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Polymorphisms in DNA Repair Pathway Genes, Body Mass Index, and Risk of Non-Hodgkin Lymphoma

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Abstract

We conducted a population-based case-control study in Connecticut women to test the hypothesis that genetic variations in DNA repair pathway genes may modify the relationship between body mass index (BMI) and risk of non-Hodgkin lymphoma (NHL). Compared to those with BMI < 25, women with BMI ≥ 25 had significantly increased risk of NHL among women who carried *BRCA1* (rs799917) CT/TT, *ERCC2* (rs13181) AA, *XRCC1* (rs1799782) CC, and *WRN* (rs1801195) GG genotypes, but no increase in NHL risk among women who carried *BRCA1* CC, *ERCC2* AC/CC, *XRCC1* CT/TT, and *WRN* GT/TT genotypes. A significant interaction with BMI was only observed for *WRN* (rs1801195, P=0.004) for T-cell lymphoma and *ERCC2* (rs13181, P=0.002) for diffuse large B-cell lymphoma. The results suggest that common genetic variation in DNA repair pathway genes may modify the association between BMI and NHL risk.

Keywords

Non-Hodgkin lymphoma; BMI; polymorphisms; DNA repair genes

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Introduction

Increasing evidence suggests that obesity may induce metabolic, endocrinologic, immunologic, and inflammatory like changes contributing to DNA damage[1–6], which may be important in the pathogenesis and development of non-Hodgkin lymphoma (NHL). Body mass index (BMI), an indirect measure of adiposity, has been linked to the risk of NHL. Results from epidemiologic studies, however, have been inconsistent [7–23]. Some studies reported a positive association between BMI and risk of NHL [10,14–16,18,19,21–23], while others found no association.[7–9,11,12,17,20]. 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 [24]. However, the validity of a pooled odds ratio is questioned due to significant heterogeneity of the analyzed studies. Genetic variation could explain some of the inconsistent findings.

DNA repair mechanisms are important in maintaining genomic stability and loss of function or inefficiencies in DNA repair leads to chromosomal aberrations, a characteristic prominent in lymphoma[25–27]. More than 130 genes are known to be involved in the repair of different types of DNA damage involving distinct pathways[28]. DNA repair gene alterations may cause a reduction in DNA repair capacity and influence an individual's susceptibility to carcinogenesis[29]. Single nucleotide polymorphisms (SNPs) in several DNA repair genes (i.e., *ERCC5*, *ERCC2*, *WRN*, *BRCA1*, *MGMT*, and *XRCC1*) have been reported to be associated with the risk of NHL and its major subtypes[30,31]. Additionally, overweight and obesity have been linked to increased DNA and oxidative damage[32,33] and as a result, may confer an increased risk of developing lymphoma. Thus, it is possible that genetic variation in the DNA repair genes may modify the relationship between BMI and NHL risk. Here, we conducted a population-based case-control study in Connecticut women to test the hypothesis.

Materials and Methods

Study Population

The study population has been described in detail elsewhere [34,35]. 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 (RCA). Enrollment criteria included age between 21–84 years, residence in Connecticut, female, alive at the time of interview, and without a previous diagnosis of cancer except for non-melanoma 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 two independent pathologists. All cases were classified according to the 2001 WHO classification [36].

Female population-based controls from Connecticut were recruited by: (1) random-digit dialing methods for those younger than 65 years of age; or (2) random selection from the Centers for Medicare and Medicaid Services records for those aged 65 years or older. Controls were frequency matched on age (± 5 years) to cases. The participation rate was 69% among persons identified via 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. 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, Foster City, CA) for this study were optimized on the ABI 7900HT detection system with 100% concordance with sequence analysis of 102 individuals as listed on the SNP500Cancer website (http://snp500cancer.nci.nih.gov). A total of 38 SNPs in 18 DNA repair genes were selected for genotyping based on a minimum allele frequency of 0.05, and evidence of association in previous epidemiology studies, evidence of function, or to extend genomic coverage for a given gene. The genes included *BRCA1* (rs16941, rs16940, rs16942, rs799917, and rs1799966), *BRCA2* (rs144848, rs1801406, rs543304, rs1799955, rs15869, rs766173, and rs1799944), *APEX1* (rs1130409), *ADPRT* (rs1136410), *ERCC1* (rs3212961), *ERCC2* (rs13181 and rs1799793), *ERCC4* (rs1799802), *ERCC5* (rs17655), *LIG4* (rs1805388), *MGMT* (rs2308321, rs2308327, and rs12917), *NBS1* (rs1805794 and rs1805329), *RAD23B* (rs1805329), *XRCC1* (rs25487, rs25489, and rs1799782), *XRCC2* (rs3218536), *XRCC3* (rs861539), *XRCC4* (rs1805377, rs1056503, and rs3734091), *XPC* (rs2228001), and *WRN* (rs1801195, rs1800391, and rs22230009). Quality control samples for all SNPs were re-checked and concordance rates were above 98% for each (100% for *WRN* Val114Ile and *XRCC1*Arg280His, and 98% for *BRCA1* Glu997Gly).

