Polymorphisms in Th1/Th2 cytokine genes, hormone replacement therapy, and risk of non-Hodgkin lymphoma

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We conducted a population-based case–control study in Connecticut women to test the hypothesis that genetic variations in Th1 and Th2 cytokine genes modify the relationship between hormone replacement therapy (HRT) and risk of non-Hodgkin lymphoma (NHL). Compared to women without a history of HRT use, women with a history of HRT use had a significantly decreased risk of NHL if they carried IFNGR2 (rs1059293) CT/TT genotypes (OR = 0.5, 95% CI: 0.3–0.9), IL13 (rs20541) GG genotype (OR = 0.6, 95% CI: 0.4–0.9), and IL13 (rs1295686) CC genotype (OR = 0.6, 95% CI: 0.4–0.8), but not among women who carried IFNGR2 CC, IL13AG/AA, and IL13CT/TT genotypes. A similar pattern was also observed for B-cell lymphoma but not for T-cell lymphoma. A statistically significant interaction was observed for IFNGR2 (rs1059293 \( P \text{ for interaction} = 0.024 \)), IL13 (rs20541 \( P \text{ for interaction} = 0.005 \)), IL13 (rs1295686 \( P \text{ for interaction} = 0.008 \)), and IL15RA (rs2296135 \( P \text{ for interaction} = 0.049 \)) for NHL overall; IL13 (rs20541 \( P \text{ for interaction} = 0.0009 \)), IL13 (rs1295686 \( P \text{ for interaction} = 0.0002 \)), and IL15RA (rs2296135 \( P \text{ for interaction} = 0.041 \)) for B-cell lymphoma. The results suggest that common genetic variation in Th1/Th2 pathway genes may modify the association between HRT and NHL risk.

Keywords: non-Hodgkin lymphoma, HRT, genetic polymorphisms, Th1/Th2 cytokines

INTRODUCTION

Female sex hormones play an important role in modulation of immune system function and autoimmune disease activities (Olsen and Kovacs, 1996; Medina et al., 2000). Non-Hodgkin lymphoma (NHL) is a tumor originating in the immune system (Hoover, 1992) and autoimmune disease is one of the few established risk factors. Epidemiological studies, however, provided inconsistent results linking hormone replacement therapy (HRT) use and risk of NHL with some studies (Cerhan et al., 1997; Nelson et al., 2001; Glaser et al., 2003; Zhang et al., 2004b) suggesting a decreased risk and others (Bernstein and Ross, 1992; Cerhan et al., 2002) suggesting an increased risk. While the mechanisms underlying the association between HRT and NHL remain unclear, it has been suggested that estrogen may act as a systemic anti-inflammatory treatment to lower the production of, or response to, pro-inflammatory cytokines (Saucedo et al., 2002). These cytokines can modulate lymphoid development and immune function (Hofmann et al., 2002; Keen, 2002; Gergely et al., 2004). Therefore, some of the inconsistent findings linking HRT and NHL risk may be explained by genetic variation in cytokine genes.

T-helper cells are vital to human immune responses. The T-helper cell response is defined by two distinct pathways involving two different subtypes of T-helper cells, T-helper 1 (Th1) cells, and T-helper 2 (Th2) cells. Th1 cytokines [i.e., interferon-γ (IFN-γ) and interleukin (IL)-2] produced by Th1 cells drive cellular immunity to fight intracellular pathogens including viruses, and remove cancerous cells, while Th2 cytokines (i.e., IL-4, IL-5, IL-9, IL-10, and IL-13) secreted by Th2 cells control humoral immunity by upregulating antibody production to protect against extracellular pathogens (Mosmann et al., 1986; Romagnani, 1991; Bouman et al., 2005; Lehrnbecher et al., 2005; Croxford and Buch, 2011). Immune dysfunction resulting from imbalanced regulation and expression of Th1 and Th2 cytokines play an important role in the development of NHL (Mori et al., 2001; Chiu and Weisenburger, 2003). Single nucleotide polymorphisms (SNPs) in several Th1/Th2 cytokine genes (i.e., IL4, IL5, IL6, IL10, IFNGR2, IL12A, IL13, IL17R, and TNF) have been reported to be associated with the risk of NHL and its major subtypes (Lan et al., 2006; Chen et al., 2011). It is possible that genetic variation in the Th1/Th2 cytokine genes may modify the relationship between HRT and NHL risk. As such, we analyzed data from 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 in other studies by our group (Zhang et al., 2004a; Chen et al., 2011). 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 and 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, and 231 (28%) refused to participate in the study. 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 (Alsheikh et al., 2001).

