Research Article

Cancer Epidemiology, Biomarkers & Prevention

Non-Hodgkin Lymphoma, Body Mass Index, and Cytokine Polymorphisms: A Pooled Analysis from the InterLymph Consortium

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Abstract

Background: Excess adiposity has been associated with lymphomagenesis, possibly mediated by increased cytokine production causing a chronic inflammatory state. The relationship between obesity, cytokine polymorphisms, and selected mature B-cell neoplasms is reported.

Method: Data on 4,979 cases and 4,752 controls from nine American/European studies from the InterLymph consortium (1988–2008) were pooled. For diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), joint associations of body mass index (from self-reported height and weight) and 12 polymorphisms in cytokines *IL1A* (rs1800587), *IL1B* (rs16944, rs1143627), *IL1RN* (rs454078), *IL2* (rs2069762), *IL6* (rs1800795, rs1800797), *IL10* (rs1800890, rs1800896), *TNF* (rs1800629), *LTA* (rs909253), and *CARD15* (rs2066847) were investigated using unconditional logistic regression. BMI-polymorphism interaction effects were estimated using the relative excess risk due to interaction (RERI).

Results: Obesity (BMI ≥ 30 kg/m^2) was associated with DLBCL risk [OR = 1.33; 95% confidence interval (CI), 1.02–1.73], as was *TNF-308GA+AA* (OR = 1.24; 95% CI, 1.07–1.44). Together, being obese and *TNF-308GA+AA* increased DLBCL risk almost 2-fold relative to those of normal weight and *TNF-308GG* (OR = 1.93; 95% CI, 1.27–2.94), with a RERI of 0.41 (95% CI, −0.05–0.84; $P_{\text{interaction}} = 0.13$). For FL and CLL/SLL, no associations with obesity or *TNF-308GA+AA*, either singly or jointly, were observed. No evidence of interactions between obesity and the other polymorphisms were detected.

Conclusions: Our results suggest that cytokine polymorphisms do not generally interact with BMI to increase lymphoma risk but obesity and *TNF-308GA+AA* may interact to increase DLBCL risk.

Impact: Studies using better measures of adiposity are needed to further investigate the interactions between obesity and *TNF-308G>A* in the pathogenesis of lymphoma. *Cancer Epidemiol Biomarkers Prev; 24(7); 1061–70. ©2015 AACR.*

Introduction

Immune dysregulation plays a pivotal role in lymphomagenesis, and epidemiologic research has tended to concentrate on factors and exposures that interact with the immune system. In this regard, obesity, which can cause a mild chronic inflammatory state, has been suggested to potentially increase the likelihood of lymphoid malignancy development. Earlier, InterLymph pooled analyses reported that obesity was associated with an increased risk of diffuse large B-cell lymphoma (DLBCL; refs. 1, 2), and recent meta-analyses provide further support for this hypothesis (3, 4).

Obesity-related inflammation is thought to result from the proinflammatory cytokines and chemokines that are produced by adipocytes and macrophages in adipose tissue (5). With weight gain, the numbers of adipocytes and macrophages increase as adipose tissue expands, increasing production of cytokines such as TNFα, leptin, IL1β, and IL6, as well as chemokines and acute phase proteins (5). Ideally, to investigate whether increased levels of inflammation-related cytokines modulate the association between obesity and lymphoid neoplasms, serum levels of cytokines would be measured before cancer diagnosis. In the absence of such measurements, single nucleotide polymorphisms (SNP) within genes that express cytokines may act as surrogates that

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indicate variation in risk of lymphoid neoplasms with obesity. Several putative functional SNPs in candidate cytokine genes were selected *a priori* by the InterLymph consortium due to their role in lymphoid development, and also in the pro-/anti-inflammatory pathways which may be altered in the obese state. Among these cytokine SNPs, *TNF* (−308G>A, rs1800629), *LTA* (−252A>G, rs909253), and *IL10* (−3575T>A, rs1800890) have been associated with lymphoid neoplasms and DLBCL in particular (6–8). There has, however, been little exploration of the relationship between obesity and cytokines on the risk of these malignancies (9–11). Here, we investigate gene–environment interactions between body mass index (BMI) and cytokine SNPs using data from case–control studies included in the International Lymphoma Epidemiology Consortium.

Materials and Methods

Data sources

Through the InterLymph consortium, nine case–control studies conducted in the United States and five European countries between 1988 and 2008 that had individual level data on BMI and cytokine polymorphisms contributed to this pooled analysis. Data were provided via the InterLymph Data Coordinating Center (DCC) at the Mayo Clinic (Rochester, MN) which was established in 2009 to centrally standardize and harmonize study data so that consistent datasets could be produced to expedite pooling projects. Descriptions of the included studies have been published (12–20); a brief outline is given in Table 1. Cases were ascertained using rapid identification techniques and controls were randomly selected from population registers (6 studies), outpatient clinics (1 study) or hospital in-patients with non-neoplastic conditions (2 studies). Each study had the appropriate ethical committees' approval and participants gave their informed consent.

Diagnoses of lymphoid neoplasms were pathologically confirmed and coded to the World Health Organization International Classification for Oncology Version 3 (ICDO3; 7 studies), REAL (Connecticut), and Working Formulation (UCSF) classifications. Diagnostic codes from the different schemas were bridged by the DCC (Mayo Clinic, Rochester, MN) using the same approach as in previous InterLymph analyses (21). The analysis here reports on specific lymphoid neoplasms: diffuse large B-cell lymphoma (DLBCL: ICDO3 codes 9679, 9680, 9684), follicular lymphoma (FL: 9690, 9691, 9695, 9698), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL: 9670, 9823) and all combined (defined by the above ICDO3 codes and 9671, 9673, 9675, 9687, 9689, 9699, 9700, 9701, 9702, 9705, 9708, 9709, 9714, 9716, 9717, 9718, 9719, 9728, 9729, 9826, 9827, 9832, 9833, 9591, and 9727). As most studies did not recruit cases with HIV-associated lymphoid neoplasms, these diagnoses were excluded.