Statistical analysis

BMI was calculated as weight (kg) divided by the square of height (m^2), using self-reported usual adult height and weight. We defined individuals as normal weight if their BMI < 25 kg/m^2 and overweight/obese if their BMI ≥ 25 kg/m^2 as defined by the WHO. 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, African-American, 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, Cary, NC).

Results

The association between BMI and risk of NHL overall and NHL subtypes are presented in Table 1. Compared to women with normal weight, BMI ≥ 25.0 was associated with 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) and T-cell lymphoma (OR=2.2, 95% CI:1.1–4.4). Among common B-cell lymphoma subtypes, non-significant increased risks were observed for diffuse large B-cell lymphoma (DLBCL, 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 each included the null value, the magnitude of the effects were similar.

As shown in Table 2, a significantly increased risk of NHL was associated with BMI among women who carried certain DNA repair gene polymorphisms. Compared to women whose BMI < 25, women with a BMI ≥ 25.0 had a significantly increased risk of NHL if they carried *BRCA1* (rs799917) CT/TT genotypes (OR=1.7, 95%CI:1.2–2.4), *ERCC2* (rs13181) AA genotype (OR=2.0, 95%CI: 1.4–3.0), and *XRCC1* (rs1799782) CC genotype (OR=1.5, 95%CI: 1.1–2.0), but not among women who carried *BRCA1* CC, *ERCC2* AC/CC, and *XRCC1* 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 *BRCA1* (rs799917 P=0.030) and *XRCC1* (rs1799782 $P_{forinteraction}$=0.038) for NHL overall; *ERCC2* (rs13181 P=0.038) for B-cell lymphoma; and *WRN* (rs1801195 P=0.004) for T-cell lymphoma. After adjustment by FDR, only the interaction with *WRN* rs1801195 for T-cell lymphoma remained statistically significant, however, it was based on small numbers.

Among common B-cell lymphoma subtypes (Table 3), a significant interaction was observed for *ERCC2* (rs13181 P=0.002) among DLBCL; *ERCC5* (rs17655 P=0.011) among MZBCL; *MGMT* (rs2308321, rs2308327, rs12917, P=0.047, 0.043, and 0.034, respectively) and *WRN* (rs1346044 P=0.046) among small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL); and *WRN* (rs1346044 P=0.021) among follicular lymphoma. After adjustment by FDR, **just** one interaction, *ERCC22* (rs13181), for DLBCL remained statistically significant. Although significantly increased risk of NHL was observed for several other polymorphisms, none of them showed a significant interaction with BMI and risk of NHL and its subtypes (Supplementary Tables 1&2).

Discussion

Our study provided the first comprehensive analysis of interaction between BMI, genetic polymorphisms in DNA repair genes, and risk of NHL and its subtypes. Suggestive interactions were observed for *BRCA1* (rs799917), *XRCC1* (rs1799782), *ERCC2* (rs13181), *ERCC5* (rs17655), *MGMT* (rs2308321, rs2308327, rs12917), and *WRN* (rs1801195, rs1346044) for NHL overall and/or various NHL subtypes.

Consistent with previous studies [10,14–16,18,19,21–23], our study suggested that overweight was associated with an increased risk of NHL overall, B-cell lymphoma and T-cell lymphoma. In addition, DNA repair gene polymorphisms may lead to a reduction in DNA repair capacity[29], could increase oxidative damage and subsequently modify the association between BMI and risk of NHL.

Tumor suppressor *BRCA1* (breast cancer susceptibility gene 1) plays an integral role in the cellular response to DNA damage, as evidenced by the fact that *BRCA1* null mice die early in embryonic development and exhibit chromosomal aberrations that are exacerbated by a p53 mutation[39]. Recent evidence suggested that *BRCA1* SNP rs799917 was not significantly associated with BMI and risk of NHL, though *BRCA1* rs16941 polymorphism was significantly associated with altered risk of NHL and DLBCL, the major NHL subtype.[30] As obesity downregulates BRCA1 expression[38], it is possible that genetic variation of *BRCA1* may modify the relationship between BMI and risk of NHL. In the current study, we found a potential interaction between *BRCA1* (rs799917) SNP, BMI, and risk of NHL overall.

