Cytokine polymorphisms in Th1/Th2 pathway genes, body mass index, and risk of non-Hodgkin lymphoma

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We conducted a population-based, case-control study in Connecticut women to test the hypothesis that genetic variations in Th1 and Th2 cytokine genes modify the relationship between body mass index (BMI) and risk of non-Hodgkin lymphoma (NHL). Compared with those with BMI less than 25 kg/m^2, women with BMI more than or equal to 25 kg/m^2 had 50% to 90% increased risk of NHL among women who carried *IFNGR2* (rs9808753) AA, *IL5* (rs2069812) CT/TT, *IL7R* (rs1494555) AA, and *TNF* (rs1799724) CC genotypes, but no increased risk among women with *IFNGR2* AG/GG, *IL5* CC, *IL7R* AG/GG, and *TNF* CT/TT genotypes. A significant interaction with BMI was only observed for *IFNGR2* (rs9808753 $P_{forinteraction}$ = .034) and *IL7R* (rs1494555 $P_{forinteraction}$ = .016) for NHL overall; *IL7R* (rs1494555 $P_{forinteraction}$ = .016) and *TNF* (1799724 $P_{forinteraction}$ = .031) for B-cell lymphoma; and *IL5* (rs2069812 $P_{forinteraction}$ = .034) for T-cell lymphoma. After stratification by common B-cell lymphoma subtypes, a significant interaction was observed for *IFNGR2* (rs9808753 $P_{forinteraction}$ = .006), *IL13* (rs20541 $P_{forinteraction}$ = .019), and *IL7R* (rs1494555 $P_{forinteraction}$ = .012) for marginal zone B-cell lymphoma; *IL7R* (rs1494555 $P_{forinteraction}$ = .017) for small lymphocytic lymphoma/chronic lymphocytic leukemia; and *IL12A* (rs568408 $P_{forinteraction}$ = .013) and *TNF* (1799724 $P_{forinteraction}$ = .04) for follicular lymphoma. The results suggest that common genetic variation in Th1/Th2 pathway genes may modify the association between BMI and NHL risk. (*Blood*. 2011;117(2):585-590)

Introduction

Excessive adipose can impair both humoral and cellular immunity,[1] which may be important in the development of non-Hodgkin lymphoma (NHL). Body mass index (BMI), an indirect measure of adiposity, has been linked with NHL risk. Results from epidemiologic studies, however, have been inconsistent.[2-18] Some studies have reported a positive association between BMI and risk of NHL,[5,9-11,13,14,16-18] whereas others found no association.[2-4,6,7,12,15] A recent pooled analysis by the International Lymphoma Epidemiology Consortium, which included 26 000 subjects, reported no association between BMI and overall risk of NHL and most subtypes.[19] However, the validity of a pooled odds ratio is questioned because of the significant heterogeneity of the analyzed studies. Genetic variation could explain some of the inconsistent findings.

Cytokines play a crucial role in the regulation of key pathways of the immune system. T helper 1 (Th1) lymphocyte cells produce interleukin-2 (IL-2) and interferon-gamma (IFN-γ), which promote cell-mediated immune responses to fight intracellular pathogens and remove cancerous cells.[20,21] T helper 2 (Th2) lymphocyte cells produce IL-4, IL-5, IL-6, IL-10, and IL-13, which favor B-cell activation and production of immunoglobulin, which can protect against extracellular pathogens.[20-25] Immune dysfunction resulting from imbalanced regulation and expression of Th1 and Th2 cytokines could play an important role in the etiology of NHL.[26,27]

Single nucleotide polymorphisms (SNPs) in several cytokine genes (ie, *IL4*, *IL5*, *IL6*, and *IL10*) have been reported to be associated with the risk of NHL and its major subtypes.[28] It is possible that genetic variation in the Th1 and Th2 cytokine genes may modify the relationship between BMI and NHL risk. As such, we conducted a population-based, case-control study in Connecticut women to test the hypothesis.

