Polymorphisms and Haplotypes in the Cytochrome *P*450 17A1, Prolactin, and Catechol-*O*-Methyltransferase Genes and Non-Hodgkin Lymphoma Risk

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Abstract

Expression of prolactin and of prolactin and estrogen receptors in lymphocytes, bone marrow, and lymphoma cell lines suggests that hormonal modulation may influence lymphoma risk. Prolactin and estrogen promote the proliferation and survival of B cells, factors that may increase non-Hodgkin lymphoma risk, and effects of estrogen may be modified by catechol-*O*-methyltransferase (COMT), an enzyme that alters estrogenic activity. Cytochrome *P*450 17A1 (CYP17A1), a key enzyme in estrogen biosynthesis, has been associated with increased cancer risk and may affect lymphoma susceptibility. We studied the polymorphisms prolactin (*PRL*) −1149G>T, *CYP17A1* −34T>C, and *COMT* 108/158Val>Met, and predicted haplotypes among a subset of participants (n = 308 cases, n = 684 controls) in a San Francisco Bay Area population-based non-Hodgkin lymphoma study (n = 1,593 cases, n = 2,515 controls) conducted from 1988 to 1995. Oral contraceptive and other hormone use also was analyzed. Odds ratios (OR) for non-Hodgkin lymphoma and follicular lymphoma were reduced for carriers of the *PRL* −1149TT genotype [OR, 0.64; 95% confidence interval (95% CI), 0.41-1.0; OR, 0.53; 95% CI, 0.26-1.0, respectively]. Diffuse large-cell lymphoma risk was increased for those with *CYP17A1* polymorphisms including *CYP17A1* −34CC (OR, 2.0; 95% CI, 1.1-3.5). ORs for all non-Hodgkin lymphoma and follicular lymphoma among women were decreased for *COMT* IVS1 701A>G [rs737865; variant allele: OR, 0.53; 95% CI, 0.34-0.82; OR, 0.42; 95% CI, 0.23-0.78, respectively]. Compared with never users of oral contraceptives, a 35% reduced risk was observed among oral contraceptive users in the total population. Reduced ORs for all non-Hodgkin lymphoma were observed with use of exogenous estrogens among genotyped women although 95% CIs included unity. These results suggest that *PRL*, *CYP17A1*, and *COMT* may be relevant genetic loci for non-Hodgkin lymphoma and indicate a possible role for prolactin and estrogen in lymphoma pathogenesis. (Cancer Epidemiol Biomarkers Prev 2005;14(10):2391–401)

Introduction

Extensive cross-talk exists between the endocrine and immune systems where hormones and their respective receptors influence immune function and, in turn, immune responses influence neuroendocrine changes (reviewed in ref. 1). Expression of prolactin and of prolactin and estrogen receptors found in normal B and T lymphocytes, bone marrow, and in leukemia and lymphoma cell lines (2, 3) suggests their importance in the lymphopoeitic system and that hormonal modulation may influence risk of lymphopoeitic diseases such as lymphoma. Prolactin and estrogens play important roles in women's reproductive physiology and they also function in both sexes as immune modulators that affect apoptosis, activation, and proliferation of immune cells and modulate B-cell development. Elevated prolactin levels have been implicated in the progression of hematologic diseases such as multiple myeloma, acute myeloid leukemia, and non-Hodgkin lymphoma (4). However, there is less agreement in the literature about the association between exogenous estrogens (using postmenopausal hormones or oral contraceptives as a proxy of estimated exposure) and lymphoma/leukemia risk with reports of positive (5, 6), null (7), and inverse associations (8). Because of the many postmenopausal hormone formulations available, misclassification and differential recall may affect the results. Further, direct measurement of circulating hormones provides data only for a single time point and levels may be affected by genetic variability in pathways involved in their production and metabolism. Thus, investigation of genetic polymorphisms that may influence prolactin and estrogen production will contribute to our knowledge and add to the interpretation of the exposure data.