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 the random-digit dialing and 47% among persons identified from the Centers for Medicare and Medicaid Services. Approximately 75% of data collection was performed using SAS Software, version 9.2 (SAS and Hochberg, 1995). All statistical analysis was performed using SAS Software, version 9.2 (SAS Institute, Cary, NC, USA). The false discovery rate (FDR) method set and Hochberg, 1995). All

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 forms 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. An open-ended question was used to ask whether the subject had taken any medicine at least once a day for a period of 6 months or longer previous to 1 year ago, which included HRT. If yes, the age at first and last use, and the total months of use of the medicine were also ascertained (Zhang et al., 2004b).

STATISTICAL ANALYSIS
Unconditional logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for associations between HRT, and risk of NHL and its subtypes in different genotype strata adjusting for age, menopausal status, and family history of hematopoietic cancers in first degree relatives. We conducted analyses by separate heterozygous and homozygous variant genotypes and found that the risks were similar between heterozygous and homozygous variant genotypes. Since the numbers for homozygous variant genotypes in several genes were very small, the risk estimates were unstable. As such, heterozygous and homozygous variant genotypes were combined for all genes to increase the statistical power. Adjustments for other variables, such as race, education, tobacco use, or alcohol consumption, did not result in material change of the observed associations, and thus were not included in the final models reported here. Significance of gene–HRT interaction was assessed by adding an interaction term in the logistic regression models. The false discovery rate (FDR) method set at 0.2 was used to control for multiple comparisons (Benjamini and Hochberg, 1995). All p values presented are two-sided and all analyses were performed using SAS Software, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS
The distributions of selected characteristics of study population are presented in Table 1. Compared to controls, cases were more likely to have family history of hematopoietic cancers (p = 0.02). The proportion of postmenopausal women was greater in cases than in controls (p = 0.01). The distributions of age, race and HRT between cases and controls were not significantly different.
Table 1 | Distributions of selected characteristics of study population.

| Characteristics                        | Cases       | Controls      | Chi-square |
|----------------------------------------|-------------|---------------|------------|
|                                        | Number (N = 518) | Percentage | Number (N = 597) | Percentage | P-value |
| **AGE**                                |             |               |             |            |         |
| <50                                    | 102         | 19.7          | 117         | 19.6       | 0.44    |
| 50–59                                  | 109         | 21.0          | 109         | 18.3       |         |
| 60–69                                  | 132         | 25.5          | 144         | 24.1       |         |
| 70+                                    | 175         | 33.8          | 227         | 38.0       | 0.09    |
| **RACE**                                |             |               |             |            |         |
| White                                  | 497         | 95.9          | 559         | 93.6       |         |
| Others                                 | 21          | 4.1           | 38          | 6.4        |         |
| **FAMILY HISTORY OF HEMATOPOIEtic CANCeR** |           |               |             |            |         |
| No                                     | 473         | 91.3          | 566         | 94.8       |         |
| Yes                                    | 45          | 8.7           | 31          | 5.2        | 0.02    |
| **MENOpausal STATUS**                   |             |               |             |            |         |
| Yes                                    | 442         | 85.3          | 475         | 79.6       |         |
| No                                     | 76          | 14.7          | 122         | 20.4       | 0.01    |
| **HORMONE REPLACEMENT THERAPy**         |             |               |             |            |         |
| No                                     | 401         | 77.4          | 452         | 75.7       | 0.50    |
| Yes                                    | 117         | 22.6          | 145         | 24.3       |         |

Compared to women without a history of HRT use, women with a history of HRT use had a significantly decreased risk of NHL if they carried IFNGR2 (rs1059293) CT/TT genotypes (OR = 0.5, 95%CI: 0.3–0.9), IL13 (rs20541) GG genotype (OR = 0.6, 95%CI: 0.4–0.9) and IL13 (rs1295686) CC genotype (OR = 0.6, 95%CI: 0.4–0.8), but not among women who carried IFNGR2 CC, IL13 AG/AA, and IL13 CT/TT genotypes (Table 2). Similar results were also observed for B-cell lymphoma, but not for T-cell lymphoma. Significant interactions were observed for IFNGR2 (rs1059293) P_{interaction} = 0.024, IL13 (rs20541) P_{interaction} = 0.005, IL13 (rs1295686) P_{interaction} = 0.008, and IL15RA (rs2296135) P_{interaction} = 0.049) for NHL overall; IL13 (rs20541) P_{interaction} = 0.0009, IL13 (rs1295686 P_{interaction} = 0.0002), and IL15RA (rs2296135 P_{interaction} = 0.041) for B-cell lymphoma. After adjustment for FDR, the interactions for IL13 (rs20541) and IL13 (rs1295686) with NHL overall and B-cell lymphoma remained statistically significant.