Methods

Study population

The study population has been described in detail elsewhere.[29,30] Briefly, all histologically confirmed incident cases of NHL (ICD-O, M-9590-9642, 9690-9701, 9740-9750) diagnosed between 1996 and 2000 in Connecticut were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource. Enrollment criteria included age between 21 and 84 years, residence in Connecticut, female, alive at the time of interview, and without a previous diagnosis of cancer, except for nonmelanoma skin cancer. Of 832 eligible cases, 601 (72%) completed in-person interviews. Pathology slides (or tissue blocks) from all patients were obtained from the original pathology departments and reviewed by 2 independent pathologists. All cases were classified according to the 2001 World Health Organization classification.[31]

Table 1. Associations between BMI and risk of NHL and common NHL subtypes

BMI, kg/m²	Overall				B-cell lymphoma			T-cell lymphoma		
	Cases	Controls	OR (95% CI)	P	Cases	OR (95% CI)	P	Cases	OR (95% CI)	P
< 25	251	326	1.0		199	1.0		14	1.0	
25-30	167	167	1.3 (1.0-1.7)	.048	132	1.3 (1.0-1.7)	.075	17	2.4 (1.2-5.0)	.019
> 30	100	104	1.3 (0.9-1.8)	.147	80	1.3 (0.9-1.9)	.129	8	1.8 (0.7-4.6)	1.187
≥ 25	267	271	1.3 (1.0-1.7)	.032	212	1.3 (1.0-1.7)	.041	25	2.2 (1.1-4.4)	.023

ORs were adjusted for age, race, and total energy intake.

Female population-based controls from Connecticut were recruited by: (1) random-digit dialing methods for those younger than 65 years; or (2) random selection from the Centers for Medicare and Medicaid Services records for those 65 years of age or older. Controls were frequency matched on age (± 5 years) to cases. The participation rate was 69% among persons identified via the random-digit dialing and 47% among persons identified from the Centers for Medicare and Medicaid Services. Approximately 75% of the study subjects (76.7% of the cases and 74.6% of the controls) provided blood samples, and approximately 10% of the subjects (11.0% of the cases and 10.4% of the controls) provided buccal cell samples for genotyping.

Data collection

The study was approved by the institutional review boards at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. Participation was voluntary, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Those who signed consent were interviewed by trained study nurses at the subject's home or at a convenient location using a standardized and structured questionnaire. Information on anthropometrics, demographics, family history of cancer, smoking and alcohol consumption, occupational exposure, medical conditions and medication use, and diet were collected through in-person interview. Usual adult height and weight were used to calculate BMI.

Genotyping

Genotyping was performed at the National Cancer Institute Core Genotyping Facility (http://cgf.nci.nih.gov). All TaqMan assays (Applied Biosystems) for this study were optimized on the ABI 7900HT detection system with 100% concordance with sequence analysis of 102 persons as listed on the SNP500Cancer website (http://snp500cancer.nci.nih.gov). A total of 39 SNPs in 20 Th1/Th2 immune genes were selected for genotyping based on the following criteria: minor allele frequencies more than 5%, laboratory evidence of function, or prior association with human disease studies.[28] Because of a limited amount of DNA available for subjects who provided only buccal cells, we first genotyped subjects who provided a blood sample. If there was suggestive evidence or if we had a relatively high prior that a given SNP was associated with risk of NHL, genotype analysis would include subjects who provided only buccal cell samples.

Duplicate samples from 100 study subjects and 40 replicate samples from each of 2 blood donors were interspersed throughout the plates used for genotype analysis. The concordance rates for quality control samples were between 99% and 100% for all assays. The genotype frequencies for 4 SNPs (rs1059293, rs231775, rs2243250, and rs2070874) 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 (rs2069822, rs2069818, rs2069807, 3024509, and rs361525) with 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

BMI was calculated as weight (kilograms) divided by the square of height (meters squared), using self-reported usual adult height and weight. We defined persons as normal weight if their BMI was less than 25 kg/m² and overweight/obese if their BMI was more than or equal to 25 kg/m² as defined by the World Health Organization. Unconditional logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations between BMI, and risk of NHL and its subtypes in different genotype strata. To increase statistical power, heterozygous and homozygous variant genotypes were combined for all genes. Potential confounding variables included in the final models were age (< 50 years, 50-70 years, > 70 years), race (white, black, other), and total energy intake (< 1385 kcal, 1385-1800 kcal, > 1800 kcal). 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-BMI 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. All *P* values presented are 2-sided, and all analyses were performed using SAS Software Version 9.2 (SAS Institute).