The prolactin (*PRL*) gene maps to regions linked to rheumatoid arthritis and systemic lupus erythematosus (9), in close proximity to the MHC on chromosome 6p. Multiple promoters and start sites are present in the *PRL* gene. *PRL* gene expression in lymphocytes and other extrapituitary tissues is directed by a promoter region that lies ~6 kb upstream of the pituitary-specific start site of transcription (10). A single-nucleotide polymorphism (SNP) in this region (rs1341239: *PRL* −1149G>T) that regulates lymphocyte prolactin production recently has been identified (11). Stevens et al. reported that the *PRL* −1149G allele was overrepresented in a cohort of systemic lupus erythematosus patients and was associated with enhanced promoter activity and elevated prolactin mRNA levels in T lymphocytes. Cytochrome *P*450 17A1 (*CYP17A1*), which catalyzes the conversion of pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively, is one of the key enzymes

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involved in estrogen and testosterone biosynthesis. A SNP in the 5′-untranslated region of the *CYP17A1* gene, 34 bp upstream of the initiation site of translation (rs743572, −34T>C; ref. 12), has been speculated to enhance *CYP17A1* transcriptional efficiency and enzyme activity. This SNP has been associated with earlier age at menarche, increased risk for breast and prostate cancers (13-16), and elevated serum estrogen levels (reviewed in refs. 17, 18). Furthermore, allelic variation in the catechol-*O*-methyltransferase (*COMT*) gene that expresses an intracellular enzyme involved in estrogen metabolism can alter circulating estrogen concentrations. The *COMT* gene encodes both a soluble protein (S-COMT) expressed in blood, liver, and kidneys and a membrane-bound protein (MB-COMT) expressed in brain neurons (19). A G>A SNP in exon 4 (rs4680) causes a valine to methionine substitution in S-*COMT* (108Val>Met) and MB-*COMT* (158Val>Met) that results in enzyme thermolability and 2- to 4-fold lower catalytic activity (20, 21). Consequently, this polymorphism could alter estrogenic activity in various target tissues.

We hypothesized that SNPs or haplotypes in the *PRL*, *CYP17A1*, and *COMT* genes associated with elevated prolactin and estrogen levels (i.e., *PRL* −1149G, *CYP17A1* −34C, and *COMT* 108/158Met alleles) promote B- and T-cell activation, survival, and proliferation, factors that may contribute to the pathogenesis of non-Hodgkin lymphoma. To test this, we evaluated these and other *PRL*, *CYP17A1*, and *COMT* SNPs and haplotypes in a population-based case-control study conducted in the San Francisco Bay Area between 1988 and 1995.

Materials and Methods

Study Population. Briefly, non-Hodgkin lymphoma patients were identified by the Northern California Cancer Center rapid case ascertainment. Eligible patients were between 21 and 74 years of age, were residents of one of the six Bay Area counties at the time of diagnosis, and could complete an interview in English. A total of 1,593 eligible patients (284 HIV positive) completed in-person interviews (72% response rate). Control participants were identified by random-digit dial and by random sampling of the Health Care Financing Administration lists to supplement recruitment of participants aged ≥65 years. Controls were frequency matched to patients by age within 5 years, sex, and county of residence. No proxy interviews were conducted. There were 2,515 (78% response rate) eligible control participants (111 HIV positive) who completed in-person interviews. The study population reported their race/ethnicity as white Hispanic (6%), white non-Hispanic (84%), Black (4%), Asian (5%), and other (1%). Race/ethnicity distribution was similar for case and control participants. Detailed methods have been published previously (22-24).

Patients and control participants who had no history of chemotherapy within the past 3 months and no contraindications to venipuncture were asked to provide a blood specimen for the laboratory portion of the study. Almost all study patients (97%) had their pathology reports and diagnostic materials rereviewed by an expert pathologist and these were classified using the Working Formulation (Non-Hodgkin's Lymphoma Classification Project). To better reflect the Revised European American Lymphoma Classification and WHO Classification systems, Working Formulation diffuse large-cell and immunoblastic lymphoma were combined for the diffuse large-cell lymphoma subtype and Working Formulation follicular small, mixed, and large-cell lymphomas were combined for the follicular lymphoma subtype (25, 26) in these analyses. Study protocols were approved by the University of California San Francisco Committee on Human Research and participants provided written informed consent before interview and collection of blood specimens.

Isolation of DNA. DNA was isolated from peripheral blood mononuclear cells using a modified QIAamp DNA Blood Maxi Kit protocol (Qiagen, Inc., Santa Clarita, CA), and DNA was quantified using PicoGreen dsDNA Quantitation kits (Molecular Probes, Eugene, OR) according to the specifications of the manufacturers.

