Published in final edited form as:

Am J Hematol. 2012 August ; 87(8): 766–769. doi:10.1002/ajh.23244.

Genetic polymorphisms in *IL10RA* and *TNF* modify the association between blood transfusion and risk of non-Hodgkin lymphoma

Xiaofeng Bi^{1,2}, Tongzhang Zheng², Qing Lan³, Zhijian Xu¹, Yingtai Chen¹, Gongjian Zhu⁴, Francine Foss⁵, Christopher Kim², Min Dai¹, Ping Zhao¹, Theodore Holford², Brian Leaderer², Peter Boyle⁶, Qian Deng⁷, Stephen J. Chanock^{3,8}, Nathaniel Rothman³, and Yawei Zhang²

¹Cancer Institute/Hospital, Chinese Academy of Medical Sciences, Beijing, China ²Yale University, School of Public Health, New Haven, Connecticut ³Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland ⁴Gansu Provincial Tumor Hospital, Gansu Provincial Academy of Medical Sciences, Lanzhou, China ⁵Yale University, School of Medicine, New Haven, Connecticut ⁶International Prevention Research Institute, Lyon, France ⁷Sichuan University School of Public Health, Chengdu, China ⁸Core Genotyping Facility, Advanced Technology Center, National Cancer Institute, NIH, DHHS, Gaithersburg, Maryland

Abstract

We conducted a population-based case-control study in Connecticut women to test the hypothesis that genetic variations in Th1 and Th2 cytokine genes may modify the association between blood transfusion and risk of non-Hodgkin lymphoma (NHL). Compared with women without blood transfusion, women with a history of transfusion had an increased risk of NHL if they carried *IL10RA* (*rs9610*) GG genotype [odds ratio (OR) = 1.9, 95% confidence interval (CI): 1.1–3.2] or *TNF* (*rs1800629*) AG/AA genotypes (OR = 1.6, 95% CI: 0.9–2.7). We also found women with a history of transfusion had a decreased risk of NHL if they carried *IL10RA* (*rs9610*) AG/AA genotypes (OR = 0.6, 95% CI: 0.4–0.9) or *TNF* (*rs1800629*) GG genotype (OR = 0.7, 95% CI: 0.5–1.0). A similar pattern was also observed for B-cell lymphoma but not for T-cell lymphoma. Statistically significant interactions with blood transfusion were observed for *IL10RA* (*rs9610*) ($P_{\text{forinteraction}} = 0.003$) and *TNF* (*rs1800629*) ($P_{\text{forinteraction}} = 0.012$) for NHL overall and *IL10RA* (*rs9610*) ($P_{\text{forinteraction}} = 0.001$) and *TNF* (*rs1800629*) ($P_{\text{forinteraction}} = 0.019$) for B-cell lymphoma. The results suggest that genetic polymorphisms in *TNF* and *IL10RA* genes may modify the association between blood transfusion and NHL risk.

Introduction

Non-Hodgkin lymphoma (NHL) is the fifth most frequently diagnosed cancer in the United States, with 65,540 new cases and 20,210 deaths estimated in 2010 [1]. Various immune dysfunctions resulting from human immunodeficiency virus infection, immunosuppressive

therapy, and autoimmune diseases are well-established risk factors for NHL [2,3]. However, the established risk factors can only explain a small portion of the cases, which leaves majority of NHL cases unexplained.

Blood transfusion particularly allogeneic blood transfusion can induce immunosuppression and has been suggested as a risk factor for NHL [4–7]. Epidemiological studies linking blood transfusion to the risk of NHL, however, provided inconsistent results [8–11]. Different genetic susceptibility in different study populations may explain some of the conflicting results.