Results

The association between BMI and risk of NHL overall and NHL subtypes are presented in Tables 1 and 2. Compared with women with normal weight, those with a BMI more than or equal to 25.0 kg/m² had an increased risk of NHL overall (OR = 1.3; 95% CI, 1.0-1.7), B-cell lymphoma (OR = 1.3; 95% CI, 1.0-1.7),

Table 2. Associations between BMI and risk of NHL and common NHL subtypes

BMI, kg/m²	DLBCL				FL			SLL/CLL			MZBCL		
	Cases	Controls	OR (95% CI)	P	Cases	OR (95% CI)	P	Cases	OR (95% CI)	P	Cases	OR (95% CI)	P
< 25	77	326	1.0		57	1.0		32	1.0		15	1.0	
25-30	56	167	1.5 (1.0-2.2)	.066	35	1.2 (0.8-2.0)	.402	18	1.1 (0.6-2.1)	.710	14	1.8 (0.8-3.7)	.146
> 30	28	104	1.1 (0.7-1.8)	.672	27	1.7 (1.0-2.8)	.060	9	0.9 (0.4-2.0)	.836	6	1.4 (0.5-3.8)	.490
≥ 25	84	271	1.3 (0.9-1.9)	.123	62	1.4 (0.9-2.1)	.119	27	1.1 (0.6-1.8)	.865	20	1.6 (0.8-3.3)	.164

ORs were adjusted for age, race, and total energy intakes.
FL indicates follicular lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; and MZBCL, marginal zone B-cell lymphoma.

Table 3. Associations between Th1/Th2 cytokine polymorphisms, BMI, and risk of NHL

| | Overall | | | | | | B-cell lymphoma | | | | T-cell lymphoma | | | |
| | BMI < 25, kg/m² | | | BMI ≥ 25, kg/m² | | | BMI < 25, kg/m² | | BMI ≥ 25, kg/m² | | BMI < 25, kg/m² | | BMI ≥ 25, kg/m² | |
SNPs	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
IFNGR2_01 (rs9808753)														
AA	247	180	1.0	189	202	1.5 (1.1-1.9)	146	1.0	161	1.4 (1.1-1.9)	8	1.0	18	2.9 (1.2-7.0)
AG or GG	62	54	1.0	69	49	0.9 (0.5-1.5)	41	1.0	41	1.0 (0.5-1.7)	5	1.0	5	0.8 (0.2-3.1)
$P_{forinteraction}$						.034				.108				.057
IL5_02 (rs2069812)														
CC	145	114	1.0	128	105	1.0 (0.7-1.4)	87	1.0	85	1.0 (0.7-1.5)	9	1.0	9	1.0 (0.4-2.6)
CT or TT	160	116	1.0	129	145	1.7 (1.2-2.4)	96	1.0	114	1.6 (1.1-2.3)	3	1.0	14	5.9 (1.6-21.5)
$P_{forinteraction}$						.081				.236				.034
IL7R_01 (rs1494555)														
AA	141	89	1.0	104	116	1.9 (1.3-2.8)	73	1.0	98	1.9 (1.3-2.9)	2	1.0	7	5.8 (1.1-31.6)
AG or GG	153	127	1.0	134	120	1.1 (0.8-1.6)	103	1.0	89	1.0 (0.7-1.4)	8	1.0	15	2.2 (0.9-5.5)
$P_{forinteraction}$						.016				.016				.120
TNF_07 (rs1799724)														
CC	243	168	1.0	188	195	1.5 (1.1-2.0)	134	1.0	161	1.6 (1.2-2.1)	8	1.0	18	2.9 (1.2-6.8)
CT or TT	59	57	1.0	66	57	0.9 (0.5-1.6)	46	1.0	41	0.8 (0.5-1.4)	3	1.0	4	1.6 (0.3-8.1)
$P_{forinteraction}$						.056				.031				.147

ORs were adjusted for age, race, and total energy intakes.

and T-cell lymphoma (OR = 2.2; 95% CI, 1.1-4.4). However, statistical significance was only achieved among those with BMI between 25 and 30 kg/m², but not among those with BMI more than 30 kg/m². After stratification by common B-cell lymphoma subtypes, an increased risk was observed for diffuse large B-cell lymphoma (OR = 1.3; 95% CI, 0.9-1.9), marginal zone B-cell lymphoma (MZBCL, OR = 1.6; 95% CI, 0.8-3.3), and follicular lymphoma (OR = 1.4; 95% CI, 0.9-2.1), although none of them was statistically significant.