SNP Selection. *PRL, CYP17A1*, and *COMT* SNPs are listed in Table 1 and were identified using SNP (http://www.ncbi.nlm.nih.gov/SNP/) and SNPper (http://snpper.chip.org/). In addition, all available Applied Biosystems TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA) were identified (http://www.appliedbiosystems.com). SNPs were chosen for investigation based on a minor allele frequency of ≥5% and location, with a preference given to coding and untranslated region SNPs. Where no suitable exonic SNPs were found, intronic SNPs were chosen to ensure adequate gene coverage.

Genotyping. DNA was available and genotyping was done on 376 case and 801 control participants using the 5′ nuclease allelic discrimination assay on the ABI Prism 7700 Sequence Detection System or GeneAmp PCR System 9700. TaqMan SNP genotyping products and custom SNP genotyping assays were used. Reactions were done with the following protocol: 95°C for 10 minutes, then 40 cycles of 95°C for 15 seconds, and 60°C for 1 minute. A post-PCR plate read on the 7700 Sequence Detection System was used to determine genotype. Probes and primer sets used for the *PRL, CYP17A1*, and *COMT* SNPs are listed in Supplementary Table 1. Replicate, blinded quality control samples were included to assess reproducibility of the genotyping procedure.

Statistical Analysis. Because of differences in SNP and haplotype frequencies across self-identified race and Hispanic ethnicity categories, we restricted all analyses to only those HIV-negative individuals who reported their race/ethnicity as white non-Hispanic (cases, $n = 308$; controls, $n = 684$). All regression analyses were conducted using SAS statistical software (SAS version 8, SAS Institute, Cary, NC). Unconditional logistic regression models were used to compute odds ratios (OR), expressed in the text as ''risk'' for non-Hodgkin lymphoma, and corresponding 95% confidence intervals (95% CI) adjusted for age in 5-year groups and sex. All SNP-specific analyses used the homozygous wild-type category as the reference group.

Linkage disequilibrium was computed for each pair of polymorphisms and linkage disequilibrium plots were generated using Haploview (27). Haplotype frequencies were estimated from phase-unknown genotypes using the tagSNPs implementation of the estimation-maximization algorithm (28). ORs and 95% CIs were estimated for haplotype associations with non-Hodgkin lymphoma by unconditional logistic regression using the single imputation approach of Zaykin et al. (29). Haplotypes with estimated frequencies <5% were considered to be low frequency and were pooled into a single category labeled ''Other''. The global test for association between common haplotypes and non-Hodgkin lymphoma was evaluated using a likelihood ratio test.

Associations between non-Hodgkin lymphoma and hormone-related factors including oral contraceptive use, menopausal status, and non-oral-contraceptive hormone use were evaluated among all HIV-negative, white non-Hispanic women ($n = 451$ patients, $n = 678$ controls) and for the subset of women for whom DNA had been genotyped for these analyses ($n = 134$ cases, $n = 220$ controls). Oral contraceptive use was analyzed by ever/never use and by duration of use (≤5 and >5 years). Women were classified as postmenopausal if they met any of the following conditions: age 55 years or older, had prior hysterectomy or oophorectomy, or reported

Table 1. ORs and 95% CIs for all non-Hodgkin lymphoma, diffuse large-cell lymphoma, and follicular lymphoma associated with SNPs in *PRL*, *CYP17A1*, and *COMT* genes among HIV-negative white non-Hispanics, San Francisco Bay Area, 1988-1995