Findings for the individual effects of BMI and cytokine SNPs on the risk of lymphoid neoplasms have been reported for the InterLymph studies (1, 6–8). In all studies, adult height and weight were self-reported, with information on weight requested for 1 year (NCI-SEER, UCSF, Connecticut), 2 years (Mayo Clinic), or 5 years (United Kingdom) before diagnosis or interview date or usual weight (SCALE, EpiLymph). BMI, calculated from weight in kilograms and height in meters, was classified according to World Health Organization guidelines as: normal weight (18.5–<25 kg/m^2); overweight (25–<30 kg/m^2); or obese (≥30 kg/m^2); the 1% of the study population who were underweight (<18.5 kg/m^2) were excluded from the analyses (22). BMI as a continuous variable was defined as per 5 kg/m^2 increase above 18.5 kg/m^2. Cytokine SNPs were tested using the TaqMan platform (Applied Biosystems), Pyrosequencing, custom Illumina GoldenGate 1,536 SNP oligonucleotide pool (OPA), or iSelect (6–8, 14). Twelve SNPs in nine candidate genes were investigated: 2q14, *IL1A* −889C→T (rs1800587; 4 studies, 2,195 cases, and 2,082 controls), *IL1B* −511C→T (rs16944; 3 studies, 1,843 cases, and 1,695 controls), and *IL1B* −31C→T (rs1143627; 4 studies, 2,188 cases, and 2,099 controls); in 2q14.2, *IL1RN* 9589A→T (rs454078; 3 studies, 1,673 cases, and 1,598 controls); in 4q26–27, *IL2* −384T→G (rs2069762; 4 studies, 2,185 cases, and 2,085 controls); in 7p21, *IL6* −174G→C (rs1800795; 4 studies, 2,203 cases, and 2,095 controls) and *IL6* −597G→A (rs1800797; 3 studies, 1,679 cases, and 1,591 controls); in 1q31–32, *IL10*−3575T→A (rs1800890; 9 studies, 5,015 cases, and 5,061 controls) and *IL10*−1082A→G (rs1800896; 7 studies, 2,844 cases, and 3,328 controls); in 6p21.3, *TNF*−308G→A (rs1800629; 9 studies, 4,979 cases, and 4,752 controls) and *LTA*252A→G (rs909253; 9 studies, 5,067 cases, and 4,879 controls); and in 16q21, *CARD15* Ex11–35→C (rs2066847; 7 studies, 4,267 cases, and 4,092 controls). SNPs were modeled as dichotomous variables assuming dominant inheritance (heterozygous/homozygous variant versus homozygous wild-type genotypes) as suggested by InterLymph analyses (6–8), to increase power and reduce the number of statistical tests. Because of potential ethnic differences in body fat and SNP distributions, analyses were restricted to persons who described themselves as of White European descent.

Statistical analyses

Risk estimates were calculated using unconditional logistic regression adjusted for study, sex, and age. Main and joint associations with BMI and each SNP on the risk of lymphoid neoplasms were estimated. Additive interactions between SNP and BMI were estimated by the relative excess risk due to interaction (RERI). When BMI was a categorical variable, the 95% confidence intervals (CI) for RERI were estimated using likelihood-based 95% CI (23). For BMI as a continuous variable, 10,000 bootstrapping samples (without replacement) of the original sample size were taken from the dataset and the 95% CIs were the 2.5th and 97.5th centile of the bootstrap sampling distribution (24).

Analyses were repeated for DLBCL, FL, and CLL/SLL, and all controls were used irrespective of the individual studies' matching techniques. Heterogeneity between study-specific risk estimates was considered present when a test for interaction between the variable of interest and study was statistically significant ($P < 0.05$). Potential sources were investigated using sensitivity analyses by: study design (population- or hospital-based); diagnosis classification; participation rates; continent; proportions of cases and controls with SNP data; whether the controls' SNP data were in Hardy–Weinberg equilibrium; or where there was no relationship between obesity and the SNP among controls. All analyses were conducted using Stata 13.1.

Results

Data were received for a total of 5,844 cases and 6,167 controls. The majority of cases were diagnosed with mature B-cell neoplasms (90%), comprising DLBCL (28%), FL (23%), CLL/SLL (19%), and other B-cell subtypes (20%); 6% were T-cell in origin and 4% had no immunophenotype or subtype recorded. A higher proportion of cases were men (53%) and the median age at diagnosis was 60

Table 1. Characteristics of case–control studies included in the pooled analysis

			Cases (*N* = 5,844)		Controls (*N* = 6,167)		
Study	**Location**	**Years of diagnosis**	**Age range**	***N***	**Participation (%)**	**Source**	***N***	**Participation (%)**
NCI-SEER (12)	Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington	1998–2001	20–70	895	76	<65 years random digit dialing; 65+ years random selection from Centers for Medicare and Medicaid Services, stratified by study area, age, sex, and race	686	52
Mayo Clinic Phases 1–3 (13, 14)	Iowa, Wisconsin, Minnesota	2002–2008	18+	887	69	Frequency matched by age, sex, and county of residence	1,046	69
UCSF (15)	San Francisco	1988–1995	21–74	309	72	Random digit dialing, frequency matched by age, sex, and county of residence	685	78
Connecticut (16)	Connecticut	1995–2001	21–84 women only	483	72	Women only: <65 years random digit dialing; 65+ years random selection from Centers for Medicare and Medicaid Services. Frequency matched within 5 years of age	553	RDD:69; CMMS:47
UK (17)	Yorkshire, Lancashire, South Lakeland and parts of Southwest England	1998–2003	16–69	626	70	Random selection from general practice lists, individually matched by age, sex, and region of residence	784	69
SCALE Denmark (18)	Denmark	2000–2002	18–74	768	81	Random selection from population register, frequency matched by sex and age	745	71
SCALE Sweden (18)	Sweden	2000–2002	18–74	1,528	81	Random selection from population register, frequency matched by sex and age	1,116	71
EpiLymph France (19)	Amiens, Dijon, and Montpellier	2000–2003	18–80	85	91	Hospital controls matched by age (±5 years), sex, and study region	129	74
EpiLymph Spain (20)	Barcelona, Tortosa, Reus, and Madrid	1998–2002	18–80	263	82	Hospital controls matched by age (±5 years), sex, and study region	423	96