T helper 1 (Th1) and T helper 2 (Th2) lymphocyte cytokines play a crucial role in regulation of key pathways of the immune system. Imbalanced regulation and expression of Th1 and Th2 lymphocyte cytokines have been linked to the development of NHL [12,13]. Single nucleotide polymorphisms (SNPs) in several Th1/Th2 cytokine genes (i.e., *TNF* and *IL10*) have been reported to be associated with the risk of NHL and its major subtypes [14,15]. Damaged autologous erythrocytes during blood transfusion has been shown to augment the cytokines TNF- α and IL-10 production of the mononuclear phagocyte system in humans [16]. We speculate that genetic variations in TNF and IL-10 and/or other Th1 and Th2 cytokine genes may modify the relationship between blood transfusion and NHL risk. As such, we analyzed data from a population-based case-control study in Connecticut women.

Materials and Methods

Study population

The study population has been described in detail elsewhere [11,17]. Briefly, all histologically confirmed incident cases of NHL (ICD-O, M-9590-9642, 9690–9701, and 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, residents 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 two independent pathologists. All cases in this article were classified according to the World Health Organization classification system.

Female population-based controls from Connecticut were recruited by random-digit dialing methods for those younger than 65 years of age; or random selection from the Centers for Medicare and Medicaid Services records for those aged 65 years or older. Controls ($n = 717$) 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. As more than 90% of the study subjects were non-Hispanic Caucasians, this project was limited to non-Hispanic Caucasians. Among those, ~75% of the study subjects (76.7% of the cases and 74.6% of the controls) provided blood samples, and ~10% of the subjects (11.0% of the cases and 10.4% of the controls) provided buccal cell samples for genotyping. We further excluded women who had autologous blood transfusion (one case and three controls), and the final study included 482 cases and 541 controls. The selected characteristics of the study population were presented in Table I.

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, environmental and lifestyle factors, and medical conditions and medication use were collected through in-person interview.

Regarding blood transfusion history, subjects were asked whether they had ever had a blood transfusion during their lifetime. If so, subjects were asked to provide information regarding the year and reason for each blood transfusion they had received. For this analysis, 31 subjects who had a blood transfusion within 1 year before diagnosis or interview were considered not to have received a blood transfusion as recent blood transfusion might be related to the disease itself. Autologous blood transfusion was defined as a subject who reported having a blood transfusion using her own blood. In contrast, allogeneic blood transfusion was defined as a subject who reported having a blood transfusion without using her own blood. This article was focused on allogeneic blood transfusion.

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 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 [14]. Due to 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 two 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 four SNPs (rs1059293, rs231775, rs2243250, and rs2070874) were not consistent with Hardy–Weinberg equilibrium among non-Hispanic white controls using a chi-square test ($P < 0.05$) and were excluded from the final analysis. Another five SNPs (rs2069822, rs2069818, rs2069807, rs3024509, 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 and rs2069705), *IFNGR1* (rs3799488), *IFNGR2* (rs9808753), *IL10RA* (rs9610), *IL12A* (rs568408 and rs582054), *IL13* (rs20541, rs1800925, and rs1295686), *IL15* (rs10833), *IL15RA* (rs2296135), *IL2* (rs2069762), *IL4* (rs2243248, rs2243290, and rs2243268), *IL4R* (rs2107356), *IL5* (rs2069812), *IL6* (rs1800795 and rs1800797), *IL7R* (rs1494555), *JAK3* (rs3008), *IL10* (rs1800871, rs1800872, rs1800896, rs3024496, rs3024491, and rs1800890), and *TNF* (rs1800629 and rs1799724) were included in the final analysis.

Statistical analysis

Unconditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations between blood transfusion, 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. The only potential confounding variable included in the final model was age (< 55 years, 55–70 years, 70+ years). 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-blood transfusion interaction was assessed by adding an interaction term in the logistic models. The false discovery rate (FDR) threshold of 0.2 was used to control for multiple comparisons [18]. All *P* values presented are two-sided, and all analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

The association between blood transfusion and risk of NHL overall and NHL subtypes are presented in Table II. Blood transfusion was not associated with the risk of NHL overall (OR = 0.9, 95% CI: 0.7–1.2), B-cell lymphoma (OR = 0.8, 95% CI: 0.6–1.2) and T-cell lymphoma (OR = 1.2, 95% CI: 0.5–2.7). The results were comparable with the results in the overall population that we reported previously [11].

