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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, *IL13* AG/AA, and *IL13* CT/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*, *IL7R*, 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 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 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).

GENOTYPING

Genotyping was performed at the National Cancer Institute Core Genotyping Facility[1]. All TaqMan assays (Applied Biosystems, Foster City, CA, USA) for this study were optimized on the ABI 7900HT detection system with 100% concordance with sequence analysis of 102 individuals as listed on the SNP500 Cancer website[2]. 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 (Lan et al., 2006). 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 priori* knowledge 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 to 40 replicate samples from each of two blood donors were interspersed throughout the plates used for genotype analysis. The concordance rates for quality control (QC) samples were between 99 and 100% for all assays. The genotype frequencies for three SNPs (rs231775, rs2243250, and rs2070874) were not consistent with Hardy–Weinberg equilibrium (HWE) among non-Hispanic white controls using a chi-square test ($p < 0.05$) and were excluded from the final analysis. To increase the statistical power for the gene–environmental interaction analysis, another five SNPs (rs2069822, rs2069818, rs2069807, 3024509, and rs361525) with minor allele frequency less than 10% were also excluded from the final analysis. A total of 31 SNPs in 17 Th1/Th2 genes: *IFNG* (rs1861494, rs2069705), *IFNGR1* (rs3799488), *IFNGR2* (rs9808753), *IFNGR2* (rs1059293), *IL10RA* (rs9610), *IL12A* (rs568408, rs582054), *IL13* (rs20541, rs1800925, rs1295686), *IL15* (rs10833), *IL15RA* (rs2296135), *IL2* (rs2069762), *IL4* (rs2243248, rs2243290, rs2243268), *IL4R* (rs2107356), *IL5* (rs2069812), *IL6* (rs1800795, rs1800797), *IL7R* (rs1494555), *JAK3* (rs3008), *IL10* (rs1800871, rs1800872, rs1800896, rs3024496, rs3024491, rs1800890), and *TNF* (rs1800629, rs1799724) were included in the final analysis.

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.

[1]http://cgf.nci.nih.gov

[2]http://snp500cancer.nci.nih.gov

Table 1 | Distributions of selected characteristics of study population.

Characteristics	Cases		Controls		Chi-square *P*-value
	Number (*N* = 518)	Percentage	Number (*N* = 597)	Percentage	
AGE					
<50	102	19.7	117	19.6	
50–59	109	21.0	109	18.3	
60–69	132	25.5	144	24.1	
70+	175	33.8	227	38.0	0.44
RACE					
White	497	95.9	559	93.6	
Others	21	4.1	38	6.4	0.09
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	
Yes	117	22.6	145	24.3	0.50

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 $P_{\text{for interaction}} = 0.024$), *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. 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 $P_{\text{for interaction}} = 0.0003$) and *IL13* (rs1295686 $P_{\text{for interaction}} = 0.0005$) 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	Overall						B-cell lymphoma			
	Hormone replacement therapy						Hormone replacement therapy			
	No			Yes			No		Yes	
	Controls	Cases	OR[1](95%CI)	Controls	Cases	OR[1](95%CI)	Cases	OR[1](95%CI)	Cases	OR[1](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)
$P_{\text{for interaction}}$			*0.024*					*0.052*		
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	45	1.4(0.8–2.4)	97	1.0	41	1.7(1.0–2.9)
$P_{\text{for interaction}}$			*0.005*					*0.0009*		
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)
$P_{\text{for interaction}}$			*0.008*					*0.0002*		
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)
$P_{\text{for interaction}}$			*0.049*					*0.041*		

[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[1].