Table 2. Demographics of cases and controls

	Cases *N* (%)	Controls *N* (%)
Total	5,844 (100)	6,167 (100)
Diagnosis		
B-cell	5,241 (90)	—
DLBCL	1,643 (28)	—
Follicular	1,344 (23)	—
CLL/SLL	1,089 (19)	
Other	1,165 (20)	—
T-cell	342 (6)	—
Not otherwise specified	261 (3)	—
Sex		
Male	3,088 (53)	3,101 (50)
Female	2,756 (47)	3,066 (50)
Age, years		
<46	803 (14)	1,128 (18)
46–55	1,319 (23)	1,236 (20)
56–65	1,824 (31)	1,710 (28)
>65	1,898 (32)	2,093 (34)
Socioeconomic status		
Low	2,130 (36)	2,045 (33)
Medium	1,825 (31)	1,945 (32)
High	1,860 (32)	2,145 (35)
Not known	29 (0.5)	32 (0.5)
BMI (kg/m^2)		
Underweight: <18.5	57 (1)	75 (1)
Normal weight: 18.5–<25	2,573 (44)	2,851 (46)
Overweight: 25–<30	2,214 (38)	2,275 (37)
Obese: ≥30	1,000 (17)	966 (16)

years. Controls were more likely to be women, of younger age, and higher socioeconomic status than cases (Table 2).

Table 3 shows findings for the twelve cytokine polymorphisms among the subsets of subjects who had genotype data for each SNP as well as BMI data. Positive associations were found with DLBCL for *TNF-308G>A* (OR = 1.24; 95% CI, 1.07–1.44), *IL10-1082A>G* (OR = 1.14; 95% CI, 1.00–1.31), and *CARD15 Ex11-35>C* (OR = 1.25; 95% CI, 1.10–1.56); with FL for the two *IL10* SNPs (*IL10-3575T>A*: OR = 1.15; 95% CI, 1.04–1.28; *IL10-1082A>G*: OR = 1.10; 95% CI, 1.05–1.15); and with CLL/SLL for *IL1RN 9589A>T* (OR = 1.50; 95% CI, 1.17–1.91). A few negative associations were also found for FL with *IL6 -597G>A* (OR = 0.81; 95% CI, 0.78–0.85) and *LTA 252A>G* (OR = 0.93; 95% CI, 0.87–0.99); and for CLL/SLL with *IL1B -511C>T* (OR = 0.84; 95% CI, 0.81–0.87). Table 4 shows findings between DLBCL, FL, and CLL/SLL and being overweight or obese for the subsets of subjects with data for the five positively associated polymorphisms; findings for BMI in the subsets for the other seven polymorphisms were similar (data not shown). Risk estimates were increased for DLBCL among obese individuals compared with those of normal weight in subsets with *TNF-308G>A* (OR = 1.33; 95% CI, 1.02–1.73), *IL10-1082A>G* (OR = 1.39; 95% CI, 1.12–1.73) and *CARD15 Ex11-35>C* (OR = 1.41; 95% CI, 1.04–1.91) data. For FL, there was no evidence that being obese increased risk (OR = 1.00; 95% CI, 0.81–1.24; OR = 1.13; 95% CI, 0.91–1.40 in the *IL10-3575T>A* and *IL10-1082A>G* subsets for example); while for CLL/SLL, some decreased associations with obesity were found (OR = 0.80; 95% CI, 0.69–0.93 in the *IL10-3575T>A* subset for example).

For DLBCL, the only subtype associated with obesity, tests for departure from additive interaction showed weak evidence for an additional effect of obesity and *TNF-308GA+AA* on DLBCL risk ($P_{interaction}$ = 0.13); there was no evidence for the other two polymorphisms positively associated with this subtype ($P_{interaction}$ = 0.77 and 0.85 for *IL10-1082A>G* and *CARD15 Ex11-35>C*, respectively). Table 5 shows joint associations of BMI and *TNF-308G>A* on DLBCL risk, with the RERI; for completeness, joint associations and RERIs of BMI and the other polymorphisms for all three subtypes are given in Supplementary Tables S1 and S2 for categorical and continuous BMI, respectively. For DLBCL, risk estimates were increased among those who were overweight or obese irrespective of *TNF-308G>A* status (overweight and GG: OR = 1.21; 95% CI, 1.02–1.44; overweight and GA+AA: OR = 1.31; 95% CI, 1.00–1.71; obese and GG: OR = 1.25; 95% CI, 1.00–1.56). However, being both obese and having the *TNF-308A* allele almost doubled the risk estimate compared with persons of normal weight who did not carry the A allele (OR = 1.93; 95% CI, 1.27–2.94); an additional risk from being obese and having *TNF-308A* variant rather than having either risk factor alone was suggested (RERI = 0.41; 95% CI, −0.05–0.84). Similarly, increased trends with 5 kg/m^2 increase in BMI above 18.5 kg/m^2 were seen in homozygous wild types and variant TNF-308A carriers (OR = 1.14; 95% CI, 1.07–1.22; OR = 1.19; 95% CI, 1.12–1.27, respectively). The corresponding RERI of 0.05 (95% CI, −0.005–0.08) suggests that with every 5 kg/m^2 rise in BMI, the risk of DLBCL is 0.05 more than if there was no interaction.

Joint associations of BMI and *TNF-308G>A* genotype on DLBCL risk were not consistent across studies ($P_{heterogeneity}$ = 0.02). Associations were similar among North American studies, with evidence of additive interaction (RERI = 1.27; 95% CI, 0.48–2.08); but not among European studies (RERI = −0.25; 95% CI, −0.84–0.28; Table 6). Heterogeneity was present among studies that were population-based, which used the ICDO3 disease classification, where participation rates were 70% or more, where 90% or more of subjects were genotyped, where control distributions of *TNF* genotypes were in Hardy–Weinberg equilibrium; or where BMI and *TNF-308G>A* genotypes were not correlated among controls. In these groupings, the risk estimates of being obese and having *TNF-308GA+AA* genotype tended to be similar, and RERIs were all above zero, although most were not statistically significant.