As shown in Table 3, a significantly increased risk of NHL was associated with BMI among women who carried certain cytokine polymorphisms. Compared with women whose BMI was less than 25 kg/m², women with a BMI more than or equal to 25.0 kg/m² had a significantly increased risk of NHL if they carried *IFNGR2* (rs9808753) AA genotype (OR = 1.5; 95% CI, 1.1-1.9), *IL5* (rs2069812) CT/TT genotypes (OR = 1.7; 95% CI, 1.2-2.4), *IL7R* (rs1494555) AA genotype (OR = 1.9; 95% CI, 1.3-2.8), and *TNF* (rs1799724) CC genotype (OR = 1.5; 95% CI, 1.1-2.0), but not among women who carried *IFNGR2* AG/GG, *IL5* CC, *IL7R* AG/GG, and *TNF* CT/TT genotypes. A similar pattern was also observed for B-cell lymphoma and T-cell lymphoma. A statistically significant interaction was only observed for *IFNGR2* (rs9808753 $P_{forinteraction}$ = .034) and *IL7R* (rs1494555 $P_{forinteraction}$ = .016) for NHL overall; *IL7R* (rs1494555 $P_{forinteraction}$ = .016) and *TNF* (1799724 $P_{forinteraction}$ = .031) for B-cell lymphoma; and *IL5* (rs2069812 $P_{forinteraction}$ = .034) for T-cell lymphoma. However, none of the interactions remained statistically significant after FDR adjustment.

After stratification by common B-cell lymphoma subtypes (Table 4), a significant interaction was observed for *IFNGR2* (rs9808753 $P_{forinteraction}$ = .006), *IL13* (rs20541 $P_{forinteraction}$ = .019), and *IL7R* (rs1494555 $P_{forinteraction}$ = .012) among MZBCL; *IL7R* (rs1494555 $P_{forinteraction}$ = .017) among small lymphocytic lymphoma/chronic lymphocytic leukemia; and *IL12A* (rs568408 $P_{forinteraction}$ = .013) and *TNF* (1799724 $P_{forinteraction}$ = .04) among follicular lymphoma. After adjustment for FDR, 3 interactions, *IFNGR2* (rs9808753), *IL13* (rs20541), and *IL7R* (rs1494555) with MZBCL, remained statistically significant. Although a significantly increased risk of NHL was observed for several other cytokine polymorphisms, none of them showed a significant interaction with BMI and risk of NHL and its subtypes (supplemental Tables 1-2, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Discussion

Our study provided the first comprehensive analysis of interaction between BMI, genetic polymorphisms in Th1/Th2 pathway genes, and risk of NHL and its subtypes. Significant interactions were observed for *IFNGR2* (rs9808753), *IL12A* (rs568408), *IL13* (rs20541), *IL5* (rs2069812), *IL7R* (rs1494555), and *TNF* (rs1799724) for NHL overall and/or various NHL subtypes.

Consistent with previous studies,[5,9-11,13,14,16-18] our study suggested that overweight/obesity was associated with an increased risk of NHL overall, B-cell lymphoma, and T-cell lymphoma. Macrophages and different types of T lymphocytes accumulating in expanding adipose tissue can interfere with both the innate and adaptive immune system.[32] In addition, cytokine polymorphisms, a germline mutation that may affect quality or quantity of cytokines, may enhance or deteriorate adipose inflammation and subsequently modify the association between BMI and risk of NHL.