SNPs	DLBCL				FL			
	Hormone replacement therapy				Hormone replacement therapy			
	No		Yes		No		Yes	
	Cases	OR[2]	Cases	OR[2](95%CI)	Cases	OR[2]	Cases	OR[2](95%CI)
IFNGR2_03 (rs1059293)								
CC	47	1.0	16	1.0(0.5–1.9)	34	1.0	12	1.1(0.5–2.3)
CT or TT	51	1.0	9	0.3(0.2–0.8)	36	1.0	11	0.7(0.3–1.5)
$P_{\text{for interaction}}$			*0.116*				*0.505*	
IL13_01(rs20541)								
GG	72	1.0	17	0.5(0.3–1.0)	54	1.0	10	0.4(0.2–0.9)
AG or AA	43	1.0	14	1.1(0.5–2.2)	24	1.0	16	2.7(1.2–5.8)
$P_{\text{for interaction}}$			*0.042*				*0.0003*	
IL13_06(rs1295686)								
CC	70	1.0	16	0.5(0.3–0.9)	53	1.0	10	0.4(0.2–0.9)
CT or TT	46	1.0	15	1.2(0.6–2.4)	26	1.0	16	2.6(1.2–5.5)
$P_{\text{for interaction}}$			*0.023*				*0.0005*	
IL15RA_02(rs2296135)								
CC	25	1.0	11	1.4(0.6–3.1)	16	1.0	8	1.6(0.6–4.4)
CT or TT	91	1.0	20	0.5(0.3–0.9)	62	1.0	17	0.7(0.4–1.3)
$P_{\text{for interaction}}$			*0.068*				*0.119*	

[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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REFERENCES

Alsheikh, A., Mohamedali, Z., Jones, E., Masterson, J., and Gilks, C. B. (2001). Comparison of the WHO/ISUP classification and cytokeratin 20 expression in predicting the behavior of low-grade papillary urothelial tumors. World/Health Organization/ Internattional Society of Urologic Pathology. *Mod. Pathol.* 14, 267–272.

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 57, 289–300.

Bernstein, L., and Ross, R. K. (1992). Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. *Cancer Res.* 52, 5510s–5515s.

Bouchaud, G., Garrigue-Antar, L., Sole, V., Quemener, A., Boublik, Y., Mortier, E., Perdreau, H., Jacques, Y., and Plet, A. (2008). The exon-3-encoded domain of IL-15ralpha contributes to IL-15 high-affinity binding and is crucial for the IL-15 antagonistic effect of soluble IL-15Ralpha. *J. Mol. Biol.* 382, 1–12.

Bouman, A., Heineman, M. J., and Faas, M. M. (2005). Sex hormones and the immune response in humans. *Hum. Reprod. Update* 11, 411–423.

Cerhan, J. R., Vachon, C. M., Habermann, T. M., Ansell, S. M., Witzig, T. E., Kurtin, P. J., Janney, C. A., Zheng, W., Potter, J. D., Sellers, T. A., and Folsom, A. R. (2002). Hormone replacement therapy and risk of non-hodgkin lymphoma and chronic lymphocytic leukemia. *Cancer Epidemiol. Biomarkers Prev.* 11, 1466–1471.

Cerhan, J. R., Wallace, R. B., Folsom, A. R., Potter, J. D., Sellers, T. A., Zheng, W., and Lutz, C. T. (1997). Medical history risk factors for non-Hodgkin's lymphoma in older women. *J. Natl. Cancer Inst.* 89, 314–318.

Chen, Y., Zheng, T., Lan, Q., Foss, F., Kim, C., Chen, X., Dai, M., Li, Y., Holford, T., Leaderer, B., Boyle, P., Chanock, S. J., Rothman, N., and Zhang, Y. (2011). Cytokine polymorphisms in Th1/Th2 pathway, body mass index, and risk of non-Hodgkin lymphoma. *Blood.* 117, 585–590.

Chiu, B. C., and Weisenburger, D. D. (2003). An update of the epidemiology of non-Hodgkin's lymphoma. *Clin. Lymphoma* 4, 161–168.

Croxford, A. L., and Buch, T. (2011). Cytokine reporter mice in immunological research: perspectives and lessons learned. *Immunology* 132, 1–8.

Deguchi, K., Kamada, M., Irahara, M., Maegawa, M., Yamamoto, S., Ohmoto, Y., Murata, K., Yasui, T., Yamano, S., and Aono, T. (2001). Postmenopausal changes in production of type 1 and type 2 cytokines and the effects of hormone replacement therapy. *Menopause* 8, 266–273.