Discussion

This InterLymph analysis of the joint associations of BMI and cytokine polymorphisms on the risk of the three most common lymphoid neoplasms found some evidence of interaction between obesity and *TNF-308G>A* (rs1800629). For DLBCL, the risk was greatest among those who were obese and carried the *TNF-308A* allele, although risk was also increased among the overweight regardless of *TNF* status. The associations showed some variation between studies, but these differences were not explained by study design, disease classification, or other factors. On the other hand, being obese and carrying *TNF-308A* did not increase the risk of either FL or CLL/SLL. Besides *TNF-308G>A*, other cytokine SNPs in *IL1A* (rs1800587), *IL1B* (rs16944, rs1143627), *IL1RN* (rs454078), *IL2* (rs2069762), *IL6* (rs1800795, rs1800797), *IL10* (rs1800890, rs1800896), *LTA* (rs909253), and *CARD15* (rs2066847) showed little evidence of altering the non-Hodgkin lymphoma (NHL) risk associated with being overweight.

Since publication of the InterLymph pooled analysis of BMI, where we reported that obesity increased DLBCL risk (1), several studies including cohorts have also found this

Table 3. Associations with cytokine polymorphisms among cases and controls with BMI data

	DLBCL			FL			CLL/SLL			Lymphoid neoplasms		
	Case/control	OR[a]	95% CI	Case/control	OR[a]	95% CI	Case/control	OR[a]	95% CI	Case/control	OR[a]	95% CI
TNF-308G→A (rs1800629)												
Number of studies = 9[b]	1,477/4,752	$\chi^2 = 12.9$	$P_{het} = 0.11$	1,176/4,752	$\chi^2 = 4.22$	$P = 0.84$	875/3,576	$\chi^2 = 13.5$	$P_{het} = 0.04$	4,979/4,752	$\chi^2 = 11.3$	$P_{het} = 0.19$
GG	951/3,322	1 ref		827/3,322	1 ref		594/2,525	1 ref		3,319/3,322	1 ref	
GA/AA	513/1,371	1.24	1.07–1.44	344/1,371	0.95	0.86–1.06	271/1,000	1.08	0.87–1.34	1,616/1,371	1.14	1.02–1.27
LTA 252A→G (rs909253)												
Number of studies = 9[b]	1,510/4,879	$\chi^2 = 19.3$	$P_{het} = 0.01$	1,184/4,879	$\chi^2 = 2.11$	$P_{het} = 0.98$	888/3,694	$\chi^2 = 10.2$	$P_{het} = 0.12$	5,067/4,879	$\chi^2 = 11.0$	$P_{het} = 0.20$
AA	620/2,201	1 ref		544/2,021	1 ref		371/1,701	1 ref		2,161/2,201	1 Ref	
AG/GG	877/2,617	1.15	0.95–1.40	634/2,617	0.93	0.87–0.99	507/1,941	1.14	0.99–1.31	2,860/2,617	1.08	0.98–1.18
IL10−3575T→A (rs1800890)												
Number of studies = 9[b]	1,515/5,061	$\chi^2 = 19.5$	$P_{het} = 0.01$	1,160/5,061	$\chi^2 = 6.57$	$P_{het} = 0.58$	883/3,895	$\chi^2 = 5.61$	$P_{het} = 0.47$	5,015/5,061	$\chi^2 = 14.6$	$P_{het} = 0.07$
TT	430/1,559	1 ref		324/1,559	1 ref		231/1,136	1 ref		1,375/1,559	1 ref	
TA/AA	1,072/3,442	1.08	0.87–1.35	830/3,442	1.15	1.04–1.28	642/2,708	0.91	0.80–1.04	3,595/3,442	1.07	0.95–1.22
IL10−1082A→G (rs1800896)												
Number of studies = 7[b]	948/3,328	$\chi^2 = 4.25$	$P_{het} = 0.64$	779/3,328	$\chi^2 = 2.00$	$P_{het} = 0.92$	340/2,161	$\chi^2 = 5.94$	$P_{het} = 0.20$	2,844/3,328	$\chi^2 = 4.66$	$P_{het} = 0.59$
AA	240/944	1 ref		199/944	1 ref		101/631	1 ref		744/944	1 ref	
AG/GG	702/2,339	1.14	1.00–1.31	576/2,339	1.10	1.05–1.15	236/1,494	0.98	0.72–1.35	2,077/2,339	1.11	1.03–1.20
CARD15 Ex11–35→C (rs2066847)												