Table 4. Associations between Th1/Th2 cytokine polymorphisms, BMI, and risk of common B-cell lymphoma subtypes

SNPs	DLBCL BMI < 25 kg/m² Cases	OR (95% CI)	BMI ≥ 25 kg/m² Cases	OR (95% CI)	MZBCL BMI < 25 kg/m² Cases	OR (95% CI)	BMI ≥ 25 kg/m² Cases	OR (95% CI)	SLL/CLL BMI < 25 kg/m² Cases	OR (95% CI)	BMI ≥ 25 kg/m² Cases	OR (95% CI)	FL BMI < 25 kg/m² Cases	OR (95% CI)	BMI ≥ 25 kg/m² Cases	OR (95% CI)
IFNGR2_01 (rs9808753)																
AA	58	1.0	61	1.3 (0.9-2.0)	8	1.0	17	2.8 (1.1-6.6)	27	1.0	21	1.1 (0.6-2.0)	39	1.0	47	1.6 (1.0-2.7)
AG or GG	15	1.0	21	1.3 (0.6-2.9)	7	1.0	2	0.3 (0.1-1.5)	3	1.0	5	1.6 (0.3-7.0)	13	1.0	11	0.8 (0.3-1.9)
$P_{\text{for interaction}}$		.834				.006				.529				.134		
IL12A_01 (rs568408)																
GG	51	1.0	56	1.3 (0.8-2.0)	10	1.0	14	1.7 (0.7-3.9)	23	1.0	19	1.0 (0.5-2.0)	47	1.0	40	1.1 (0.7-1.7)
AG or AA	23	1.0	26	1.6 (0.8-3.1)	5	1.0	5	1.7 (0.4-6.2)	8	1.0	7	1.1 (0.3-3.3)	5	1.0	20	5.5 (1.9-15.5)
$P_{\text{for interaction}}$		.770				.788				.646				.013		
IL13_01 (rs20541)																
GG	43	1.0	46	1.2 (0.8-2.0)	14	1.0	9	0.7 (0.3-1.8)	18	1.0	18	1.2 (0.6-2.4)	31	1.0	33	1.3 (0.7-2.2)
AG or AA	23	1.0	34	2.1 (1.1-3.9)	1	1.0	8	12.5 (1.5-106)	11	1.0	7	0.9 (0.3-2.4)	17	1.0	23	1.9 (0.9-3.9)
$P_{\text{for interaction}}$		.157				.019				.680				.817		
IL7R_01 (rs1494555)																
AA	31	1.0	36	1.6 (0.9-2.8)	3	1.0	10	5.2 (1.3-19.7)	9	1.0	16	2.9 (1.2-7.3)	23	1.0	29	1.9 (1.0-3.5)
AG or GG	36	1.0	41	1.3 (0.8-2.2)	12	1.0	5	0.5 (0.2-1.4)	20	1.0	9	0.5 (0.2-1.1)	26	1.0	26	1.2 (0.7-2.2)
$P_{\text{for interaction}}$		.381				.012				.017				.348		
TNF_07 (rs1799724)																
CC	52	1.0	66	1.6 (1.1-2.5)	12	1.0	14	1.5 (0.7-3.4)	21	1.0	21	1.3 (0.7-2.6)	38	1.0	49	1.8 (1.1-3.0)
CT or TT	17	1.0	16	0.9 (0.4-1.9)	3	1.0	4	1.4 (0.3-7.0)	8	1.0	6	0.7 (0.2-2.1)	13	1.0	9	0.6 (0.2-1.6)
$P_{\text{for interaction}}$		.141				.882				.325				.040		

ORs were adjusted for age, race, and total energy intake.

SLL/CLL indicates small lymphocytic lymphoma/chronic lymphocytic leukemia; and FL, follicular lymphoma.

The study suggested that *IFNGR2* polymorphism (rs9808753) may have modified the relationship between BMI and NHL risk for both B-cell lymphoma and T-cell lymphoma. The gene *IFNGR2* encodes the non–ligand-binding β-chain of the IFN-γ located on chromosome 21.[33] Initiation of the IFN-γ signal transduction cascade serves to directly inhibit viral replication and both stimulates and modulates the immune system. Recent evidence suggested that IFN-γ regulates fat inflammation and enhances adaptive immunity, which may contribute to the complications of obesity.[34] Although SNP rs9808753 leads to an amino acid substitution of arginine for glutamine (Gln64Arg) within *IFNGR2*, it is currently unclear whether this change would interfere with the binding ability with IFN-γ or alter other biologic functions. Effect modification was observed for T-cell and several B-cell lymphomas, suggesting that the IFN-γ transduction pathway could play a role in the relationship between BMI and risk of NHL.