X-ray cross-complementing gene 1 (*XRCC1*) plays a central role in base excision repair (BER) and single-strand break repair (SSBR). A common polymorphism within the *XRCC1* gene was identified at codon 194 (Arg194Trp, rs1799782). This non-conserved amino acid change may alter *XRCC1* function and subsequently increase oxidative damage[37]. Additionally, obesity has an additive effect to increased blood glucose levels contributing to oxidative DNA damage[32]. A suggestive effect modification observed in the current study for *XRCC1* (rs1799782) may indicate a synergy between XRCC1 and BMI on the risk of NHL.

Nucleotide excision repair (NER) is the primary DNA repair pathway that repairs bulky DNA adducts such as those induced by ultraviolet light (UV), and large chemically-induced adducts. Both *ERCC2* and *ERCC5* are NER-related genes. The *ERCC2* protein possesses both single-strand DNA-dependent ATPase and 5′-3′ DNA helicase activities and participates in DNA unwinding during NER. Previous studies showed that SNP in *ERCC2* (rs13181) was associated with decreased risk of diffuse large B-cell lymphoma, the major subtype of NHL[40,41]. Potential effect modification by *ERCC2* (rs13181) was observed for B-cell lymphoma, and DLBCL in the current study. This allele change results in a amino acid change, which could change the functionality of this gene product, and the additional stress caused by adiposity may hamper the DNA repair capacity of the variant protein. We also observed a potential interaction between *ERCC5* (rs17655) and BMI and MZBCL risk. *ERCC5* encodes a structure-specific endonuclease and also a 5′-3′ exonuclease, which is required for both transcription-coupled NER (TC-NER) and global genomic NER[42]. Our own results suggested that *ERCC5* (rs17655) was associated with increased risk of NHL overall, DLBCL, and also T cell lymphoma[30]. The observed effect modifications could be due to the disruption of the NER pathway or some other unknown mechanism(s).

A major defense against endogenous and exogenous methylating agents is provided by O^6-methylguanine-DNA methyltransferase (*MGMT*)[43], a specific DNA direct reversal repair protein which ameliorates mutagenic, carcinogenic and cytotoxic adducts from O^6-methylguanine in DNA[44]. SNPs in the *MGMT* gene have been associated with increased risk of cancer, especially among those exposed to alkylating mutagens[45,46]. Specifically, two SNPs in *MGMT* (rs2308321, and rs2308327) were associated with increased risk of NHL[31], which suggests alkyl adducts may contribute to lymphomagenesis. The current study found suggestive effect modification by *MGMT* (rs2308321, rs2308327, rs12917) on the association between BMI and risk of SLL/CLL. All three SNPs variant allele are missense substitutions, resulting in different protein products, and as a result, the additional oxidative stress caused by adiposity may cause an extra burden on this protein to adequately demethylate and fix adducts.

WRN encodes a multifunctional nuclear protein of RecombinaseQ (RecQ) family with an intrinsic 3′ to 5′ DNA helicase activity, a DNA-dependent ATPase characteristic, and a 3′ to 5′ exonuclease activity. The *WRN* protein migrates from nucleoli to discrete nuclear foci after exposure to several DNA-damaging agents[47,48] and interacts with a number of DNA metabolic pathway proteins[47,48]. *WRN* could play an important role in monitoring genome integrity and controlling the cell's response to DNA damage. Mutations in *WRN* could lead to a loss of function of the protein and a breakdown in genome integrity[49]. Mutations in *WRN* gene (rs1346044) have been associated with decreased risk of NHL overall and DLBCL, as well as follicular lymphoma[30]. Castro et al. reported that polymorphisms in the *WRN* gene may increase the risk of obesity by regulating plasminogen activator inhibitor type I (PAI-1) levels[50]. As such, it is possible that genetic variation of *WRN* may modify the relationship between BMI and risk of NHL. In the present study, potential effect modifications by *WRN* (rs1801195, rs1346044) were observed for T-cell lymphoma, SLL/CLL and follicular lymphoma. These SNPs are also missense changes, and reduced helicase

activity may cause inaccurate DNA replication in combination with metabolic stress caused by adiposity may elevate opportunities for aberrant cellular growth.