Number of studies = 6[b]	1,261/4,092	$\chi^2 = 3.26$	$P_{het} = 0.66$	972/4,092	$\chi^2 = 12.6$	$P_{het} = 0.03$	735/2,645	$\chi^2 = 2.65$	$P_{het} = 0.45$	4,267/4,092	$\chi^2 = 3.71$	$P_{het} = 0.59$
–	1,199/3,098	1 ref		937/3,098	1 ref		703/2,530	1 ref		4,081/3,098	1 ref	
−+/++	51/138	1.25	1.01–1.56	32/138	1.06	0.48–2.36	23/83	1.28	0.79–2.08	147/138	1.17	0.92–1.49
IL1A−889C→T (rs1800587)												
Number of studies = 4[b]	778/2,082	$\chi^2 = 1.49$	$P_{het} = 0.68$	634/2,082	$\chi^2 = 2.63$	$P_{het} = 0.45$	234/1,601	$\chi^2 = 2.77$	$P_{het} = 0.25$	2,195/2,082	$\chi^2 = 3.83$	$P_{het} = 0.28$
CC	396/998	1 ref		311/998	1 ref		108/770	1 ref		1,082/998	1 ref	
CT/TT	377/1,054	0.90	0.80–1.00	320/1,054	0.96	0.81–1.13	124/808	1.09	0.80–1.48	1,096/1,054	0.95	0.84–1.08
IL1B−31C→T (rs1143627)												
Number of studies = 4[b]	769/2,099	$\chi^2 = 5.99$	$P_{het} = 0.11$	633/2,099	$\chi^2 = 6.28$	$P_{het} = 0.10$	232/1,621	$\chi^2 = 2.65$	$P_{het} = 0.27$	2,188/2,099	$\chi^2 = 5.08$	$P_{het} = 0.17$
CC	340/922	1 ref		284/922	1 ref		107/730	1 ref		988/922	1 ref	
CT/TT	423/1,147	0.97	0.75–1.26	346/1,147	0.96	0.75–1.23	123/868	0.98	0.70–1.37	1,182/1,147	0.96	0.83–1.11
IL2−384T→G (rs2069762)												
Number of studies = 4[b]	770/2,085	$\chi^2 = 4.83$	$P_{het} = 0.19$	635/2,085	$\chi^2 = 2.40$	$P_{het} = 0.49$	232/1,604	$\chi^2 = 2.30$	$P_{het} = 0.32$	2,185/2,085	$\chi^2 = 4.70$	$P_{het} = 0.20$
TT	388/1,007	1 ref		309/1,007	1 ref		112/775	1 ref		1,062/1,007	1 ref	
TG/GG	376/1,048	0.93	0.79–1.09	323/1,048	0.99	0.85–1.15	118/806	1.03	0.80–1.33	1,105/1,048	1.00	0.86–1.16
IL6−174G→C (rs1800795)												
Number of studies = 4[b]	772/2,095	$\chi^2 = 3.77$	$P_{het} = 0.29$	640/2,095	$\chi^2 = 4.70$	$P_{het} = 0.20$	234/1,620	$\chi^2 = 2.71$	$P_{het} = 0.26$	2,203/2,095	$\chi^2 = 2.13$	$P_{het} = 0.55$
GG	271/703	1 ref		222/703	1 ref		81/541	1 ref		777/703	1 ref	
GC/CC	495/1,362	0.94	0.79–1.12	415/1,362	0.94	0.73–1.21	151/1,056	0.92	0.66–1.22	1,408/1,362	0.93	0.83–1.03
IL1B−511C→T (rs16994)												
Number of studies = 3[b]	708/1,695	$\chi^2 = 6.77$	$P_{het} = 0.03$	542/1,695	$\chi^2 = 2.99$	$P_{het} = 0.22$	136/1,217	$\chi^2 = 0.01$	$P_{het} = 0.92$	1,843/1,695	$\chi^2 = 3.96$	$P_{het} = 0.14$
CC	311/733	1 ref		247/733	1 ref		67/543	1 ref		832/733	1 ref	
CT/TT	392/934	0.98	0.71–1.35	292/934	0.92	0.74–1.14	68/653	0.84	0.59–1.20	996/934	0.94	0.79–1.12
IL1RN 9589A→T (rs454078)												
Number of studies = 3[b]	478/1,598	$\chi^2 = 5.75$	$P_{het} = 0.06$	422/1,598	$\chi^2 = 2.78$	$P_{het} = 0.25$	231/1,598	$\chi^2 = 2.07$	$P_{het} = 0.36$	1,673/1,598	$\chi^2 = 3.98$	$P_{het} = 0.14$
AA	250/885	1 ref		210/885	1 ref		105/885	1 ref		849/885	1 ref	
AT/TT	224/691	1.16	0.88–1.53	209/691	1.26	0.96–1.65	124/691	1.50	1.17–1.91	808/691	1.22	1.01–1.48
IL6−597G→A (rs1800797)												
Number of studies = 3[b]	488/1,591	$\chi^2 = 3.99$	$P_{het} = 0.14$	421/1,591	$\chi^2 = 0.08$	$P_{het} = 0.96$	233/1,591	$\chi^2 = 2.17$	$P_{het} = 0.34$	1,679/1,591	$\chi^2 = 0.31$	$P_{het} = 0.86$
GG	169/536	1 ref		160/536	1 ref		85/536	1 ref		615/535	1 ref	
GA/AA	315/1,031	0.95	0.71–1.28	258/1,031	0.81	0.78–0.85	146/1,031	0.87	0.67–1.12	1,048/1,031	0.87	0.82–0.93

