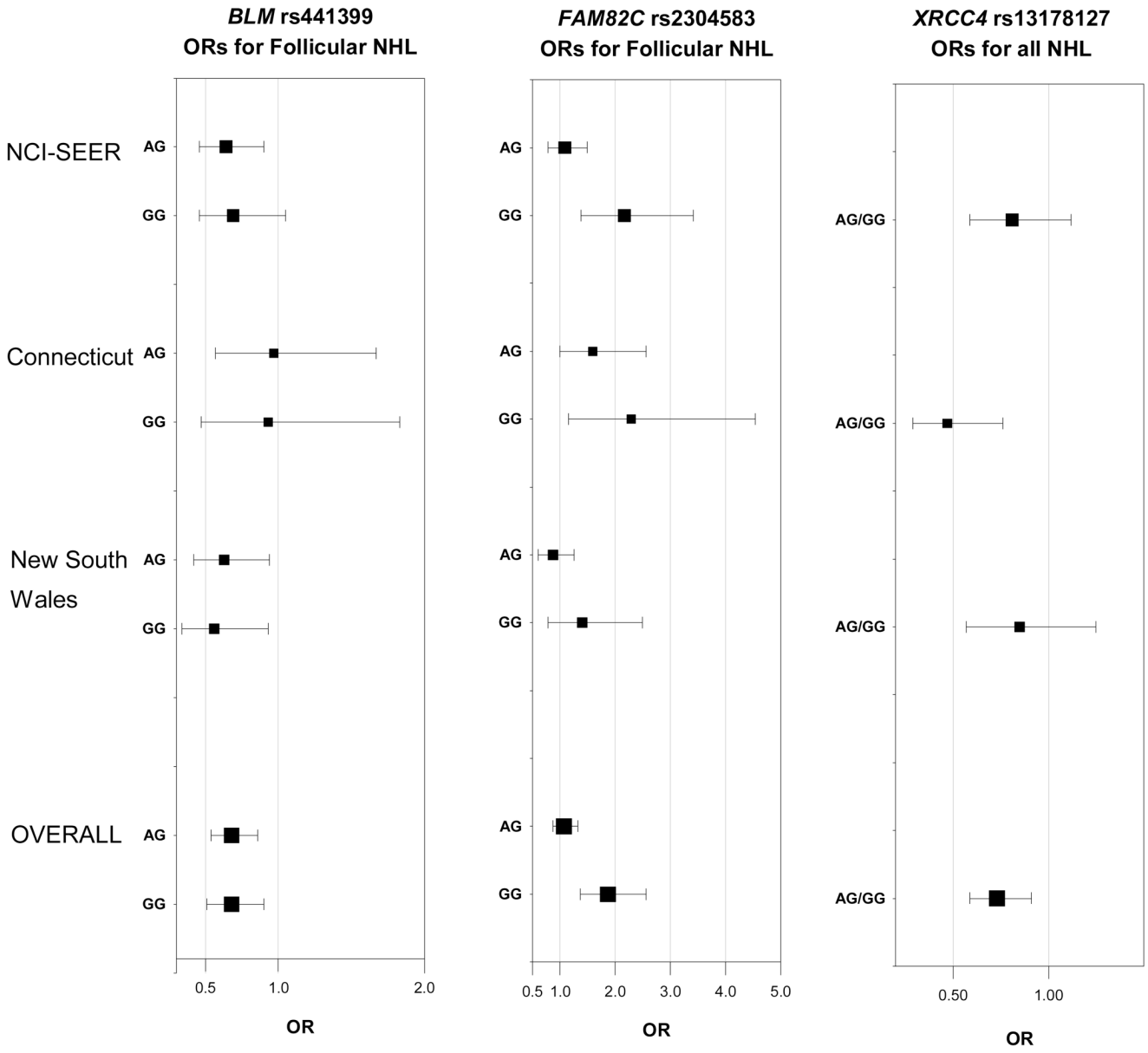

Figure 1. Study-specific associations between *BLM* rs441399, *FAM82C* rs2304583, and *XRCC4* rs13178127 and the risk of NHL overall or follicular lymphoma

Figures of odds ratios (OR) for study-specific and pooled results for *BLM* rs441399, *FAM82C* rs2304583, and *XRCC4* rs13178127. Square symbols represent ORs; symbol size is proportional to the number of cases. Horizontal lines represent 95% confidence intervals. *BLM* rs441399 ($P_{trend} = 0.004$) and *FAM82C* rs2304583 ($P_{trend} = 0.001$) were associated with follicular lymphoma; *XRCC4* rs13178127 ($P_{trend} = 0.006$) was associated with non-Hodgkin lymphoma overall significantly.

Table 1

P values of tail strength analysis for DNA repair pathways by NHL subtype.