Dijsselbloem, N., Vanden Berghe, W., De Naeyer, A., and Haegeman, G. (2004). Soy isoflavone phyto-pharmaceuticals in interleukin-6 affections. Multi-purpose nutraceuticals at the crossroad of hormone replacement, anti-cancer and anti-inflammatory therapy. *Biochem. Pharmacol.* 68, 1171–1185.

Diniz, S. N., Pendeloski, K. P., Morgun, A., Chepelev, I., Gerbase-Delima, M., and Shulzhenko, N. (2010). Tissue-specific expression of IL-15RA alternative splicing transcripts and its regulation by DNA methylation. *Eur. Cytokine Netw.* 21, 308–318.

Gergely, L., Aleksza, M., Varoczy, L., Ponyi, A., Sipka, S., Illes, A., and Szegedi, G. (2004). Intracellular IL-4/IFN-gamma producing peripheral T lymphocyte subsets in B cell non-Hodgkin's lymphoma patients. *Eur. J. Haematol.* 72, 336–341.

Glaser, S. L., Clarke, C. A., Nugent, R. A., Stearns, C. B., and Dorfman, R. F. (2003). Reproductive factors in Hodgkin's disease in women. *Am. J. Epidemiol.* 158, 553–563.

Hofmann, S. R., Ettinger, R., Zhou, Y. J., Gadina, M., Lipsky, P., Siegel, R., Candotti, F., and O'shea, J. J. (2002). Cytokines and their role in lymphoid development, differentiation and homeostasis. *Curr. Opin. Allergy Clin. Immunol.* 2, 495–506.

Hoover, R. N. (1992). Lymphoma risks in populations with altered immunity – a

search for mechanism. *Cancer Res.* 52, 5477s–5478s.

Keen, L. J. (2002). The extent and analysis of cytokine and cytokine receptor gene polymorphism. *Transpl. Immunol.* 10, 143–146.

Lan, Q., Zheng, T., Rothman, N., Zhang, Y., Wang, S. S., Shen, M., Berndt, S. I., Zahm, S. H., Holford, T. R., Leaderer, B., Yeager, M., Welch, R., Boyle, P., Zhang, B., Zou, K., Zhu, Y., and Chanock, S. (2006). Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma. *Blood* 107, 4101–4108.

Lehrnbecher, T., Bernig, T., Hanisch, M., Koehl, U., Behl, M., Reinhardt, D., Creutzig, U., Klingebiel, T., Chanock, S. J., and Schwabe, D. (2005). Common genetic variants in the interleukin-6 and chitotriosidase genes are associated with the risk for serious infection in children undergoing therapy for acute myeloid leukemia. *Leukemia* 19, 1745–1750.

Lin, J. X., Migone, T. S., Tsang, M., Friedmann, M., Weatherbee, J. A., Zhou, L., Yamauchi, A., Bloom, E. T., Mietz, J., John, S., and Leonard, W. J. (1995). The role of shared receptor motifs and common stat proteins in the generation of cytokine pleiotropy and redundancy by IL-2, IL-4, IL-7, IL-13, and IL-15. *Immunity* 2, 331–339.

Medina, K. L., Strasser, A., and Kincade, P. W. (2000). Estrogen influences the differentiation, proliferation, and survival of early B-lineage precursors. *Blood* 95, 2059–2067.

Mogensen, K. E., Lewerenz, M., Reboul, J., Lutfalla, G., and Uze, G. (1999). The type I interferon receptor: structure, function, and evolution of a family business. *J. Interferon Cytokine Res.* 19, 1069–1098.

Mori, T., Takada, R., Watanabe, R., Okamoto, S., and Ikeda, Y. (2001). T-helper (Th)1/Th2 imbalance in patients with previously untreated B-cell diffuse large cell lymphoma. *Cancer Immunol. Immunother.* 50, 566–568.

Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A., and Coffman, R. L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol.* 136, 2348–2357.