After stratified by common B-cell lymphoma subtypes, significant interactions were observed for diffuse large B-cell lymphoma and follicular lymphoma (Table 3). Compared to women without a history of HRT use, women with a history of HRT use experienced a significantly decreased risk of diffuse large B-cell lymphoma if they carried IFNGR2 (rs1059293) CT/TT genotypes (OR = 0.3, 95%CI: 0.2–0.8), IL13 (rs1295686) CC genotype (OR = 0.5, 95%CI: 0.3–0.9), or IL15RA (rs2296135) CT/TT genotypes (OR = 0.5, 95%CI: 0.3–0.9). Compared to women without a history of HRT use, women with a history of HRT use also experienced a significantly decreased risk of follicular lymphoma if they carried IL13 (rs20541) GG genotype (OR = 0.4, 95%CI: 0.2–0.9) or IL13 (rs1295686) CC genotype (OR = 0.4, 95%CI: 0.2–0.9) and a significantly increased risk if they carried IL13 (rs20541) AG/AA genotypes (OR = 2.7, 95%CI: 1.2–5.8) or IL13 (rs1295686) CT/TT genotypes (OR = 2.6, 95%CI: 1.2–5.5). The interactions between HRT and IL13 (rs20541 P_{interaction} = 0.0003) and IL13 (rs1295686 P_{interaction} = 0.0005) in follicular lymphoma remained statistically significant after adjustment for FDR. Although increased or decreased risks were observed for several other cytokine polymorphisms, but none of them were statistically significant (Table A1 in Appendix).

**DISCUSSION**

To our knowledge, this is the first comprehensive analysis of interaction between HRT, genetic polymorphisms in Th1/Th2 pathway genes, and the risk of NHL and its subtypes. Significant interactions were observed for IFNGR2 (rs1059293), IL13 (rs20541, rs1295686), and IL15RA (rs2296135) for NHL overall and/or B-cell NHL subtypes.

The study suggested that IL13 polymorphisms modify the association between HRT use and risk of B-cell lymphoma, particularly for follicular lymphoma. The IL13 gene encodes the IL-13 cytokine which exerts anti-apoptotic functions and is linked to leukemogenesis (Waldele et al., 2004). *In vitro* study also suggested that IL-13 was a weak inducer and an amplifier of IL6 expression in vascular endothelial cells (Sironi et al., 1994). Estrogen has been shown to downregulate IL6 gene expression by endocrinological feedback mechanisms (Dijsselbloem et al., 2004). Studies have shown that higher serum levels of IL-6 were associated with an increased risk of B-cell lymphoma (Preti et al., 1997). It is biologically plausible that IL-6 expression may play an important role in our observed interaction between IL13 polymorphisms and HRT on the risk of B-cell lymphoma. Although it is currently unclear whether the two IL13 polymorphisms (rs20541 and rs1295686) causes over expression or enhanced function of IL-13, rs20541 has been linked to the risk of NHL (Wang et al., 2009).
Table 2 | Associations between Th1/Th2 cytokine polymorphisms, hormone replacement therapy, and risk of non-Hodgkin lymphoma.

| SNPs                  | IFNGR2_03 (rs1059293) | IL13_01 (rs20541) | IL13_06 (rs1295686) | IL15RA_02 (rs2296135) |
|-----------------------|------------------------|-------------------|---------------------|-----------------------|
|                       |                        |                   |                     |                       |
|                       | Controls | Cases | OR (95%CI) | Controls | Cases | OR (95%CI) | Controls | Cases | OR (95%CI) | Controls | Cases | OR (95%CI) |
| IFNGR2_03 (rs1059293) | CC        | 175   | 136   | 1.0 | 55   | 54   | 1.1(0.8–1.9) | 105   | 1.0 | 42   | 1.2(0.8–2.0) |
|                       | CT or TT  | 125   | 160   | 1.0 | 47   | 36   | 0.5(0.3–0.9) | 128   | 1.0 | 31   | 0.5(0.3–0.9) |
| P for interaction     | 0.024     |       |       | 0.052 |       |       | 0.005 |       | 0.009 |       | 0.002 |
| IL13_01 (rs20541) | GG        | 249   | 229   | 1.0 | 98   | 61   | 0.6(0.4–0.9) | 183   | 1.0 | 47   | 0.6(0.4–0.9) |
|                       | AG or AA  | 161   | 127   | 1.0 | 34   | 46   | 1.4(0.8–2.4) | 97    | 1.0 | 41   | 1.7(1.0–2.9) |
| P for interaction     | 0.042     |       |       | 0.0009 |       |       | 0.005 |       | 0.0003 |       | 0.049 |
| IL13_06 (rs1295686) | CC        | 227   | 216   | 1.0 | 94   | 56   | 0.6(0.4–0.8) | 174   | 1.0 | 44   | 0.5(0.4–0.8) |
|                       | CT or TT  | 175   | 135   | 1.0 | 37   | 51   | 1.6(1.0–2.6) | 104   | 1.0 | 45   | 1.8(1.1–3.1) |
| P for interaction     | 0.008     |       |       | 0.0002 |       |       | 0.049 |       | 0.041 |       |       |
| IL15RA_02 (rs2296135) | GG       | 119   | 80    | 1.0 | 32   | 33   | 1.3(0.7–2.4) | 64    | 1.0 | 29   | 1.5(0.8–2.8) |
|                       | GT or TT  | 283   | 269   | 1.0 | 97   | 73   | 0.7(0.5–1.0) | 213   | 1.0 | 59   | 0.7(0.5–1.1) |
| P for interaction     | 0.049     |       |       | 0.0003 |       |       | 0.042 |       | 0.0003 |       | 0.023 |