	NHL	DLBCL	FL	MZL	CLL/SLL
All genes	**0.005**	0.25	0.51	0.61	0.80
Double strand break repair[1]	**0.02**	0.28	0.50	0.58	0.76
Nucleotide excision repair[2]	**0.04**	0.29	0.55	0.25	0.82
Base excision repair[3]	0.16	0.78	0.13	0.23	0.05

[1] Including *BLM, WRN, BRCA1, FRY/BRCA2/CG018, MRE11A, NBN/DECR1, RAD50, RAD51/FAM82C, RAD54L, XRCC2, KNS2/XRCC3/ZFYVE21, LIG4/C13ORF6, PRKDC/MCM4, RAG1/RAG2/LOC119710,* and *XRCC4*.

[2] Including *ERCC2/PPP1R13L/CD3EAP/ERCC1, ERCC3/MAP3K2, BIVM/ERCC5/LOC121952, ERCC6,* and *LIG1/LOC374920*.

[3] Including *CCDC16/LIG3/RFFL* and *ZNF575/XRCC1/IRGQ*.

Table 2

P values of gene-region-based permutation test by NHL overall and NHL subtypes.

Gene region	Genes included	NHL	DLBCL	FL	MZL	CLL/SLL
Double strand break repair						
BLM	*BLM*	0.45	0.29	**0.05**	0.48	0.35
WRN	*WRN*	0.26	0.56	0.68	0.50	0.61
BRCA1	*BRCA1*	0.78	0.91	0.41	0.87	0.66
BRCA2	*FRY/BRCA2/CG018*	0.43	0.55	0.82	0.83	0.78
MRE11A	*MRE11A*	0.53	0.42	0.96	0.45	0.44
NBN	*NBN/DECR1*	0.20	0.26	0.70	0.92	0.39
RAD50	*RAD50*	0.43	**0.04**	0.86	0.51	0.50
RAD51	*RAD51/FAM82C*	0.25	0.80	**0.005**	0.57	0.28
RAD54L	*RAD54L*	0.08	0.29	0.82	0.56	0.18
XRCC2	*XRCC2*	0.37	0.14	0.27	0.18	0.25
XRCC3	*KNS2/XRCC3/ZFYVE21*	0.50	0.37	0.08	0.37	0.45
LIG4	*LIG4/C13ORF6*	0.10	0.43	0.21	0.38	0.53
PRKDC	*PRKDC/MCM4*	0.39	0.15	0.62	0.53	0.29
RAG1/RAG2	*RAG1/RAG2/LOC119710*	0.08	0.45	0.20	0.17	0.69
XRCC4	*XRCC4*	0.11	0.37	0.48	0.58	0.69
Nucleotide excision repair						
ERCC2/ERCC1	*ERCC2/PPP1R13L/CD3EAP/ERCC1*	0.69	0.32	0.90	0.50	0.62
ERCC3	*ERCC3/MAP3K2*	0.24	0.46	0.79	**0.008**	0.55
ERCC5	*BIVM/ERCC5/LOC121952*	0.12	0.50	0.32	0.24	0.51
ERCC6	*ERCC6*	0.37	0.78	0.74	0.56	0.85
LIG1	*LIG1/LOC374920*	0.20	0.25	0.26	0.71	0.57

Table 3

5% confidence intervals and P value in additive and dominant models for statistically significant SNPs associated with NHL in pooled analysis
nt gene region tests based on the permutation test[1]