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 DNA repair pathway 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. Small sample size limited some associations, such as obesity (BMI>30), which was not significantly associated with NHL despite an elevated effect estimate (OR: 1.3). When the BMI categories were collapsed (25–30 BMI + >30 BMI), the overall effect was similar and significant. After adjustment by FDR, two significant interactions remained (*WRN* rs1801195 for T-cell lymphoma and *ERCC2* rs13181 for diffuse large B-cell lymphoma. Additionally, because this study was the first to assess the interaction between genetic polymorphisms and BMI and risk of NHL, the topic warrants further investigation. BMI was self reported, so there may be some inaccurate measurements, as BMI tends to be underreported. However, this should be nondifferential and would likely cause attenuation, not inflation, of these results. As this study focused on a specific pathway, additional SNPs should be tested in the future. Utilizing the high-throughput analytic methods available (eg. Genome-wide association) would allows for a wider range of associations to be detected in genomic regions which have not previously been tested. Finally, the study only included women, so the results may not be generalizable to men.

In summary, our study suggests that common genetic variations in the DNA repair 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Associations between boday mass index and risk of NHL and common NHL subtypes[1]

Body Mass Index	Overall				B-cell lymphoma			T-cell lymphoma			DLBCL				FL			SLL/CLL			MZBCL		
	Cases	Controls	OR[2](95%CI)	P value	Cases	OR[2](95%CI)	P value	Cases	OR[2](95%CI)	P value	Cases	Controls	OR[2](95%CI)	P value	Cases	OR[2](95%CI)	P value	Cases	OR[2](95%CI)	P value	Cases	OR[2](95%CI)	P value
<25	251	326	1.0		199	1.0		14	1.0		77	326	1.0		57	1.0		32	1.0		15	1.0	
25–30	167	167	1.3(1.0–1.7)	0.048	132	1.3(1.0–1.7)	0.075	17	2.4(1.2–5.0)	0.019	56	167	1.5(1.0–2.2)	0.066	35	1.2(0.8–2.0)	0.402	18	1.1(0.6–2.1)	0.710	14	1.8(0.8–3.7)	0.146
≥25	267	271	1.3(1.0–1.7)	0.032	212	1.3(1.0–1.7)	0.041	25	2.2(1.1–4.4)	0.023	84	271	1.3(0.9–1.9)	0.123	62	1.4(0.9–2.1)	0.119	27	1.1(0.6–1.8)	0.865	20	1.6(0.8–3.3)	0.164
>30	100	104	1.3(0.9–1.8)	0.147	80	1.3(0.9–1.9)	0.129	8	1.8(0.7–4.6)	0.187	28	104	1.1(0.7–1.8)	0.672	27	1.7(1.0–2.8)	0.060	9	0.9(0.4–2.0)	0.836	6	1.4(0.5–3.8)	0.490
P for trend				0.018			0.033			0.020				0.077			0.127			0.635			0.084

[1] DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphom; SLL/CLL=small lymphocytic lymphoma/chronic lymphocytic leukemia; MZBCL=marginal zone B-cell lymphoma.

[2] Adjusted for age, race, and total energy intake.

Table 2

Associations between DNA repair genes polymorphisms, body mass index and risk of non-Hodgkin lymphoma.