1 Adjusted for age, race, menopausal status, and family history.

Table 3 | Associations between Th1/Th2 cytokine polymorphisms, hormone replacement therapy, and risk of common B-cell lymphoma subtypes.

| SNPs                  | Overall | B-cell lymphoma |
|-----------------------|---------|-----------------|
|                       | Hormone replacement therapy | Hormone replacement therapy |
|                       | No | Cases | OR (95%CI) | Yes | Cases | OR (95%CI) | No | Cases | OR (95%CI) | Yes | Cases | OR (95%CI) |
| IFNGR2_03 (rs1059293) | CC | 47 | 16 | 1.0(0.5–1.9) | 34 | 1.0 | 12 | 1.1(0.5–2.3) |
|                       | CT or TT | 51 | 9 | 0.3(0.2–0.8) | 36 | 1.0 | 11 | 0.7(0.3–1.5) |
| P for interaction     | 0.116 |       |       | 0.505 |       |       | 0.042 |       | 0.0003 |       | 0.023 |
| IL13_01 (rs20541) | GG | 72 | 17 | 0.5(0.3–1.0) | 54 | 1.0 | 10 | 0.4(0.2–0.9) |
|                       | AG or AA | 43 | 14 | 1.1(0.5–2.2) | 24 | 1.0 | 16 | 2.7(1.2–5.8) |
| P for interaction     | 0.042 |       |       | 0.0003 |       |       | 0.042 |       | 0.0003 |       | 0.023 |
| IL13_06 (rs1295686) | CC | 70 | 16 | 0.5(0.3–0.9) | 53 | 1.0 | 10 | 0.4(0.2–0.9) |
|                       | CT or TT | 46 | 15 | 1.2(0.6–2.4) | 26 | 1.0 | 16 | 2.6(1.2–5.5) |
| P for interaction     | 0.023 |       |       | 0.0005 |       |       | 0.023 |       | 0.0005 |       | 0.005 |
| IL15RA_02 (rs2296135) | CC | 25 | 11 | 1.4(0.6–3.1) | 16 | 1.0 | 8 | 1.6(0.6–4.4) |
|                       | CT or TT | 91 | 20 | 0.5(0.3–0.9) | 62 | 1.0 | 17 | 0.7(0.4–1.3) |
| P for interaction     | 0.068 |       |       | 0.119 |       |       | 0.068 |       | 0.119 |       | 0.068 |

1 DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.
2 Adjusted for age, race, menopausal status, and family history.
Our study also suggested IFNGR2 polymorphism (rs1059293) modified the association between HRT and NHL. The gene IFNGR2 encodes the non-ligand-binding beta chain of the IFN-γ located on chromosome 21 (Mogensen et al., 1999). Initiation of the IFN-γ signal transduction cascade, serves to directly inhibit viral replication and serves to stimulate and modulate the immune system. A recent study suggested that HRT could improve postmenopausal women’s immune system by inducing a significant decrease in the production of IL-10 and IFN-γ (Deguchi et al., 2001). Effect modification was observed for NHL suggesting the IFN-γ transduction pathway could play a role in the relationship between HRT and risk of NHL. Further knowledge of the functional impact of IFNGR2 polymorphism (rs1059293) on IFNGR2 gene is needed to help elucidate its role between HRT and NHL.

Potential effect modification by IL15RA (rs2296135) polymorphism was observed. The IL15RA gene encodes the alpha chain of the IL-15 receptor which is expressed in a variety of immune and non-immune cell types from different tissues and generates multiple splicing events of functional importance (Bouchaud et al., 2008; Diniz et al., 2010). IL-15 and IL-2 receptors share the beta and gamma(c) subunits with private alpha chains, which presumably ensure the binding of the appropriate cytokine and the specificity of the immune response (Vamosi et al., 2004). IL-15 and IL-2 can activate similar janus kinase/signal transducer and activator of transcription (JAK/STAT)-dependent signaling pathway at the presence of both beta and gamma(c) subunits, suggesting a significant overlap between the functions of IL-2 and IL-5 (Lin et al., 1995). Recent study demonstrated that both IL-2 and IL-5 alpha subunits co-expressed in a supramolecular receptor cluster in lipid rafts of the T cells (Vamosi et al., 2004). HRT has been found to reduce IL-2 production (Stopinska-Gluszak et al., 2006) suggesting that IL-2 cytokine network plays a role in the association between HRT and NHL. As such, the observed interaction between genetic variation of IL15RA and HRT on the risk of NHL could be due to the change of IL-2 cytokine network.