	SNP database identifier	Genotype	Controls (N = 684)	All non-Hodgkin lymphomas (N = 308)		Diffuse large-cell lymphoma (N = 98)		Follicular lymphoma (N = 112)	
			n (%)*	n (%)*	OR (95% CI)†	n (%)*	OR (95% CI)†	n (%)*	OR (95% CI)†
PRL									
SNP1	rs1341239	−1149GG	253 (37)	138 (45)	1.0 (reference)	38 (39)	1.0 (reference)	51 (46)	1.0 (reference)
		−1149GT	326 (48)	130 (43)	0.73 (0.54-0.98)	46 (47)	0.95 (0.59-1.5)	48 (43)	0.69 (0.45-1.1)
		−1149TT	102 (15)	37 (12)	0.64 (0.41-1.0)	14 (14)	0.91 (0.47-1.8)	12 (11)	0.53 (0.26-1.0)
SNP2	rs849877	−1488AA	267 (39)	133 (43)	1.0 (reference)	42 (43)	1.0 (reference)	51 (46)	1.0 (reference)
		−1488AG	319 (47)	140 (45)	0.88 (0.65-1.2)	44 (45)	0.88 (0.56-1.4)	50 (45)	0.78 (0.51-1.2)
		−1488GG	98 (14)	35 (11)	0.70 (0.45-1.1)	12 (12)	0.77 (0.39-1.5)	11 (10)	0.55 (0.27-1.1)
SNP3	rs7739889	214CC	401 (59)	187 (61)	1.0 (reference)	63 (64)	1.0 (reference)	65 (58)	1.0 (reference)
		214CT	242 (36)	109 (36)	0.91 (0.68-1.2)	31 (32)	0.78 (0.49-1.2)	43 (38)	1.0 (0.65-1.5)
		214TT	36 (5)	11 (4)	0.63 (0.31-1.3)	4 (4)	0.66 (0.23-1.9)	4 (4)	0.65 (0.22-1.9)
SNP4	rs6239	570GG	652 (95)	300 (97)	1.0 (reference)	97 (99)	1.0 (reference)	110 (98)	1.0 (reference)
		570GA/AA	32 (5)	8 (3)	0.51 (0.23-1.2)	1 (1)	0.20 (0.03-1.5)	2 (2)	0.34 (0.08-1.5)
CYP17A1									
SNP1	rs743572	−34TT	249 (36)	113 (37)	1.0 (reference)	35 (36)	1.0 (reference)	45 (40)	1.0 (reference)
		−34TC	341 (50)	137 (44)	0.88 (0.65-1.2)	39 (40)	0.83 (0.51-1.4)	51 (46)	0.83 (0.53-1.3)
		−34CC	94 (14)	58 (19)	1.4 (0.95-2.1)	24 (24)	2.0 (1.1-3.5)	16 (14)	1.0 (0.55-2.0)
SNP2	rs6162	137GG	237 (35)	99 (32)	1.0 (reference)	32 (33)	1.0 (reference)	39 (35)	1.0 (reference)
		137GA	339 (50)	149 (48)	1.1 (0.78-1.4)	42 (43)	0.94 (0.57-1.5)	55 (49)	0.98 (0.62-1.5)
		137AA	106 (16)	60 (19)	1.4 (0.95-2.1)	24 (24)	1.8 (1.0-3.3)	18 (16)	1.1 (0.61-2.1)
SNP3	rs6163	195CC	244 (36)	114 (37)	1.0 (reference)	35 (36)	1.0 (reference)	45 (40)	1.0 (reference)
		195CA	343 (50)	132 (43)	0.83 (0.61-1.1)	37 (38)	0.77 (0.47-1.3)	49 (44)	0.79 (0.50-1.2)
		195AA	95 (14)	62 (20)	1.5 (0.99-2.2)	26 (27)	2.1 (1.2-3.6)	18 (16)	1.1 (0.62-2.1)
SNP4	rs3781287	−270AA	226 (33)	96 (31)	1.0 (reference)	32 (33)	1.0 (reference)	39 (35)	1.0 (reference)
		−270AC	353 (52)	149 (48)	0.99 (0.73-1.4)	43 (44)	0.87 (0.53-1.4)	53 (47)	0.85 (0.54-1.3)
		−270CC	105 (15)	63 (20)	1.5 (0.99-2.2)	23 (23)	1.7 (0.92-3.0)	20 (18)	1.2 (0.68-2.3)
SNP5	rs743575	105AA	338 (50)	149 (49)	1.0 (reference)	46 (47)	1.0 (reference)	57 (51)	1.0 (reference)
		105AC	287 (42)	124 (40)	1.0 (0.76-1.4)	38 (39)	1.0 (0.65-1.6)	45 (40)	1.0 (0.65-1.5)
		105CC	52 (8)	34 (11)	1.5 (0.93-2.5)	14 (14)	2.1 (1.1-4.2)	10 (9)	1.2 (0.56-2.5)