[a]OR and 95% CIs estimated using logistic regression adjusted for sex, age, and study.

[b]Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the cytokine and study variables with the basic model which adjusted for study. For FL, EpiLymph- France and Spain were considered together due to small numbers of cases in some strata. Fewer studies had data for CLL/SLL (7 studies with *TNF-308G>A, LTA252A>G*, or *IL10−3575T>A* data; 5 studies with *IL10−1082A>G* or *CARD15 Ex11–35→C* data; 3 studies with *IL1A-889C>T, IL1B-31C>T, IL2−384T>G*, or *IL6−174G>C* data; and 2 studies with *IL1B-511C>T* data).

Table 4. Associations with BMI among cases and controls where there is an association with the cytokine polymorphism

	DLBCL			FL			CLL/SLL			Lymphoid neoplasms		
BMI[a]	Case/control	OR[b]	95% CI	Case/control	OR[b]	95% CI	Case/control	OR[b]	95% CI	Case/control	OR[b]	95% CI
TNF-308G→A (rs1800629)												
Number of studies = 9[c]	1,477/4,752	$\chi^2 = 31.2$	$P_{het} = 0.01$	1,176/4,752	$\chi^2 = 11.6$	$P_{het} = 0.77$	875/3,576	$\chi^2 = 6.79$	$P_{het} = 0.87$	4,979/4,752	$\chi^2 = 30.1$	$P_{het} = 0.02$
Normal	650/2,275	1 ref		567/2,275	1 Ref		396/1,580	1 ref		2,262/2,275	1 Ref	
Overweight	548/1,689	1.14	0.91–1.43	422/1,689	1.05	0.92–1.20	344/1,310	0.90	0.75–1.10	1,862/1,689	1.05	0.90–1.21
Obese	266/729	1.33	1.02–1.73	182/729	1.05	0.87–1.26	125/635	0.80	0.67–0.96	811/729	1.08	0.90–1.30
Per 5 kg/m^2		1.16	1.09–1.23		1.02	0.95–1.10		0.93	0.85–1.02		1.05	1.01–1.10
IL10−3575T→A (rs1800890)												
Number of studies = 9[c]	1,515/5,061	$\chi^2 = 29.9$	$P_{het} = 0.02$	1,160/5,061	$\chi^2 = 14.0$	$P_{het} = 0.60$	883/3,895	$\chi^2 = 8.02$	$P_{het} = 0.78$	5,015/5,061	$\chi^2 = 30.2$	$P_{het} = 0.02$
Normal	660/2,406	1 ref		565/2,406	1 ref		399/1,717	1 ref		2,281/2,406	1 Ref	
Overweight	575/1,822	1.15	0.93–1.42	413/1,822	1.03	0.89–1.19	347/1,449	0.89	0.72–1.11	1,882/1,822	1.02	0.87–1.20
Obese	267/773	1.29	0.98–1.69	176/773	1.00	0.81–1.24	127/678	0.80	0.69–0.93	807/773	1.04	0.86–1.27
Per 5 kg/m^2		1.15	1.08–1.22		1.01	0.94–1.09		0.92	0.84–1.01		1.04	0.99–1.09
IL10−1082A→G (rs1800896)												
Number of studies = 7[c]	948/3,328	$\chi^2 = 19.7$	$P_{het} = 0.07$	779/3,328	$\chi^2 = 8.57$	$P_{het} = 0.74$	340/2,161	$\chi^2 = 2.28$	$P_{het} = 0.97$	2,844/3,328	$\chi^2 = 16.0$	$P_{het} = 0.19$
Normal	404/1,568	1 ref		362/1,568	1 Ref		132/878	1 Ref		1,215/1,568	1 Ref	
Overweight	343/1,151	1.20	1.05–1.38	273/1,151	1.09	0.93–1.28	140/778	0.96	0.76–1.20	1,040/1,151	1.10	1.00–1.21
Obese	195/564	1.39	1.12–1.73	140/564	1.13	0.91–1.40	65/469	0.75	0.63–0.90	566/564	1.15	1.00–1.33
Per 5 kg/m^2		1.15	1.07–1.24		1.04	0.96–1.13		0.89	0.79–1.01		1.06	1.01–1.12
CARD15 Ex11–35→C (rs2066847)												
Number of studies = 6[c]	1,261/4,092	$\chi^2 = 19.5$	$P_{het} = 0.03$	972/4,092	$\chi^2 = 7.43$	$P_{het} = 0.68$	735/2,645	$\chi^2 = 6.46$	$P_{het} = 0.37$	4,267/4,092	$\chi^2 = 23.5$	$P_{het} < 0.01$
Normal	553/2,005	1 ref		486/2,005	1 ref		345/1,165	1 ref		1,983/2,005	1 ref	
Overweight	469/1,483	1.10	0.85–1.42	356/1,483	1.03	0.89–1.18	285/1,010	0.85	0.67–1.08	1,614/1,483	1.01	0.85–1.20
Obese	228/558	1.41	1.04–1.91	127/558	0.94	0.78–1.14	96/438	0.79	0.61–1.01	631/558	1.04	0.81–1.34
Per 5 kg/m^2		1.19	1.11–1.27		0.99	0.91–1.08		0.91	0.82–1.02		1.04	0.99–1.09
IL1RN 9589A→T (rs454078)												
Number of studies = 3[c]	478/1,598	$\chi^2 = 3.99$	$P_{het} = 0.41$	422/1,598	$\chi^2 = 2.94$	$P_{het} = 0.57$	231/1,598	$\chi^2 = 2.06$	$P_{het} = 0.72$	1,673/1,598	$\chi^2 = 1.37$	$P_{het} = 0.85$
Normal	163/650	1 ref		175/650	1 ref		88/650	1 Ref		628/650	1 ref	
Overweight	186/575	1.30	1.25–1.35	143/575	0.94	0.78–1.13	94/575	0.97	0.64–1.46	625/575	1.09	0.98–1.22
Obese	125/351	1.43	0.99–2.05	101/351	1.05	0.79–1.41	47/351	0.79	0.61–1.03	404/351	1.16	1.12–1.19
Per 5 kg/m^2		1.16	1.06–1.28		1.01	0.91–1.12		0.93	0.80–1.07		1.07	1.00–1.14

[a]BMI: Normal weight, 18.5–<25 kg/m^2; overweight, 25–<30 kg/m^2; obese $\geq$ 30 kg/m^2.

[b]ORs and 95% CI estimated using logistic regression adjusted for sex, age, and study.

[c]Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the BMI and study variables with the basic model which adjusted for study. For FL, EpiLymph- France and Spain were considered together due to small numbers of cases in some strata. Fewer studies had data for CLL/SLL (7 studies with *TNF-308G>A* or *IL10–3575T>A* data; and 5 studies with *IL10–1082A>G* or *CARD15 Ex11–35→C* data).

Table 5. Joint associations and relative excess risks due to interaction between BMI and *TNF-308G>A* (rs1800629) for DLBCL

	TNF-308GG		*TNF-308GA/AA*		
BMI[a]	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	RERI (95% CI)[c]
Normal	412/1,591	1 (ref)	238/684	1.27 (1.07–1.52)	—
Overweight	372/1,201	1.21 (1.02–1.44)	176/488	1.31 (1.00–1.71)	−0.18 (−0.47–0.10)
Obese	167/530	1.25 (1.00–1.56)	99/199	1.93 (1.27–2.94)	0.41 (−0.05–0.84)
		$\chi^2 = 59.9$; $P_{het} = 0.02$[d]			$\chi^2 = 4.10$; $P_{int} = 0.13$[e]
Per 5 kg/m^2		1.14 (1.07–1.22)		1.19 (1.12–1.27)	0.05 (−0.005–0.08)

[a]BMI: Normal weight, 18.5–<25 kg/m^2; overweight; 25–<30 kg/m^2; obese, ≥30 kg/m^2.

[b]ORs and 95% CIs estimated using logistic regression adjusted for sex, age, and study.

[c]RERI estimated using linear odds ratio regression adjusted for sex, age, and study and its 95% CI for categorical BMI were likelihood-based, derived using maximum likelihood estimation; or by bootstrapping percentile method for continuous BMI.

[d]Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the joint effect and study variables with the basic model which adjusted for study.