Several strengths are included in our study. First, it is a population-based case–control study with histologically confirmed incident NHL cases which minimized potential disease misclassification. Second, this study used a rapid case identification system to identify all eligible NHL cases eliminated survival bias given the aggressive nature of NHL. Eligible cases were identified within 1 month after their diagnosis through the RCA. And finally, this study, for the first time, reported the effect modification of Th1/Th2 genes on the association between HRT and NHL.

While our study included more than 1,000 study subjects, the statistical power is limited when investigating the relationship by NHL subtypes. Given the number of SNPs investigated in the study, chance cannot be ruled out for some of the significant findings. However, several significant findings remained after adjusted for multiple comparisons using the FDR approach.

In summary, our study provided the first suggestive evidence that common genetic variations in the Th1/Th2 pathway genes may modify the association between HRT and risk of NHL. The observed results could not only advance our understanding of the relationship between HRT use and risk of NHL but also have a potential impact on future clinical practices using HRT. Further larger population-based studies or pooled analyses with greater power are needed to replicate the results.

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### Table A1 | Associations between Th1/Th2 cytokine polymorphisms, hormone replacement therapy, and risk of non-Hodgkin lymphoma and its common subtypes.

| SNPs          | Overall   | B cell lymphoma | DLBCL | Follicular |
|---------------|-----------|-----------------|-------|------------|
|               | No        | Yes             | No    | Yes        | No           | Yes           | No            | Yes          |
|               | Controls  | Cases OR        | Controls  | Cases OR | Controls  | Cases OR | Controls  | Cases OR | Controls  | Cases OR | Controls  | Cases OR | Controls  | Cases OR | Controls  | Cases OR |
| IFNG_07 (rs8161494) | | | | | | | | | | | | | | | |
| AA           | 203       | 188 1.0        | 72    | 60 0.8 (0.5–1.2) | 150         | 1.0 51 0.8 (0.5–1.3) | 63          | 1.0 19 0.7 (0.4–1.2) | 43          | 1.0 15 0.8 (0.4–1.6) |
| AG or GG     | 201       | 164 1.0        | 59    | 47 0.9 (0.6–1.4) | 129         | 1.0 38 0.9 (0.6–1.5) | 53          | 1.0 12 0.6 (0.3–1.3) | 36          | 1.0 11 1.0 (0.5–2.3) |
| P-interaction| 0.86      |                |       |             | 0.94        |                | 0.82        |                | 0.93        |                | |
| IFNG_10 (rs2069705) | | | | | | | | | | | | | | | |
| TT           | 172       | 157 1.0        | 62    | 51 0.7 (0.5–1.2) | 128         | 1.0 43 0.8 (0.5–1.2) | 53          | 1.0 17 0.7 (0.4–1.3) | 38          | 1.0 11 0.6 (0.3–1.3) |
| CT or CC     | 230       | 195 1.0        | 68    | 55 0.9 (0.6–1.3) | 151         | 1.0 45 0.9 (0.6–1.4) | 63          | 1.0 13 0.6 (0.3–1.1) | 41          | 1.0 15 1.2 (0.6–2.4) |
| P-interaction| 0.80      |                |       |             | 0.76        |                | 0.68        |                | 0.38        |                | |
| IFNGR105 (RS3799488) | | | | | | | | | | | | | | | |
| AA           | 315       | 276 1.0        | 98    | 82 0.9 (0.6–1.2) | 219         | 1.0 68 0.9 (0.6–1.3) | 90          | 1.0 23 0.7 (0.4–1.2) | 68          | 1.0 23 1.0 (0.6–1.8) |
| AG or GG     | 89        | 74 1.0         | 33    | 24 0.7 (0.4–1.3) | 58          | 1.0 20 0.8 (0.4–1.5) | 25          | 1.0 7 0.5 (0.2–1.3) | 11          | 1.0 3 0.4 (0.1–1.7) |
| P-interaction| 0.78      |                |       |             | 0.8         |                | 0.67        |                | 0.58        |                | |
| IFNGR201 (RS9808753) | | | | | | | | | | | | | | | |
| AA           | 332       | 291 1.0        | 104   | 91 0.9 (0.7–1.3) | 233         | 1.0 74 0.9 (0.7–1.3) | 96          | 1.0 23 0.7 (0.4–1.1) | 64          | 1.0 22 1.0 (0.6–1.8) |
| AG or GG     | 96        | 87 1.0         | 35    | 16 0.4 (0.2–0.7) | 67          | 1.0 15 0.4 (0.2–0.8) | 28          | 1.0 8 0.5 (0.2–1.2) | 20          | 1.0 4 0.3 (0.1–1.0) |
| P-interaction| 0.04      |                |       |             | 0.12        |                | 0.92        |                | 0.23        |                | |
| IL10RA_02 (rs9610) | | | | | | | | | | | | | | | |
| GG           | 139       | 122 1.0        | 33    | 32 1.0 (0.5–1.7) | 92          | 1.0 26 1.0 (0.6–1.9) | 38          | 1.0 9 0.8 (0.3–1.9) | 31          | 1.0 8 0.9 (0.4–2.2) |
| A Gor AA     | 296       | 250 1.0        | 102   | 76 0.8 (0.5–1.1) | 201         | 1.0 63 0.8 (0.5–1.1) | 80          | 1.0 23 0.7 (0.4–1.1) | 53          | 1.0 18 0.9 (0.5–1.6) |
| P-interaction| 0.47      |                |       |             | 0.4         |                | 0.81        |                | 0.77        |                | |
| IL12A_01 (rs568408) | | | | | | | | | | | | | | | |
| GG           | 319       | 279 1.0        | 104   | 82 0.8 (0.6–1.1) | 214         | 1.0 72 0.9 (0.6–1.3) | 84          | 1.0 23 0.6 (0.4–1.1) | 66          | 1.0 21 0.8 (0.5–1.5) |
| A Gor AA     | 124       | 109 1.0        | 35    | 26 0.7 (0.4–1.3) | 89          | 1.0 17 0.6 (0.3–1.1) | 39          | 1.0 10 0.8 (0.3–1.8) | 20          | 1.0 5 0.7 (0.2–2.3) |
| P-interaction| 0.86      |                |       |             | 0.27        |                | 0.76        |                | 0.87        |                | |
| IL12A_07 (rs582054) | | | | | | | | | | | | | | | |
| TT           | 130       | 99 1.0         | 41    | 37 1.0 (0.6–1.8) | 80          | 1.0 31 1.1 (0.6–1.9) | 33          | 1.0 11 0.8 (0.4–1.8) | 22          | 1.0 8 0.8 (0.3–2.0) |
| A Tor AA     | 274       | 251 1.0        | 89    | 70 0.8 (0.5–1.1) | 198         | 1.0 58 0.8 (0.5–1.2) | 83          | 1.0 20 0.6 (0.4–1.1) | 57          | 1.0 18 0.9 (0.5–1.7) |
| P-interaction| 0.27      |                |       |             | 0.31        |                | 0.48        |                | 0.86        |                | |
| IL13_03 (rs808025) | | | | | | | | | | | | | | | |
| CC           | 272       | 234 1.0        | 96    | 58 0.6 (0.4–0.9) | 189         | 1.0 45 0.6 (0.4–0.9) | 75          | 1.0 18 0.5 (0.3–1.0) | 51          | 1.0 12 0.6 (0.3–1.2) |

(Continued)
### Table A1 | Continued.