Nelson, R. A., Levine, A. M., and Bernstein, L. (2001). Reproductive factors and risk of intermediate- or high-grade B-Cell non-Hodgkin's lymphoma in women. *J. Clin. Oncol.* 19, 1381–1387.

Olsen, N. J., and Kovacs, W. J. (1996). Gonadal steroids and immunity. *Endocr. Rev.* 17, 369–384.

Preti, H. A., Cabanillas, F., Talpaz, M., Tucker, S. L., Seymour, J. F., and Kurzrock, R. (1997). Prognostic value of serum interleukin-6 in diffuse large-cell lymphoma. *Ann. Intern. Med.* 127, 186–194.

Romagnani, S. (1991). Type 1 T helper and type 2 T helper cells: functions, regulation and role in protection and disease. *Int. J. Clin. Lab. Res.* 21, 152–158.

Saucedo, R., Rico, G., Basurto, L., Ochoa, R., and Zarate, A. (2002). Transdermal estradiol in menopausal women depresses interleukin-6 without affecting other markers of immune response. *Gynecol. Obstet. Invest.* 53, 114–117.

Sironi, M., Sciacca, F. L., Matteucci, C., Conni, M., Vecchi, A., Bernasconi, S., Minty, A., Caput, D., Ferrara, P., Colotta, F., and Mantovani, A. (1994). Regulation of endothelial and mesothelial cell function by interleukin-13: selective induction of vascular cell adhesion molecule-1 and amplification of interleukin-6 production. *Blood* 84, 1913–1921.

Stopinska-Gluszak, U., Waligora, J., Grzela, T., Gluszak, M., Jozwiak, J., Radomski, D., Roszkowski, P. I., and Malejczyk, J. (2006). Effect of estrogen/progesterone hormone replacement therapy on natural killer cell cytotoxicity and immunoregulatory cytokine release by peripheral blood mononuclear cells of postmenopausal women. *J. Reprod. Immunol.* 69, 65–75.

Vamosi, G., Bodnar, A., Vereb, G., Jenei, A., Goldman, C. K., Langowski, J., Toth, K., Matyus, L., Szollosi, J., Waldmann, T. A., and Damjanovich, S. (2004). IL-2 and IL-15 receptor alpha-subunits are coexpressed in a supramolecular receptor cluster in lipid rafts of T cells. *Proc. Natl. Acad. Sci. U.S.A.* 101, 11082–11087.

Waldele, K., Schneider, G., Ruckes, T., and Grassmann, R. (2004). Interleukin-13 overexpression by tax transactivation: a potential autocrine stimulus in human T-cell leukemia virus-infected lymphocytes. *J. Virol.* 78, 6081–6090.

Wang, S. S., Carreon, J. D., Hanchard, B., Chanock, S., and Hisada, M. (2009). Common genetic variants and risk for non-Hodgkin lymphoma and adult T-cell lymphoma/leukemia in Jamaica. *Int. J. Cancer* 125, 1479–1482.

Zhang, Y., Holford, T. R., Leaderer, B., Boyle, P., Zahm, S. H., Flynn, S., Tallini, G., Owens, P. H., and Zheng, T. (2004a). Hair-coloring product use and risk of non-Hodgkin's lymphoma: a population-based case-control study in Connecticut. *Am. J. Epidemiol.* 159, 148–154.

Zhang, Y., Holford, T. R., Leaderer, B., Zahm, S. H., Boyle, P., Morton, L. M., Zhang, B., Zou, K., Flynn, S., Tallini, G., Owens, P. H., and Zheng, T. (2004b). Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control* 15, 419–428.