Compared with women without a history of blood transfusion, women with a history of transfusion had an increased risk of NHL overall and B-cell lymphoma if they carried *IL10RA* (*rs9610*) GG genotype (OR = 1.9, 95% CI: 1.1–3.2; OR = 2.1, 95% CI: 1.2–3.9, respectively, Table III), and a reduced risk if they carried *IL10RA* (*rs9610*) AG/AA genotypes (OR = 0.6, 95% CI: 0.4–0.9 for NHL overall; OR = 0.5, 95% CI: 0.3–0.8 for B-cell lymphoma). The interaction was statistically significant ($P_{\text{forinteraction}} = 0.003$ and 0.001 for NHL overall and B-cell lymphoma, respectively) after adjustment for FDR.

Among women who carried *TNF* (*rs1800629*) (Table III) AG/AA genotypes, blood transfusion was associated with an increased risk of NHL overall (OR = 1.6, 95% CI: 0.9–2.7) and B-cell lymphoma (OR = 1.5, 95% CI: 0.8–2.7). Among women who carried *TNF* (*rs1800629*) GG genotype, blood transfusion was associated with a decreased risk of NHL overall (OR = 0.7, 95% CI: 0.5–1.0) and B-cell lymphoma (OR = 0.7, 95% CI: 0.5–1.0). A statistically significant interaction between *TNF* (*rs1800629*) and blood transfusion was observed for NHL overall ($P_{\text{forinteraction}} = 0.012$), and for B-cell lymphoma ($P_{\text{forinteraction}} = 0.019$). Only the interaction for NHL overall remained statistically significant after adjustment for FDR.

After stratification by common B-cell lymphoma subtypes (Table IV), a significant association between blood transfusion and NHL was only observed for small lymphocytic lymphoma/ chronic lymphocytic leukemia (SLL/CLL) if women carried *IL10RA* (*rs9610*) GG genotypes (OR = 5.3, 95% CI: 1.5–18.9) and for follicular lymphoma if women carried *IL10RA* (*rs9610*) AG/AA genotypes (OR = 0.3, 95% CI: 0.1–0.7) with $P_{\text{forinteraction}}$ of 0.008 for SLL/CLL and 0.012 for follicular lymphoma. However, none of these interactions remained statistically significant after adjustment for FDR. Increased or decreased risks were also observed for several other cytokine polymorphisms, but none of them showed a statistically significant interaction with blood transfusion and risk of NHL and its subtypes after adjustment for FDR (Supporting Information Tables I and II).

Discussion

To our knowledge, this is the first comprehensive analysis of interaction between blood transfusion, genetic polymorphisms in Th1/Th2 pathway genes, and the risk of NHL and its subtypes. Significant interactions were observed for *IL10RA* (*rs9610*) and *TNF* (*rs1800629*) for NHL overall and B-cell lymphoma. No interactions were observed for T-cell lymphoma; however, they were based on small numbers. Future larger studies with greater statistical power are needed to clarify the association with T-cell lymphoma.

IL10 and *TNF* are key genes to be linked to lymphomagenesis. Both genes encode immunoregulatory cytokines that are critical mediators of inflammation, apoptosis, and Th1/Th2 balance, and function as autocrine growth factors in lymphoid tumors [19–21]. Studies of *IL10* and *TNF* knockout mice have shown that each cytokine affects B-cell lymphomagenesis directly or indirectly [22–24]. Prolonged red blood cell storage before transfusion has been reported can increase intracellular iron, which can exacerbate the systemic inflammatory response syndrome and lead to deleterious consequences [25]. Blood transfusions also can suppress cellular immunity and transmit infectious agents and allogeneic cells [26]. Therefore, it is possible that genetic variation in *TNF* and *IL10RA* genes may modify the association between blood transfusion and risk of NHL.