| SNPs | Overall | B cell lymphoma | DLBCL | Follicular |
|------|---------|----------------|-------|------------|
|      | No | Yes | OR | OR\(^{\text{a}}\) (95\% CI) | No | Yes | OR | OR\(^{\text{a}}\) (95\% CI) | No | Yes | OR | OR\(^{\text{a}}\) (95\% CI) |
| Controls | Cases | OR | Controls | Cases | OR\(^{\text{a}}\) (95\% CI) | Controls | Cases | OR | Cases | OR\(^{\text{a}}\) (95\% CI) | Controls | Cases | OR | Cases | OR\(^{\text{a}}\) (95\% CI) |
| CTT or TT | 170 | 154 | 1.0 | 45 | 52 | 1.1 (0.7–1.7) | 115 | 1.0 | 46 | 1.3 (0.8–2.1) | 117 | 1.0 | 15 | 0.9 (0.5–1.9) | 35 | 1.0 | 14 | 1.2 (0.6–2.5) |
| P-interaction | 0.05 | 0.01 | 0.19 | 0.13 |
| **IL15_02 (rs10833)** | | | | | | | | | | | | | | |
| CC | 178 | 150 | 1.0 | 58 | 51 | 1.0 (0.6–1.6) | 118 | 1.0 | 44 | 1.1 (0.7–1.8) | 54 | 1.0 | 10 | 0.5 (0.2–1.1) | 29 | 1.0 | 14 | 1.3 (0.6–2.8) |
| P-interaction | 0.05 | 0.01 | 0.19 | 0.13 |
| **IL2_01 (rs2069762)** | | | | | | | | | | | | | | |
| TT | 221 | 182 | 1.0 | 75 | 49 | 0.8 (0.5–1.1) | 140 | 1.0 | 42 | 0.8 (0.5–1.3) | 69 | 1.0 | 17 | 0.6 (0.3–1.2) | 37 | 1.0 | 12 | 0.8 (0.4–1.8) |
| P-interaction | 0.51 | 0.51 | 0.51 | 0.51 |
| **IL4_02 (rs2243248)** | | | | | | | | | | | | | | |
| TT | 338 | 326 | 1.0 | 120 | 85 | 0.7 (0.5–1.1) | 259 | 1.0 | 75 | 0.8 (0.6–1.1) | 102 | 1.0 | 27 | 0.7 (0.4–1.1) | 76 | 1.0 | 21 | 0.7 (0.4–1.3) |
| P-interaction | 0.58 | 0.58 | 0.58 | 0.58 |
| **IL4_10 (rs2243290)** | | | | | | | | | | | | | | |
| CC | 284 | 253 | 1.0 | 99 | 79 | 0.8 (0.6–1.2) | 198 | 1.0 | 66 | 0.9 (0.6–1.3) | 79 | 1.0 | 24 | 0.8 (0.4–1.3) | 55 | 1.0 | 17 | 0.8 (0.4–1.5) |
| P-interaction | 0.57 | 0.73 | 0.76 | 0.39 |
| **IL4_11 (rs2243268)** | | | | | | | | | | | | | | |
| AA | 285 | 254 | 1.0 | 98 | 80 | 0.8 (0.6–1.2) | 200 | 1.0 | 67 | 0.9 (0.6–1.3) | 80 | 1.0 | 24 | 0.8 (0.3–1.3) | 56 | 1.0 | 17 | 0.8 (0.4–1.5) |
| P-interaction | 0.75 | 0.92 | 0.73 | 0.41 |
| **IL4R 23 (rs2107356)** | | | | | | | | | | | | | | |
| CC | 157 | 115 | 1.0 | 43 | 35 | 0.8 (0.5–1.6) | 96 | 1.0 | 28 | 0.9 (0.5–1.5) | 42 | 1.0 | 9 | 0.6 (0.3–1.4) | 28 | 1.0 | 6 | 0.6 (0.2–1.7) |
| P-interaction | 0.35 | 0.35 | 0.73 | 0.41 |
| **IL5_02 (rs2069812)** | | | | | | | | | | | | | | |
| CC | 203 | 165 | 1.0 | 70 | 54 | 0.8 (0.5–1.2) | 124 | 1.0 | 48 | 0.9 (0.6–1.5) | 45 | 1.0 | 17 | 0.9 (0.4–1.6) | 33 | 1.0 | 12 | 0.8 (0.4–1.7) |