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APPENDIX

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[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)
IFNG_07 (rsI861494)																		
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)
AGorAA	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)
AGorAA	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)
ATorAA	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 (rsI800925)																		
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			No		Yes		No		Yes		No		Yes	
	Controls	Cases	OR	Controls	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)
CTorTT	170	154	1.0	45	52	1.1 (0.7–1.7)	115	1.0	46	1.3 (0.8–2.1)	48	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 (rsl0833)																		
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)
CT orTT	226	200	1.0	73	56	0.7 (0.5–1.1)	159	1.0	45	0.7 (0.5–1.1)	62	1.0	21	0.8 (0.5–1.5)	50	1.0	12	0.6 (0.3–1.3)
P-interaction	0.51						0.39				0.17				0.16			
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)
GTorGG	213	212	1.0	66	59	0.8 (0.5–1.2)	171	1.0	47	0.8 (0.5–1.2)	57	1.0	14	0.6 (0.3–1.2)	53	1.0	15	0.7 (0.4–1.4)
P-interaction	0.89						0.76				0.85				0.82			
IL4_02 (rs2243248)																		
TT	338	326	1.0	120	85	0.7 (0.5–1.0)	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)
GT or GG	50	58	1.0	20	24	1.0 (0.5–2.1)	43	1.0	16	0.9 (0.4–2.1)	21	1.0	6	0.7 (0.2–2.2)	8	1.0	5	1.8 (0.5–7.4)
P-interaction	0.58						0.94				0.76				0.5			
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)
AC or AA	120	95	1.0	31	28	0.9 (0.5–1.7)	78	1.0	23	1.0 (0.5–1.8)	36	1.0	7	0.5 (0.2–1.4)	23	1.0	9	1.3(0.5–3.3)
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)
AC or CC	119	92	1.0	32	27	0.9 (0.5–1.6)	75	1.0	22	0.9 (0.5–1.7)	35	1.0	7	0.5 (0.2–1.4)	23	1.0	9	1.2 (0.5–3.1)
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)
CT orTT	262	245	1.0	91	69	0.7 (0.5–1.1)	186	1.0	59	0.8 (0.6–1.2)	71	1.0	21	0.7 (0.4–1.2)	53	1.0	19	0.9 (0.5–1.7)
P-interaction	0.35					0.73				0.86				0.6				
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)
CT orTT	223	206	1.0	66	55	0.8 (0.5–1.3)	167	1.0	43	0.8 (0.5–1.3)	74	1.0	15	0.6 (0.3–1.1)	47	1.0	14	0.9 (0.5–1.8)
P-interaction	0.89						0.42				0.3				0.89			