Our study found that *IL10RA* polymorphisms modified the association between blood transfusion and risk of NHL, particularly for B-cell lymphoma. *IL10RA* gene encodes the interleukin 10 receptor-alpha chain of the IL10 receptor complex and plays a dominant role in mediating high affinity ligand binding and signal transduction [27,28]. The *IL10R* signaling causes transcriptional activation of several hundred genes, which play important roles in immunological diseases [29]. *IL10RA* expression levels correlate with the strengths of the effects of IL10 on immune cells [30]. Serum IL10 levels have been found to be higher in NHL patients [31]. On the other hand, studies have shown that allogeneic nonleukofiltered red cell transfusion can significantly increase the production of IL10 [32] and damaged autologous erythrocytes during blood transfusion can also elevate IL10 production [16]. Although the underlying mechanism has yet to be established, effect modification observed in this study suggesting the *IL10RA* pathway could play a role in the relationship between blood transfusion and risk of NHL. *IL10RA* (rs9610) does not lead to amino acid substitution, but its importance to gene expression (translation and mRNA stability) cannot be ruled out.

The relationship between *TNF*(rs1800629) polymorphism and NHL risk has been reported in several studies [33–36], including this study [14]. The *TNF*(rs1800629) polymorphism has been found to be associated with higher constitutive and inducible expression of TNF- α and increased susceptibility to several infectious and inflammatory conditions [37]. High levels of TNF- α promote activation of the transcription factor NF- κ B, which has antiapoptotic effects on B cells [38]. Inappropriate activation of NF- κ B has also been linked to lymphomagenesis [39] and to autoimmune diseases, which are known risk factors for NHL [3]. Study also found that *TNF*(rs1800629) polymorphism can induce immune suppression through an increased production of TNF- α [16,40]. Recent evidence suggests that blood transfusion can increase serum levels of TNF- α [41]. As such, the observed interaction between genetic variation of *TNF*(rs1800629) and blood transfusion on the risk of NHL could be due to the change of TNF- α production.

Strengths and limitations should be considered in explaining the observed results. This study is a population-based case-control study with histologically confirmed incident NHL cases, which minimized potential disease misclassification. The study has a modest sample size, and therefore, the statistical power is limited particularly for NHL subtype analysis. As such, chance cannot be ruled out for some of the significant findings. Because of a number of SNPs being examined in the study, we adjusted for multiple comparisons using FDR approach. The study only included women, so the results may not be generalizable to men.

In summary, this is the first study to examine the effect modifications of common genetic variations in the Th1/Th2 pathways genes on the association between blood transfusion and risk of NHL. The observed significant interactions between *IL10RA* and *TNF* and blood transfusion on the risk of NHL need to be replicated in other study populations with greater statistical power.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Contract grant sponsor: NIH; Contract grant numbers: CA62006, 1D43TW008323-01, 1D43TW007864-01, HD70324-01, CA165923-01; Contract grant sponsor: Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute.

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TABLE I

Distributions of Selected Characteristics of the Study Population

Characteristics	Cases (N = 482)		Controls (N = 541)		P-value ^b
	Number	%	Number	%	
Age (Years)					
<55	146	30.3	161	29.8	
55–69	172	35.7	163	30.1	
70	164	34.0	217	40.1	0.08
Family history of hematopoietic cancers					
Yes	42	8.7	31	5.7	
No	440	91.3	510	94.3	0.06
Alcohol consumption					
Yes	313	64.9	372	68.8	
No	169	35.1	169	31.2	0.19
Cigarette smoking					
Yes	271	56.2	290	53.6	
No	211	43.8	251	46.4	0.40
Common NHL subtypes ^a					
DLBCL	150	31.1			
FL	114	23.6			
SLL/CLL	55	11.4			
MZBCL	33	6.9			
T-cell lymphoma	35	7.2			
Others	95	19.7			

^aDLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; MZBCL, marginal zone B-cell lymphoma.