[e]Tests for departure from additive interaction between BMI and *TNF* were conducted using the likelihood ratio test on linear odds ratio model.

relationship (25–29) while others have not (11, 30–36). In summarizing published data for DLBCL and obesity, two meta-analyses have noted an increased risk (3, 4), the latest including all but the most recent publications (27, 28). Unfortunately, however, several studies which reported no association with total NHL did not stratify their data by subtype (32, 37–39). To further explore the mechanisms underlying the relationship between obesity and lymphoma, chronic inflammation involving cytokine production is one possible pathway that has been investigated mostly by examining SNPs (9–11), although the functional roles for some are not yet conclusive (40). One study measured prediagnosis serum levels of cytokines and found no association between TNF levels and NHL among either normal or overweight persons (9). When examining SNPs in *TNF*, Wang and colleagues noted an excess risk of DLBCL among obese individuals carrying the *TNF-308A* allele and, although Chen and colleagues did not report joint associations, a similar finding among overweight women is suggested (crude OR = 1.8; 95% CI, 1.0–3.2; refs. 10, 11). To our knowledge, these are the only studies to have investigated cytokine SNPs in relation to the effect obesity may have on lymphoma risk, and both are included in this pooled analysis.

TNF has been implicated in the relationship between obesity and several other cancers including breast, endometrium, and gastrointestinal (41–43); the promotion of tumor cell proliferation through activation of NFκB being suggested as the most likely explanation (44). In obesity, B cells, T cells, and macrophages infiltrate the expanding adipose tissue, and not only lead to, but also maintain, a chronic inflammatory state (5). The macrophages secrete most of the TNF produced by adipose tissue, which escapes into circulation to bind to and activate its receptor TNFR, which is expressed in all human tissues (5, 41). TNF activates IL6 in adipose tissue and downstream of both cytokines are the NFκB and STAT3 cycles. These pathways have important roles in lymphocyte development, function, and survival, and deregulation of these cycles are seen in lymphoid malignancies including DLBCL, the most common aggressive subtype examined here (26). Obesity-related lymphomagenesis is likely to be complex involving the actions of additional proinflammatory cytokines and immunomodulatory mediators that trigger downstream targets that promote the clonal expansion and transformation of B cells with premalignant lesions. Further studies will be needed to investigate possible disease mechanisms.

When assessing gene–environment interactions, differential misclassification can bias the interaction estimate in either direction (45). Our data may not be free from differential case–control participation and reporting. Among controls, obesity-related health problems may have influenced their participation and for cases, although rapid ascertainment techniques were employed, those with poor survival, which may be related to different degrees of adiposity (46), could have been missed. Our anthropometric data were self-reported and BMI could be biased toward "normal" weight as respondents tend to overestimate their height and underestimate their weight to varying degrees dependent on their gender and age (47). Cases' responses could also have been influenced by weight loss associated with lymphoma, although several studies attempted to compensate for this by requesting weight at a year or more before diagnosis. The effect of participation bias on our finding of an interaction will be limited if obesity and *TNF-308G>A* are associated in the general population. *TNF-308G>A* SNP has been suggested to be related, albeit weakly, to obesity, but the mechanism for *TNF* gene involvement in obesity pathogenesis is unclear (48). If there is an association, persons carrying the variant allele may be under- (or over-) represented in our data if body fatness is related to participation, or the stratum-specific frequencies on gene and BMI category could be inaccurate, biasing the interaction estimate in either direction. Among our controls, *TNF* genotype and BMI overall were not correlated in all but two of our studies (NCI-SEER, EpiLymph-Spain); the removal of these did not alter our findings.

Strengths of our study include its large sample size, giving the potential to examine interactions and explore differences in interactions among the most common lymphoid neoplasms. Obesity prevalence varies across countries, which could relate differently to subjects' participation and responses in the studies included. Most studies had not published on this topic before, and while data were a subset of studies and subjects included in the main effects analyses, the risk estimates for BMI and SNPs were consistent with those published previously (1, 6–8). A reduced risk of CLL/SLL with obesity was found in some subsets of data, which could relate to disease-related weight loss; but in larger InterLymph datasets, no obesity associations for CLL/SLL have been reported (1). Other limitations are the low power to assess interactions in less common lymphoid neoplasms and some SNPs which were tested in only a few studies. Indeed, statistically significant interactions were found with SNPs genotyped in all nine studies, and others with fewer may have shown an effect had we had more data. Many other candidate cytokine SNPs were not associated with lymphoid neoplasms, and so it is not surprising that no joint association was found between obesity and these SNPs. BMI in this analysis related to weight at older age and there was no evidence that associations were different among those aged under or over 65 years; data on BMI in young

Table 6. Sensitivity analyses by study design factors on overall risk estimates and relative excess risks due to interaction for DLBCL associated with being obese and *TNF-308A* genotype (rs1800629)