IL6 01 (rs1800795)																	
GG	184	160	1.0	57	51	0.8 (0.5–1.3)	119	1.0	41	0.9 (0.5–1.4)	43	1.0	14	0.7 (0.4–1.5)	41	1.0	10	0.6 (0.3–1.3)
CG or CC	263	235	1.0	86	64	0.8 (0.5–1.1)	191	1.0	55	0.8 (0.5–1.2)	81	1.0	20	0.7 (0.4–1.2)	49	1.0	19	1.1 (0.6–2.1)
P-interaction	0.47						0.48				0.52				0.36			
IL6 04 (rs 1800797)																	
GG	175	161	1.0	58	51	0.8 (0.5–1.3)	118	1.0	41	0.8 (0.5–1.4)	40	1.0	14	0.8 (0.4–1.5)	41	1.0	9	0.5 (0.2–1.2)
AG or AA	257	224	1.0	81	57	0.7 (0.5–1.1)	183	1.0	49	0.8 (0.5–1.1)	83	1.0	17	0.5 (0.3–1.0)	45	1.0	17	1.1 (0.6–2.1)
P-interaction	0.54						0.49				0.31				0.22			
IL7R 01 (rs1494555)																	
AA	186	158	1.0	59	47	0.8 (0.5–1.3)	128	1.0	43	0.9 (0.6–1.5)	50	1.0	17	1.0 (0.5–1.8)	41	1.0	11	0.7 (0.3–1.5)
AG or GG	215	189	1.0	72	58	0.8 (0.5–1.3)	148	1.0	44	0.8 (0.5–1.2)	64	1.0	13	0.5 (0.2–0.9)	38	1.0	14	1.0 (0.5–2.1)
P-interaction	0.87						0.73				0.33				0.58			
JAK3 01 (rs3008)																	
CC	70	69	1.0	25	16	0.6 (0.3–1.2)	51	1.0	14	0.6 (0.3–1.4)	28	1.0	6	0.4 (0.2–1.2)	8	1.0	5	1.4 (0.4–5.3)
CT orTT	334	280	1.0	106	91	0.9 (0.7–1.3)	226	1.0	75	1.0 (0.7–1.4)	87	1.0	25	0.8 (0.4–1.3)	71	1.0	21	0.8 (0.5–1.5)
P-interaction	0.26						0.45				0.5				0.36			
IL10_01 (rs1800871)																	
CC	250	215	1.0	79	59	0.8 (0.5–1.2)	163	1.0	49	0.9 (0.6–1.3)	66	1.0	15	0.6 (0.3–1.2)	39	1.0	14	1.0 (0.5–2.0)
CT+TT	186	167	1.0	59	50	0.8 (0.5–1.2)	137	1.0	42	0.8 (0.5–1.3)	56	1.0	18	0.7 (0.4–1.4)	44	1.0	12	0.7 (0.3–1.4)
P-interaction	0.98						0.63				0.59				0.43			
IL10_02 (rs1800872)																	
CC	250	215	1.0	81	58	0.8 (0.5–1.1)	165	1.0	48	0.8 (0.5–1.2)	67	1.0	15	0.6 (0.3–1.2)	41	1.0	14	0.9 (0.5–1.9)
AC or AA	178	160	1.0	54	49	0.8 (0.5–1.3)	130	1.0	41	0.9 (0.5–1.4)	53	1.0	17	0.7 (0.4–1.4)	43	1.0	11	0.7 (0.3–1.5)
P-interaction	0.68						0.83				0.55				0.48			
IL10_03 (rs1800896)																	
AA	138	102	1.0	46	35	0.9 (0.5–1.5)	77	1.0	26	0.8 (0.4–1.5)	30	1.0	10	0.8 (0.3–1.8)	22	1.0	9	0.8 (0.3–1.9)
AG or GG	308	293	1.0	95	80	0.8 (0.6–1.1)	233	1.0	70	0.9 (0.6–1.3)	96	1.0	24	0.6 (0.4–1.1)	67	1.0	20	0.9 (0.5–1.7)
P-interaction	0.75						0.81				0.74				0.74			
IL10_06 (rs3024496)																	
TT	129	92	1.0	41	33	0.9 (0.5–1.6)	71	1.0	26	0.9 (0.5–1.6)	31	1.0	10	0.8 (0.3–1.7)	20	1.0	8	0.8 (0.3–2.1)
CT or CC	272	258	1.0	87	74	0.8 (0.6–1.2)	206	1.0	63	0.9 (0.6–1.3)	85	1.0	21	0.7 (0.4–1.1)	59	1.0	18	0.9 (0.5–1.7)
P-interaction	0.64						0.79				0.71				0.71			
IL10_07 (rs3024491)																	
GG	132	94	1.0	45	36	0.9 (0.5–1.6)	73	1.0	26	0.8 (0.5–1.5)	31	1.0	10	0.7 (0.3–1.6)	21	1.0	8	0.8 (0.3–2.1)
GT orTT	270	254	1.0	86	71	0.8 (0.6–1.2)	202	1.0	63	0.9 (0.6–1.3)	83	1.0	21	0.7 (0.4–1.2)	58	1.0	18	0.9 (0.5–1.7)

(Continued)

Table A1 | Continued.

SNPs	Overall						B cell lymphoma				DLBCL				Follicular			
	No			Yes			No		Yes		No		Yes		No		Yes	
	Controls	Cases	OR	Controls	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)	Cases	OR	Cases	OR[1] (95% CI)
P-interaction	0.59						0.93				0.86				0.93			
IL10_17 (rs1800890)																		
TT	200	140	1.0	61	48	1.0 (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	68	0.7 (0.5–1.1)	201	1.0	60	0.8 (0.5–1.2)	83	1.0	19	0.6 (0.3–1.0)	59	1.0	19	0.9 (0.5–1.7)
P-interaction	0.33						0.62				0.33				0.97			
TNF_02 (rs1800629)																		
GG	328	278	1.0	102	82	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	33	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	79	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	27	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			

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