^bBased on Chi-Square test.

Associations between Blood Transfusion and Risk of Non-Hodgkin Lymphoma Overall and Its Common Subtypes^a

TABLE II

Blood transfusion	Overall			B-cell lymphoma			T-cell lymphoma		
	Controls	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)
No	417	384	1.0	311	1.0	26	1.0		
Yes	124	98	0.9 (0.7–1.2)	75	0.8 (0.6–1.2)	9	1.2 (0.5–2.7)		
		DLBCL			FL		SLL/CLL		
Blood transfusion	Controls	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)		
	Controls	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)	Cases	OR ^b (95% CI)		
No	417	121	1.0	96	1.0	41	1.0		
Yes	124	29	0.9 (0.6–1.4)	18	0.7 (0.4–1.2)	14	1.1 (0.6–2.1)		

^aDLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia.

^bAdjusted for age.

TABLE III
Associations Between *IL10RA* and *TNF* Polymorphisms, Blood Transfusion, and Risk of Non-Hodgkin Lymphoma

SNPs	Overall						B cell lymphoma				T cell lymphoma			
	Blood transfusion						Blood transfusion				Blood transfusion			
	No			Yes			No		Yes		No		Yes	
	Controls	Cases	OR	Controls	Cases	OR ^a (95%CI)	Cases	OR	Cases	OR ^a (95%CI)	Cases	OR	Cases	OR ^a (95%CI)
<i>IL10RA (rs9610)</i>														
GG	121	103	1.0	32	43	1.9(1.1–3.2)	79	1.0	35	2.1(1.2–3.9)	10	1.0	2	0.7(0.1–3.8)
AG or AA	276	252	1.0	87	47	0.6(0.4–0.9)	209	1.0	35	0.5(0.3–0.8)	14	1.0	5	1.1(0.4–3.4)
<i>p</i> -interaction	0.003						0.001				0.68			
<i>TNF (rs1800629)</i>														
GG	288	272	1.0	96	60	0.7(0.5–1.0)	220	1.0	46	0.7(0.5–1.0)	21	1.0	7	1.1(0.4–2.8)
AG or AA	127	108	1.0	28	37	1.6(0.9–2.7)	88	1.0	29	1.5(0.8–2.7)	5	1.0	1	0.8(0.1–7.2)
<i>p</i> -interaction	0.012						0.019				0.93			

^a Adjusted for age.

TABLE IV
Associations Between *IL10RA* and *TNF* Polymorphisms, Blood transfusion, and Risk of Common B-cell Lymphoma Subtypes^a

SNPs	DLBCL					FL					SLL/CLL				
	Blood transfusion					Blood transfusion					Blood transfusion				
	No		Yes			No		Yes			No		Yes		
	Controls	Cases	OR	Controls	Cases	OR ^b (95%CI)	Cases	OR	Cases	OR ^b (95%CI)	Cases	OR	Cases	OR ^b (95%CI)	
<i>IL10RA (rs9610)</i>															
GG	121	32	1.0	32	13	2.4(1.0–5.5)	27	1.0	10	2.0(0.8–4.9)	7	1.0	7	5.3(1.5–18.9)	
AG or AA	276	79	1.0	87	15	0.6(0.3–1.1)	62	1.0	6	0.3(0.1–0.7)	32	1.0	5	0.4(0.2–1.2)	
<i>p</i> -interaction	0.058					0.012					0.008				
<i>TNF (rs1800629)</i>															
GG	288	80	1.0	96	19	0.8(0.5–1.4)	72	1.0	12	0.6(0.3–1.1)	32	1.0	8	0.7(0.3–1.6)	
AG or AA	127	40	1.0	28	10	1.1(0.5–2.6)	24	1.0	6	1.2(0.4–3.3)	8	1.0	6	3.2(1.0–10.1)	
<i>p</i> -interaction	0.38					0.19					0.029				

^aDLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; MZBCL, marginal zone B-cell lymphoma.

^bAdjusted for age.