CTRL		All NHL				DLBCL				Follicular				MZL				CLL/SLL				P for heterogeneity [2]
		NHL	OR	95% CI	P	DLB	OR	95% CI	P	FOLL	OR	95% CI	P	MGZN	OR	95% CI	P	CLL	OR	95% CI	P	
	*7712 A>G																					
	430	525	1			138	1			167	1			45	1			43	1			
	888	926	0.85	0.73–1.00	**0.05**	303	1.05	0.83–1.32	0.69	243	0.68	0.54–0.86	**0.001**	74	0.80	0.54–1.18	0.26	69	0.79	0.53–1.19	0.26	
	388	381	0.83	0.69–1.01	0.07	125	1.04	0.79–1.38	0.78	101	0.68	0.51–0.90	**0.008**	30	0.75	0.46–1.23	0.26	35	0.94	0.59–1.52	0.81	
	1276	1307	0.85	0.73–0.99	**0.03**	428	1.05	0.84–1.31	0.69	344	0.68	0.55–0.85	**0.001**	104	0.79	0.54–1.14	0.20	104	0.84	0.57–1.22	0.35	
	1706	1832	0.91	0.83–1.00	**0.05**	566	1.02	0.89–1.17	0.77	511	0.81	0.70–0.93	**0.004**	149	0.86	0.68–1.10	0.24	147	0.96	0.75–1.23	0.75	0.12
60	IVS21-1922 T>C																					
	666	707	1			229	1			181	1			56	1			64	1			
	813	913	0.99	0.86–1.15	0.89	285	0.93	0.76–1.15	0.50	267	1.09	0.87–1.36	0.45	72	1.05	0.72–1.53	0.79	70	0.86	0.60–1.24	0.42	
	310	301	0.86	0.71–1.05	0.14	76	0.65	0.48–0.88	**0.005**	91	0.96	0.71–1.28	0.77	31	1.21	0.75–1.94	0.43	25	0.83	0.51–1.36	0.47	
	1123	1214	0.96	0.83–1.10	0.52	361	0.86	0.70–1.04	0.12	358	1.05	0.85–1.30	0.63	103	1.09	0.77–1.55	0.62	95	0.85	0.61–1.20	0.36	
	1789	1921	0.94	0.85–1.03	0.19	590	0.83	0.73–0.96	**0.01**	539	1.00	0.86–1.15	0.95	159	1.10	0.86–1.39	0.45	159	0.90	0.71–1.14	0.39	0.14
583	IVS7+193 A>G																					
	860	885	1			283	1			224	1			78	1			74	1			
	774	812	0.99	0.86–1.13	0.86	245	0.92	0.75–1.12	0.42	227	1.07	0.87–1.33	0.51	64	0.90	0.63–1.28	0.56	62	0.92	0.64–1.31	0.64	
	153	222	1.35	1.07–1.70	**0.01**	63	1.16	0.84–1.61	0.36	81	1.87	1.37–2.56	**8×10^-5**	17	1.22	0.70–2.13	0.49	22	1.64	0.98–2.75	0.06	
	927	1034	1.05	0.92–1.19	0.49	308	0.96	0.79–1.16	0.67	308	1.21	0.99–1.48	0.07	81	0.95	0.68–1.33	0.77	84	1.04	0.74–1.44	0.84	
	1787	1919	1.10	0.99–1.21	0.07	591	1.02	0.88–1.17	0.83	532	1.27	1.10–1.47	**0.001**	159	1.02	0.80–1.32	0.86	158	1.15	0.90–1.48	0.26	0.16
127	IVS7+34936 A>G																					
	1606	1774	1			550	1			491	1			149	1			146	1			
	197	167	0.73	0.59–0.91	**0.005**	48	0.67	0.48–0.94	**0.02**	47	0.70	0.50–0.99	**0.04**	11	0.57	0.30–1.08	0.09	15	0.84	0.48–1.47	0.54	
	4	4	0.87	0.22–3.50	0.84	2	1.32	0.24–7.26	0.75	1												
	201	171	0.73	0.59–0.91	**0.005**	50	0.68	0.49–0.95	**0.02**	48	0.70	0.50–0.98	**0.04**	11	0.56	0.30–1.06	0.08	15	0.82	0.47–1.44	0.50	
	1807	1945	0.75	0.61–0.92	**0.006**	600	0.71	0.52–0.97	**0.03**	539	0.71	0.52–0.99	**0.04**	160	0.56	0.30–1.06	0.07	161	0.81	0.47–1.40	0.46	0.86
de excision repair																						
06	IVS12-1624 G>A																					

CTRL	All NHL				DLBCL				Follicular				MZL				CLL/SLL				P for heterogeneity *2*
	NHL	OR	95% CI	P	DLB	OR	95% CI	P	FOLL	OR	95% CI	P	MGZN	OR	95% CI	P	CLL	OR	95% CI	P	
1111	1257	1			379	1			334	1			119	1			106	1			
625	601	0.83	0.72–0.95	**0.008**	188	0.85	0.70–1.04	0.12	182	0.93	0.75–1.14	0.48	36	0.52	0.35–0.76	**0.001**	46	0.79	0.55–1.14	0.20	
72	86	1.05	0.75–1.45	0.79	32	1.28	0.83–1.98	0.26	24	1.06	0.65–1.72	0.83	5	0.63	0.25–1.59	0.33	9	1.40	0.67–2.90	0.37	
697	687	0.85	0.74–0.97	**0.02**	220	0.89	0.74–1.09	0.26	206	0.94	0.77–1.15	0.55	41	0.53	0.36–0.76	**0.001**	55	0.85	0.60–1.20	0.36	0.06
1808	1944	0.90	0.81–1.01	0.08	599	0.96	0.82–1.13	0.65	540	0.97	0.82–1.15	0.70	160	0.60	0.43–0.83	**0.002**	161	0.94	0.71–1.26	0.70	

were adjusted for age, race/ethnicity, sex and study center in logistic regression models;

heterogeneity between NHL subtypes.