SNP6	rs1004467	35TT	556 (81)	247 (80)	1.0 (reference)	78 (80)	1.0 (reference)	94 (84)	1.0 (reference)
		35TC	119 (17)	56 (18)	1.1 (0.76-1.6)	19 (19)	1.2 (0.67-2.0)	17 (15)	0.88 (0.50-1.6)
		35CC	8 (1)	4 (1)	0.86 (0.25-3.0)	1 (1)	0.72 (0.09-6.0)	1 (1)	0.55 (0.07-4.6)
SNP7	rs3740397	75CC	253 (37)	107 (35)	1.0 (reference)	34 (35)	1.0 (reference)	46 (41)	1.0 (reference)
		75CG	343 (50)	142 (46)	0.97 (0.71-1.3)	38 (39)	0.83 (0.51-1.4)	50 (45)	0.80 (0.51-1.2)
		75GG	88 (13)	59 (19)	1.6 (1.1-2.5)	26 (27)	2.3 (1.3-4.1)	16 (14)	1.1 (0.58-2.1)
SNP8	rs10883783	114AA	310 (45)	147 (48)	1.0 (reference)	46 (47)	1.0 (reference)	57 (51)	1.0 (reference)
		114AT	284 (42)	124 (40)	0.96 (0.71-1.3)	38 (39)	0.95 (0.60-1.5)	44 (39)	0.91 (0.59-1.4)
		114TT	89 (13)	37 (12)	0.97 (0.62-1.5)	14 (14)	1.3 (0.65-2.4)	11 (10)	0.75 (0.37-1.5)
SNP9	rs4919685	2930GG	340 (50)	148 (48)	1.0 (reference)	45 (46)	1.0 (reference)	57 (51)	1.0 (reference)
		2930GT	285 (42)	124 (40)	1.1 (0.77-1.4)	38 (39)	1.0 (0.66-1.7)	45 (40)	1.0 (0.66-1.6)
		2930TT	58 (8)	35 (11)	1.5 (0.90-2.4)	15 (15)	2.2 (1.1-4.3)	10 (9)	1.1 (0.53-2.4)
COMT									
SNP1	rs737865	701AA	309 (45)	157 (51)	1.0 (reference)	50 (51)	1.0 (reference)	60 (54)	1.0 (reference)
		701AG	300 (44)	126 (41)	0.85 (0.63-1.1)	42 (43)	0.87 (0.56-1.4)	47 (42)	0.85 (0.56-1.3)
		701GG	73 (11)	22 (7)	0.60 (0.36-1.0)	6 (6)	0.51 (0.21-1.2)	5 (4)	0.37 (0.14-0.97)
		701AG/GG	373 (55)	148 (49)	0.80 (0.61-1.1)	48 (49)	0.80 (0.52-1.2)	52 (46)	0.78 (0.50-1.1)
SNP2	rs4633	186CC	194 (29)	80 (26)	1.0 (reference)	24 (25)	1.0 (reference)	30 (27)	1.0 (reference)
		186CT	314 (46)	144 (47)	1.1 (0.78-1.5)	48 (50)	1.2 (0.72-2.1)	52 (47)	1.0 (0.64-1.7)
		186TT	169 (25)	80 (26)	1.1 (0.78-1.7)	25 (26)	1.2 (0.66-2.2)	29 (26)	1.1 (0.63-1.9)
		186CT/TT	483 (71)	224 (74)	1.1 (0.81-1.5)	75 (75)	1.2 (0.74-2.0)	81 (73)	1.1 (0.67-1.7)
SNP3	rs4680	108/158 VV	193 (28)	75 (25)	1.0 (reference)	23 (24)	1.0 (reference)	26 (23)	1.0 (reference)
		108/158 VM	323 (48)	153 (50)	1.2 (0.86-1.7)	48 (50)	1.2 (0.72-2.1)	59 (53)	1.3 (0.79-2.2)
		108/158 MM	163 (24)	77 (25)	1.2 (0.80-1.8)	25 (26)	1.3 (0.70-2.4)	27 (24)	1.2 (0.66-2.1)
		108/158 VM/MM	486 (72)	230 (75)	1.2 (0.87-1.7)	73 (76)	1.3 (0.76-2.1)	86 (77)	1.3 (0.79-2.1)
SNP4	rs165599	6731AA	318 (47)	152 (50)	1.0 (reference)	52 (54)	1.0 (reference)	59 (53)	1.0 (reference)
		6731AG	285 (42)	124 (40)	0.91 (0.68-1.2)	38 (39)	0.82 (0.52-1.3)	44 (39)	0.82 (0.54-1.3)
		6731GG	78 (11)	31 (10)	0.87 (0.55-1.4)	7 (7)	0.57 (0.25-1.3)	9 (8)	0.64 (0.30-1.4)
		6731AG/GG	363 (53)	155 (50)	0.90 (0.68-1.2)	45 (46)	0.77 (0.50-1.2)	53 (47)	0.78 (0.52-1.2)