| P-interaction | 0.99 | 0.99 | 0.99 | 0.99 |
| Gene | SNP         | Genotype | MAF | Global | P-value | P-interaction |
|------|-------------|----------|-----|--------|---------|---------------|
| **IL6 01 (rs1800795)** | GG          | 0.57    |     | 1.0    | 0.8 (0.5–1.3) | 0.13 (0.5–1.3) |
|      | CG or CC    | 0.55    |     | 1.0    | 0.8 (0.5–1.2) | 0.13 (0.5–1.2) |
|      | P-interaction | 0.47   |     | 0.52   | 0.36     |
| **IL6 04 (rs1800797)** | GG          | 0.58    |     | 1.0    | 0.9 (0.6–1.5) | 0.13 (0.5–1.5) |
|      | AG or AA    | 0.44    |     | 1.0    | 0.8 (0.5–1.2) | 0.13 (0.5–1.2) |
|      | P-interaction | 0.73   |     | 0.33   | 0.58     |
| **IL7R 01 (rs1494555)** | AA          | 0.59    |     | 1.0    | 0.9 (0.6–1.5) | 0.13 (0.5–1.5) |
|      | AG or GG    | 0.50    |     | 1.0    | 0.8 (0.5–1.2) | 0.13 (0.5–1.2) |
|      | P-interaction | 0.45   |     | 0.5    | 0.36     |
| **JAK3 01 (rs3008)** | CC          | 0.56    |     | 1.0    | 0.9 (0.6–1.3) | 0.13 (0.5–1.3) |
|      | CT or TT    | 0.44    |     | 1.0    | 0.9 (0.6–1.2) | 0.13 (0.5–1.2) |
|      | P-interaction | 0.63   |     | 0.59   | 0.43     |
| **IL10 01 (rs1800871)** | CC          | 0.59    |     | 1.0    | 0.9 (0.6–1.2) | 0.13 (0.5–1.2) |
|      | CT or TT    | 0.51    |     | 1.0    | 0.9 (0.6–1.2) | 0.13 (0.5–1.2) |
|      | P-interaction | 0.68   |     | 0.55   | 0.48     |
| **IL10 02 (rs1800872)** | AA          | 0.45    |     | 1.0    | 0.9 (0.6–1.3) | 0.13 (0.5–1.3) |
|      | AC or AA    | 0.49    |     | 1.0    | 0.9 (0.6–1.3) | 0.13 (0.5–1.3) |
|      | P-interaction | 0.75   |     | 0.74   | 0.74     |
| **IL10 03 (rs1800896)** | TT          | 0.50    |     | 1.0    | 0.9 (0.6–1.2) | 0.13 (0.5–1.2) |
|      | CT or CC    | 0.51    |     | 1.0    | 0.9 (0.6–1.2) | 0.13 (0.5–1.2) |
|      | P-interaction | 0.76   |     | 0.71   | 0.71     |
| **IL10 06 (rs3024496)** | GG          | 0.55    |     | 1.0    | 0.8 (0.5–1.5) | 0.13 (0.5–1.5) |
|      | GT or TT    | 0.51    |     | 1.0    | 0.9 (0.6–1.3) | 0.13 (0.5–1.3) |
|      | P-interaction | 0.79   |     | 0.71   | 0.71     |
| **IL10 07 (rs3024491)** | GG          | 0.55    |     | 1.0    | 0.8 (0.5–1.5) | 0.13 (0.5–1.5) |
|      | GT or TT    | 0.51    |     | 1.0    | 0.9 (0.6–1.3) | 0.13 (0.5–1.3) |
|      | P-interaction | 0.79   |     | 0.71   | 0.71     |