	Overall						B cell lymphoma				T cell lymphoma			
	BMI<25			BMI≥25			BMI<25		BMI≥25		BMI<25		BMI≥25	
SNPs	**Controls**	**Cases**	**OR[1](95%CI)**	**Controls**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**
BRCA1 (rs799917)														
CC	125	111	1.0	105	104	1.1(0.8–1.6)	89	1.0	85	1.1(0.8–1.7)	7	1.0	9	1.5(0.5–4.1)
CT/TT	171	107	1.0	131	137	**1.7(1.2–2.4)**	87	1.0	106	**1.6(1.1–2.4)**	4	1.0	13	**4.6(1.6–14.8)**
p-interaction		***0.030***					*0.085*				*0.082*			
ERCC2 (rs13181)														
AA	122	85	1.0	85	118	**2.0(1.4–3.0)**	68	1.0	95	**2.0(1.3–3.1)**	4	1.0	10	**4.0(1.2–13.5)**
AC/CC	171	129	1.0	152	124	1.1(0.8–1.6)	106	1.0	97	1.1(0.7–1.5)	6	1.0	12	2.5(0.9–6.8)
p-interaction		*0.052*					***0.038***				*0.678*			
ERCC5 (rs17655)														
GG	195	131	1.0	157	129	1.2(0.9–1.7)	106	1.0	108	1.3(0.9–1.8)	6	1.0	9	1.9(0.7–5.6)
CG/CC	104	90	1.0	94	114	1.5(1.0–2.2)	71	1.0	85	1.4(0.9–2.2)	4	1.0	13	**4.0(1.2–13.1)**
p-interaction		*0.621*					*0.981*				*0.401*			
MGMT (rs2308321)														
AA	245	182	1.0	201	205	**1.4(1.1–1.8)**	150	1.0	165	**1.4(1.1–1.8)**	7	1.0	19	**3.5(1.5–8.6)**
AG/GG	59	43	1.0	53	40	1.0(0.6–1.9)	30	1.0	32	1.1(0.6–2.20	4	1.0	3	-
p-interaction		*0.280*					*0.496*				*0.153*			
MGMT (rs2308327)														
AA	239	176	1.0	188	198	**1.5(1.1–2.0)**	146	1.0	158	**1.4(1.0–1.9)**	7	1.0	19	**3.7(1.5–9.0)**
AG/GG	52	43	1.0	44	34	0.9(0.5–1.8)	31	1.0	26	0.9(0.5–1.9)	4	1.0	2	-
p-interaction		*0.254*					*0.330*				*0.107*			
MGMT (rs12917)														
CC	230	159	1.0	194	186	**1.4(1.1–1.9)**	123	1.0	149	**1.5(1.1–2.0)**	9	1.0	17	**2.4(1.0–5.5)**
CT/TT	74	66	1.0	59	59	1.7(0.7–2.0)	56	1.0	47	1.1(0.6–1.8)	2	1.0	5	2.8(0.5–16.5)
p-interaction		*0.593*					*0.360*				*0.713*			
XRCC1 (rs1799782)														

	Overall						B cell lymphoma				T cell lymphoma			
	BMI<25			BMI≥25			BMI<25		BMI≥25		BMI<25		BMI≥25	
SNPs	**Controls**	**Cases**	**OR[1](95%CI)**	**Controls**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**	**Cases**	**OR[1](95%CI)**
CC	261	192	1.0	209	222	**1.5(1.1–2.0)**	157	1.0	175	**1.4(1.1–1.9)**	8	1.0	22	**3.6(1.5–8.3)**
CT/TT	42	34	1.0	41	24	0.7(0.3–1.4)	23	1.0	22	1.0(0.5–2.1)	3	1.0	0	-
p-interaction		***0.038***					*0.263*				*0.934*			
WRN (rs1346044)														
TT	150	141	1.0	134	140	1.2(0.8–1.6)	116	1.0	115	1.2(0.8–1.7)	7	1.0	10	1.5(0.5–4.2)
CT/CC	146	76	1.0	105	97	**1.8(1.2–2.6)**	60	1.0	74	**1.7(1.1–2.6)**	4	1.0	11	**4.1(1.2–13.4)**
p-interaction		*0.221*					0.289				0.236			
WRN (rs1801195)														
GG	94	65	1.0	80	81	1.5(0.9–2.3)	56	1.0	62	1.3(0.8–2.1)	2	1.0	10	-
GT/TT	174	144	1.0	141	145	1.3(0.9–1.8)	112	1.0	119	1.4(1.0–1.9)	9	1.0	10	1.5(0.6–3.7)
p-interaction		*0.155*					*0.495*				***0.004***			

[1]Adjusted for age, race, and total energy intakes.

Table 3

Associations between DNA repair genes polymorphisms, body mass index and risk of common B-cell lymphoma subtypes [2].