	Studies	Study heterogeneity[a]	Normal GA+AA[b] OR (95% CI)[c]	Obese GG[b] OR (95% CI)[c]	Obese GA+AA[b] OR (95% CI)[c]	Departure from additive interaction[d]	RERI (95% CI)[e]
Continent							
North America	NCI-SEER, Mayo, UCSF1, Connecticut	$\chi^2 = 12.0$; $P_{het} = 0.68$	1.25 (0.91–1.70)	1.19 (0.88–1.62)	2.71 (1.84–4.01)	$\chi^2 = 7.56$; $P_{interaction} = 0.02$	1.27 (0.48–2.08)
Europe	UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France, EpiLymph-Spain	$\chi^2 = 38.1$; $P_{het} = 0.01$	1.29 (1.02–1.63)	1.37 (1.01–1.85)	1.40 (0.95–2.07)	$\chi^2 = 2.45$; $P_{interaction} = 0.29$	−0.25 (−0.84–0.28)
Study design							
Population-based	NCI-SEER, UCSF1, Connecticut, UK, SCALE-Denmark, SCALE-Sweden	$\chi^2 = 39.7$; $P_{het} = 0.03$	1.25 (1.03–1.52)	1.29 (1.00–1.65)	2.05 (1.27–3.32)	$\chi^2 = 5.31$; $P_{interaction} = 0.07$	0.51 (0.004–1.00)
Clinic/hospital-based	Mayo, EpiLymph-France, EpiLymph-Spain	$\chi^2 = 16.0$; $P_{het} = 0.10$	1.62 (1.23–2.14)	1.06 (0.71–1.58)	1.34 (0.54–3.35)	$\chi^2 = 0.33$; $P_{interaction} = 0.85$	−0.33 (−1.79–1.13)
Diagnosis classification							
ICDO3	NCI-SEER, Mayo, UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France, Epilymph-Spain	$\chi^2 = 47.1$; $P_{het} = 0.02$	1.29 (1.03–1.62)	1.34 (1.07–1.69)	1.84 (1.13–3.00)	$\chi^2 = 2.19$; $P_{interaction} = 0.33$	0.20 (−0.31–0.68)
Other	UCSF1, Connecticut	$\chi^2 = 8.02$; $P_{het} = 0.16$	1.21 (1.06–1.38)	0.83 (0.72–0.96)	2.66 (0.59–12.1)	$\chi^2 = 5.24$; $P_{interaction} = 0.07$	1.62 (0.41–2.97)
Participation rate							
≥70%	UCSF1, SCALE-Denmark, SCALE-Sweden, EpiLymph-France, EpiLymph-Spain	$\chi^2 = 44.1$; $P_{het} < 0.01$	1.21 (0.87–1.69)	1.14 (0.81–1.60)	1.56 (0.80–3.02)	$\chi^2 = 0.43$; $P_{interaction} = 0.81$	0.20 (−0.41–0.78)
<70%	NCI-SEER, Mayo, Connecticut, UK	$\chi^2 = 14.9$; $P_{het} = 0.46$	1.36 (1.26–1.46)	1.34 (1.00–1.80)	2.32 (1.52–3.56)	$\chi^2 = 4.77$; $P_{interaction} = 0.09$	0.63 (−0.08–1.30)
Proportion of study subjects with TNF genotype							
≥90%	NCI-SEER, UCSF1, Connecticut, SCALE-Denmark, EpiLymph-France, EpiLymph-Spain	$\chi^2 = 38.9$; $P_{het} = 0.04$	1.12 (0.89–1.42)	1.24 (0.95–1.62)	2.36 (1.47–3.77)	$\chi^2 = 6.84$; $P_{interaction} = 0.03$	1.00 (0.37–1.64)
<90%	Mayo, UK, SCALE-Sweden	$\chi^2 = 7.10$; $P_{het} = 0.72$	1.46 (1.42–1.51)	1.30 (0.80–2.13)	1.45 (0.89–2.36)	$\chi^2 = 7.08$; $P_{interaction} = 0.03$[f]	−0.32 (−1.04–0.30)
Controls' TNF genotypes in Hardy–Weinberg Equilibrium							
Yes	NCI-SEER, Mayo, Connecticut, UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France	$\chi^2 = 43.4$, $P_{het} = 0.05$	1.28 (1.05–1.58)	1.26 (0.98–1.61)	1.88 (1.22–2.90)	$\chi^2 = 4.19$; $P_{interaction} = 0.12$	0.34 (−0.15–0.79)
No	UCSF1, EpiLymph-Spain	$\chi^2 = 15.4$, $P_{het} < 0.01$	1.21 (0.95–1.53)	1.20 (0.84–1.73)	2.37 (0.26–21.8)	$\chi^2 = 1.59$; $P_{interaction} = 0.45$	0.96 (−0.50–2.55)
BMI-TNF association among Controls							
No	Mayo, UCSF1, Connecticut, UK, SCALE-Denmark, SCALE-Sweden, EpiLymph-France	$\chi^2 = 44.5$; $P_{het} = 0.04$	1.27 (1.04–1.56)	1.17 (0.85–1.62)	1.76 (1.16–2.67)	$\chi^2 = 4.60$; $P_{interaction} = 0.10$	0.31 (−0.20–0.80)
Yes	NCI-SEER, EpiLymph-Spain	$\chi^2 = 8.21$; $P_{het} = 0.15$	1.33 (1.20–1.48)	1.43 (1.40–1.46)	2.60 (1.09–6.22)	$\chi^2 = 1.65$ $P_{interaction} = 0.44$	0.84 (−0.32–1.93)

[a]Tests for heterogeneity between studies were conducted using the likelihood ratio test to compare the model with an interaction term between the joint association and study variables with the basic model which adjusted for study.

[b]Normal weight, 18.5–<25 kg/m^2; obese, ≥30 kg/m^2; GG and GA+AA are *TNF-308G>A* genotypes where G is considered wild type, and A the variant, allele.

[c]ORs and 95% CIs estimated using logistic regression adjusted for sex, age, and study where referent group was normal weight and *TNF-308GG* genotype. ORs shown for normal GA+AA and obese GG to aid interpretation of relative excess risk due to interaction.

[d]Tests for departure from additive interaction between BMI and *TNF* were conducted using the likelihood ratio test on linear odds ratio model.

[e]RERI estimated using linear OR regression adjusted for sex, age, and study and its likelihood-based 95% CI were derived using maximum likelihood estimation.

[f]Statistically significant departure from additive interaction due to RERI for overweight (25–<30 kg/m^2) and GA+AA.

adulthood, which has been associated with DLBCL (2, 31), were too sparse. As for generalizability, our findings may not translate to all populations as our subjects were Caucasian and resident in developed nations. Furthermore, the BMI was developed to estimate body fat in Caucasians of working age and so may not be applicable to other groups; no other indicators such as waist-to-hip ratio were available. There is certainly variation in obesity rates worldwide (49) and also the distribution of *TNF-308G>A* genotypes and those of the other SNPs studied here differ between populations too (50).

In conclusion, we found some evidence of interaction between *TNF-308G>A* and BMI on the risk of DLBCL. The increased risk among persons carrying the variant *TNF-308A* allele and being obese was not necessarily consistent across studies, and the possibility that differential biases affected the findings cannot be ruled out. One way to potentially reduce these biases is to examine gene–environment associations in large cohort studies using more specific measures of adiposity such as total body fat, and obtaining data on circulating levels of TNF and other cytokines. Furthermore, within InterLymph, genome-wide association scans are now completed for more studies than included here (51), and findings from these may identify other adipose tissue–related cytokines and adipokines.

Disclosure of Potential Conflicts of Interest

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