(Continued)
Table A1 | Continued.

| SNPs | Overall | B cell lymphoma | DLBCL | Follicular |
|------|---------|-----------------|-------|-----------|
|      | No | Yes | OR (95% CI) | No | Yes | OR (95% CI) | No | Yes | OR (95% CI) | No | Yes | OR (95% CI) |
|      | Controls | Cases | OR | Controls | Cases | OR | Controls | Cases | OR | Controls | Cases | OR | Controls | Cases | OR |
| P-interaction | 0.59 | 0.93 | 0.86 | 0.93 |
| **IL10_17 (rs1800890)** | TT 200 | 140 | 1.0 | 61 | 0.8 (0.6–1.5) | 108 | 1.0 | 37 | 0.8 (0.6–1.5) | 43 | 1.0 | 15 | 0.9 (0.4–1.7) | 30 | 1.0 | 10 | 0.7 (0.3–1.7) |
| AT or AA 252 | 254 | 1.0 | 84 | 0.7 (0.5–1.1) | 201 | 1.0 | 60 | 0.8 (0.5–1.2) | 83 | 1.0 | 19 | 0.6 (0.3–1.1) | 59 | 1.0 | 19 | 0.9 (0.5–1.7) |
| P-interaction | 0.33 | 0.62 | 0.62 | 0.97 |
| **TNF_02 (rs1800629)** | GG 328 | 278 | 1.0 | 102 | 0.9 (0.6–1.2) | 218 | 1.0 | 67 | 0.9 (0.6–1.3) | 83 | 1.0 | 23 | 0.8 (0.4–1.3) | 65 | 1.0 | 22 | 1.0 (0.5–1.7) |
| AG or AA 123 | 120 | 1.0 | 42 | 0.7 (0.4–1.1) | 94 | 1.0 | 29 | 0.7 (0.4–1.3) | 44 | 1.0 | 10 | 0.5 (0.2–1.1) | 25 | 1.0 | 7 | 0.8 (0.3–2.0) |
| P-interaction | 0.7 | 0.87 | 0.54 | 0.58 |
| **TNF_07 (rs1799724)** | CC 330 | 284 | 1.0 | 101 | 0.8 (0.5–1.1) | 229 | 1.0 | 66 | 0.8 (0.5–1.1) | 95 | 1.0 | 23 | 0.6 (0.4–1.0) | 66 | 1.0 | 21 | 0.9 (0.5–1.6) |
| CT or TT 92 | 87 | 1.0 | 33 | 0.9 (0.5–1.6) | 65 | 1.0 | 22 | 1.0 (0.5–1.8) | 25 | 1.0 | 8 | 0.8 (0.3–2.1) | 17 | 1.0 | 5 | 0.7 (0.2–2.2) |
| P-interaction | 0.99 | 0.92 | 0.81 | 0.75 |

¹Adjusted for age, race, menopausal status and family history.