We also observed a potential interaction between interleukin 12A (*IL12A*) and BMI and NHL overall, follicular lymphoma, and T-cell lymphoma risk. *IL12A* encodes the p35 subunit of *IL12* that is a heterodimeric cytokine consisting of 2 subunits, p35 (α-chain) and p40 (β-chain). IL12 is a key cytokine inducing the production of IFN-γ, eliciting the differentiation of Th1 cells and forming a link between innate resistance and adaptive immunity.[35,36] The observed effect modification could be the result of the disruption of the IFN-γ transduction pathway or some other unknown mechanism(s).

The gene *IL13* encodes an immunoregulatory cytokine produced primarily by activated Th2 cells. The IL13 cytokine exerts antiapoptotic functions and is linked to leukemogenesis.[37] Overexpression of *IL13* has been confirmed in HTLV-1-positive and Tax-transformed cells,[37] and a recent study reported that *IL13* (rs20541) AG/AA genotypes were associated with a reduced risk of T-cell lymphoma.[38] The current study found suggestive effect modification by *IL13* (rs20541) on the association between BMI and risk of T-cell lymphoma, diffuse large B-cell lymphoma, and MZBCL. Although the underlying mechanism is currently unclear, it is possible that the role of *IL13* on NHL risk is the result of unbalanced regulation and expression of Th1 and Th2 cytokines.

Potential effect modification by *IL7R* (rs1494555) was observed for MZBCL and small lymphocytic lymphoma/chronic lymphocytic leukemia in the current study. The *IL7R* encodes a receptor for IL-7. Proper functioning of *IL7R* requires the IL-2 receptor, a γ-chain, which is shared by various cytokines. It has been shown that *IL7R* plays a critical role in V(D)J recombination during lymphocyte development.[39-41] Mutations in the *IL7R* gene have been associated with severe combined immunodeficiency.[42] Further knowledge of genetic polymorphisms and the relationship to the cytokine network would help elucidate the association between BMI and NHL.

To date, *TNF* is one of the most promising candidate genes leading to increased susceptibility of NHL.[43-48] The *TNF* gene regulates the expression of the cytokine TNF-α, which gives rise to the inflammatory response to infection. Furthermore, high levels of TNF-α promote activation of the transcription factor nuclear factor-κB, which has antiapoptotic effects on B cells.[49] As obesity promotes increased production of TNF-α,[1] it is possible that genetic variations in *TNF* may modify the relationship between BMI and risk of NHL. In the current study, we found a potential interaction between *TNF* (rs1799724) SNP, BMI, and risk of follicular lymphoma.

The study has several strengths. First, it is a population-based, case-control study with histologically confirmed incident NHL cases, which minimized potential disease misclassification. Second, our study, for the first time, reported the effect of modification by Th1/Th2 genes and the association between BMI and NHL. The major limitation of our study is the modest sample size, particularly for NHL subtype analysis. As such, chance cannot be ruled out for some of the significant findings. However, we adjusted for multiple comparisons using the FDR approach because of the number of SNPs examined in the study. In addition, as the study to assess the interaction between genetic polymorphisms and BMI and risk of NHL, the topic warrants further investigation. Finally, the study was designed to investigate the role of hair dye use in relation to NHL risk. Only women were included in the study because of the higher prevalence of hair dye use among women. As such, the results may not be generalizable to men.

In conclusion, our study suggests that common genetic variations in the Th1/Th2 pathways genes may modify the association between BMI and risk of NHL. The positive results in our study need to be replicated in larger population studies with greater power.

Acknowledgments

Authorship

Contribution: Y.C., T.Z., F.F., X.C., M.D., Y.L., P.B., and Y.Z. conceived and led the study; T.Z., T.H., B.L., and Y.Z. carried out the population-based, case-control study; Q.L., N.R., and S.J.C. performed the genotyping at NCI; Y.C. and Y.Z. carried out the statistical analysis; Y.C., C.K., and Y.Z. drafted and revised the manuscript; and all authors reviewed and approved the manuscript.

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