SNPs		DLBCL				MZBCL				SLL/CLL				FL			
		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25	
	Controls	Cases	OR [1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)
BRCA1 (rs799917)																	
CC	125	35	1.0	38	1.2(0.8–2.2)	8	1.0	7	1.1(0.4–3.2)	12	1.0	11	1.2(0.5–2.8)	26	1.0	24	1.1(0.6–2.1)
CT/TT	171	31	1.0	42	**1.9(1.1–3.2)**	7	1.0	9	1.6(0.6–4.4)	17	1.0	14	1.1(0.5–2.4)	24	1.0	31	**1.9(1.0–3.4)**
p-interaction		*0.184*				*0.831*				*0.875*				*0.066*			
ERCC2 (rs13181)																	
AA	122	25	1.0	49	**2.8(1.6–4.9)**	3	1.0	5	2.6(0.6–11.9)	13	1.0	15	1.7(0.7–3.7)	20	1.0	21	1.5(0.8–3.0)
AC/CC	171	42	1.0	31	0.8(0.5–1.4)	12	1.0	11	1.1(0.4–2.5)	15	1.0	10	0.9(0.4–2.0)	30	1.0	35	1.5(0.8–2.5)
p-interaction		***0.002***				*0.944*				*0.283*				*0.771*			
ERCC5 (rs17655)																	
GG	195	41	1.0	43	1.3(0.8–2.1)	4	1.0	12	**4.4(1.4–14.2)**	20	1.0	15	0.9(0.5–1.9)	34	1.0	31	1.1(0.7–2.0)
CG/CC	104	26	1.0	38	1.8(1.0–3.2)	11	1.0	5	0.5(0.2–1.5)	9	1.0	9	1.3(0.5–3.7)	17	1.0	24	1.8(0.9–3.7)
p-interaction		*0.692*				***0.011***				*0.805*				*0.287*			
MGMT (rs2308321)																	
AA	245	58	1.0	71	**1.5(1.0–2.3)**	12	1.0	15	1.6(0.7–3.4)	29	1.0	19	0.8(0.4–1.5)	38	1.0	46	1.5(1.0–2.5)
AG/GG	59	10	1.0	10	1.1(0.4–3.0)	3	1.0	2	-	1	1.0	7	-	12	1.0	11	1.0(0.4–2.4)
p-interaction		*0.527*				*0.291*				***0.047***				*0.317*			
MGMT (rs2308327)																	
AA	239	56	1.0	69	**1.6(1.0–2.4)**	12	1.0	14	1.5(0.7–3.4)	28	1.0	18	0.8(0.4–1.6)	38	1.0	43	1.5(0.9–2.5)
AG/GG	52	11	1.0	10	1.1(0.4–3.0)	3	1.0	1	-	1	1.0	6	-	12	1.0	8	0.7(0.2–1.9)
p-interaction		*0.419*				*0.183*				***0.043***				*0.200*			
MGMT (rs12917)																	
CC	230	44	1.0	58	**1.6(1.0–2.5)**	10	1.0	14	1.6(0.7–3.8)	20	1.0	24	1.5(0.8–2.8)	36	1.0	42	1.5(0.9–2.4)
CT/TT	74	24	1.0	22	1.1(0.5–2.1)	4	1.0	4	1.4(0.3–5.8)	10	1.0	1	-	14	1.0	15	1.4(0.6–3.3)
p-interaction		*0.544*				*0.895*				***0.034***				*0.883*			
XRCC1 (rs1799782)																	

SNPs		DLBCL				MZBCL				SLL/CLL				FL			
		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25		BMI<25	
	Controls	Cases	OR [1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)
CC	261	58	1.0	68	1.5(1.0–2.2)	13	1.0	15	1.5(0.7–3.2)	25	1.0	23	1.2(0.7–2.3)	45	1.0	55	**1.6(1.0–2.5)**
CT/TT	42	10	1.0	13	1.3(0.5–3.4)	2	1.0	2	-	5	1.0	3	-	6	1.0	2	-
p-interaction		*0.764*				*0.650*				*0.404*				*0.058*			
WRN (rs1346044)																	
TT	150	43	1.0	50	1.4(0.8–2.2)	11	1.0	10	1.1(0.5–2.8)	14	1.0	19	1.6(0.7–3.3)	38	1.0	29	1.0(0.6–1.8)
CT/CC	146	23	1.0	30	1.7(0.9–3.2)	4	1.0	5	1.7(0.4–7.1)	15	1.0	6	0.6(0.2–1.5)	12	1.0	25	**2.8(1.3–5.9)**
p-interaction		*0.917*				*0.454*				***0.046***				***0.021***			
WRN (rs1801195)																	
GG	94	17	1.0	29	**2.2(1.1–4.3)**	6	1.0	7	1.1(0.3–3.7)	11	1.0	4	0.5(0.1–1.6)	15	1.0	20	1.6(0.8–3.5)
GT/TT	174	47	1.0	48	1.3(0.8–2.0)	9	1.0	9	1.4(0.5–3.6)	15	1.0	19	1.6(0.8–3.4)	32	1.0	32	1.4(0.8–2.4)
p-interaction		*0.217*				*0.895*				*0.354*				*0.158*			

[1]Adjusted for age, race, and total energy intakes.

[2]DLBCL=diffuse large B-cell lymphoma; MZBCL=marginal zone B-cell lymphoma; SLL/CLL=small lymphocytic lymphoma/chronic lymphocytic leukemia; FL=follicular lymphoma