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Genetic Polymorphisms in Oxidative Stress Pathway Genes and Modification of BMI and Risk of Non-Hodgkin Lymphoma

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Abstract

Background—Being overweight and obese increases oxidative stress in the body. To test the hypothesis that genetic variations in oxidative stress pathway genes modify the relationship between body mass index (BMI) and risk of non-Hodgkin lymphoma (NHL), we conducted a population-based case–control study in Connecticut women.

Methods—Individuals who were overweight/obese (BMI ≥ 25) were compared with normal and underweight individuals (BMI < 25), and their risk of NHL stratified assuming a dominant allele model for each oxidative stress pathway single-nucleotide polymorphism.

Results—Polymorphisms in *AKR1A1, AKR1C1, AKR1C3, CYBA, GPX1, MPO, NCF2, NCF4, NOS1, NOS2A NOS3, OGG1, ATG9B, SOD1, SOD2, SOD3,RAC1*, and *RAC2* genes after false discovery rate adjustment did not modify the association between BMI and risk of NHL overall and histologic subtypes.

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: Q. Lan, X. Chen, T. Holford, P. Boyle, S.J. Chanock, and Y. Zhang.
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Conclusions—The results suggest that common genetic variations in oxidative stress genes do not modify the relationship between BMI and risk of NHL.

Impact—Studies of BMI and oxidative stress independently may elevate NHL risk, but this study suggests no interaction of the two risk factors. Future studies with larger study populations may reveal interactions.

Introduction

Obesity may be related to risk of non-Hodgkin lymphoma (NHL). A recent meta-analysis suggested an increased risk of NHL by 20% in individuals who are overweight/obese (1). Few known established risk factors of NHL are known outside of immunosuppression and autoimmunity, but obesity is related to altered immune function and chronic inflammatory responses (2).

Reactive oxygen species (ROS) are hazardous to all living organisms and damage all major cellular constituents when not tightly controlled in their enzymes such as NO synthase or NADPH oxidase isoform (3). An increase in body mass index (BMI) elevates systematic oxidative stress in the body (4). In addition, previous studies suggest that single-nucleotide polymorphisms (SNP) in genes related to immunity and inflammation or removal of ROS may confer additional risk of NHL (5). However, no studies have assessed the modification of oxidative stress gene polymorphisms on risk of NHL by BMI. To test the hypothesis that polymorphisms in oxidative stress pathway genes modify the association between BMI and risk of NHL, a population-based case–control study was conducted among women in Connecticut.

Methods

The study population (6, 7) and genotyping (5) have been described in detail elsewhere. Cases were histologically confirmed incident cases at Yale cancer center (ICD-O, M-9590-9642, 9690–9701, 9740–9750). To estimate risk of NHL, ORs and 95% confidence intervals were estimated using unconditional logistic regression, adjusting for age (continuous), race (white, other), caloric intake (daily average), smoking (pack-years), and alcohol consumption (lifetime). Results are stratified by SNP genotype comparing the risk of NHL in BMI ≥25 kg/m^2 compared with the reference of BMI < 25 kg/m^2. To improve statistical stability, dominant risk allele models were employed by collapsing the genotypes into homozygous wild type and heterozygous/homozygous variant. SNPs with a minor allele frequency lower than 10% were excluded from the analysis. A total of 123 SNPs in 18 genes were included in the final analysis. Wald χ^2 for the interaction term between BMI and genotype were reported with adjustment for multiple comparisons by false discovery rate (FDR) in which a *Q* value of < 0.20 was considered significant (8).

Results

Selected characteristics are presented in Table 1. Histologies for cases were predominantly B cell (79.34%), followed by T cell (7.53%) and other (4.44%). Age, race, and alcohol consumption were similarly distributed between cases and controls (*P* value: 0.50, 0.24, and 0.48, respectively). Compared with controls, cases were more likely to have been regular smokers (*P* value: 0.028), consumed more calories (*P* value: 0.037) and have a greater BMI (*P* value: 0.0413) than controls.

ORs of NHL risk comparing ≥25 BMI versus <25 BMI stratified by SNP genotype are presented in Supplementary Table S1. Although significant risks of NHL were associated with overweight/obesity compared with normal weight among certain genotypes, no effect

modification of the BMI and NHL relationship was noted for genetic polymorphisms in *AKR1A1, AKR1C1, AKR1C3, CYBA, GPX1, MPO, NCF2, NCF4, NOS1, NOS2A NOS3, OGG1, ATG9B, SOD1, SOD2, SOD3, RAC1*, and *RAC2* genes after FDR adjustment for NHL overall and major histologic subtypes.

Conclusions

In this analysis, SNPs in oxidative stress pathway genes did not modify the relationship between BMI and NHL risk. This study was a population-based case–control study with histologically confirmed cases of NHL and accurate genotyping. The primary limitation of the study was the modest sample size for NHL subtype analyses. In addition, 123 SNPs in 18 oxidative stress pathway genes were assessed. It is possible that unassessed polymorphisms in these genes or other oxidative stress pathway genes could modify the association between BMI and NHL risk. Future full genomic scans with larger populations can elucidate further information on potential associations. Several polymorphisms (i.e., SOD2, GPX1, NOS2, AKR1A1, and CYBA) associated with NHL risk in previous studies were not found to modify the association of NHL and BMI. These results suggest that the additional oxidative stress caused by polymorphisms may not modify the effect of BMI on NHL risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographics and characteristic distribution of study population between NHL cases and controls

	Cases (%)	Controls (%)	*P*
NHL histology			
B-cell lymphoma	411 (79.34)	—	—
Diffuse large B cell	161	—	
Follicular lymphoma	119	—	
CLL/SLL[a]	59	—	
Marginal zone B cell	35	—	
T-cell lymphoma	39 (7.53)	—	
Other	23 (4.44)	—	
Unknown	45 (8.69)	—	
BMI (kg/m^2)			
<25	251 (48.46)	326 (54.61)	0.0413
≥25	267 (51.54)	271 (45.39)	
Calories (kcal/d)			
1,973+	149 (28.76)	127 (21.27)	0.0371
1,609–1,973	121 (23.36)	155 (25.96)	
1,275–1,609	120 (23.17)	157 (26.30)	
<1,275	128 (24.71)	158 (26.47)	
Age (y)			
73+	131 (25.29)	165 (27.64)	0.4975
64–72	129 (24.90)	147 (24.62)	
52–63	136 (26.25)	135 (22.61)	
<52	122 (23.55)	150 (25.13)	
Smoking (pack-years)			
56+	28 (5.41)	28 (4.69)	0.0276
21–56	123 (23.75)	105 (17.59)	
<21	367 (70.85)	464 (77.72)	
Alcohol lifetime (kg)			
244+	30 (5.79)	44 (7.37)	0.4828
100–244	48 (9.27)	64 (10.72)	
32–100	86 (16.60)	105 (17.59)	
<32	354 (68.34)	384 (64.32)	
Race			
White	497 (95.95)	559 (94.59)	0.2444
Other	21 (4.05)	32 (5.41)	

[a]CLL/SLL: Chronic lymphocytic leukemia/small lymphocytic lymphoma.