*Numbers may not add to 308 cases and 684 controls due to missing genotypes.
†ORs and 95% CIs computed using unconditional logistic regression, adjusted for age and sex.

non-oral-contraceptive hormone use before age 55. Non-oral-contraceptive hormone use among postmenopausal women also was analyzed by ever/never use and by duration of use (≤5 and >5 years). Never users composed the reference category for all analyses of oral contraceptives and non-oral-contraceptive hormones. χ^2 tests for linear trend in duration of use were conducted using the β coefficients computed from adjusted logistic regression models that included duration coded as an ordinal categorical variable.

Interactions between haplotypes and sex and body mass index (ordinal categories; <25, 25 to <30, ≥30) were evaluated for men and women combined. Gene-environment interaction terms were created by multiplying each environmental factor by each predicted haplotype as a continuous variable. Body mass index-haplotype interaction terms were generated by multiplying the ordinal body mass index category by each predicted haplotype. The Wald test was used to evaluate each haplotype interaction term. All models for women and men

combined were adjusted for age and sex, whereas all analyses among women were adjusted for age alone. Results were considered statistically significant for two-sided $P \leq 0.05$ and borderline significant for $0.05 < P \leq 0.10$.

Results

***PRL*, *CYP17A1*, and *COMT* Genotypes and Non-Hodgkin Lymphoma Risk.** Figure 1 illustrates the scaled locations of the *PRL*, *CYP17A1*, and *COMT* SNPs genotyped. Control genotype distributions of all SNPs were in Hardy-Weinberg equilibrium. For *PRL*, inverse associations with non-Hodgkin lymphoma were observed for SNP1 (heterozygotes: OR, 0.73; 95% CI, 0.54-0.98; homozygous variants: OR, 0.64; 95% CI, 0.41-1.0) and SNP2 (heterozygotes: OR, 0.88; 95% CI, 0.65-1.2; homozygous variants: OR, 0.70; 95% CI, 0.45-1.1; Table 1). ORs showed inverse associations with follicular lymphoma for SNP1 (heterozygotes: OR, 0.69; 95% CI, 0.45-1.1; homozygous variants: OR, 0.53; 95% CI, 0.26-1.0) and SNP2 (heterozygotes: OR, 0.78; 95% CI, 0.51-1.2; homozygous variants: OR, 0.55; 95% CI, 0.27-1.1). There was no evidence of interaction between *PRL* SNPs and sex (Tables 2 and 3).

For *CYP17A1*, an increased non-Hodgkin lymphoma risk was observed among homozygous variant carriers of SNP3 (OR, 1.5; 95% CI, 0.99-2.2), SNP4 (OR, 1.5; 95% CI, 0.99-2.2), and SNP7 (OR, 1.6; 95% CI, 1.1-2.5; Table 1). Increased ORs for diffuse large-cell lymphoma were observed among homozygous variant allele carriers of SNP1 (OR, 2.0; 95% CI, 1.1-3.5), SNP2 (OR, 1.8; 95% CI, 1.0-3.3), SNP3 (OR, 2.1; 95% CI, 1.2-3.6), SNP5 (OR, 2.1; 95% CI, 1.1-4.2), SNP7 (OR, 2.3; 95% CI, 1.3-4.1), and SNP9 (OR, 2.2; 95% CI, 1.1-4.3). Diffuse large-cell lymphoma was increased among women who were carriers of the homozygous variant alleles for SNP1 (OR, 2.4; 95% CI, 1.0-5.7), SNP3 (OR, 2.4; 95% CI, 1.0-5.8), and SNP7 (OR, 2.5; 95% CI, 1.0-5.9; Table 3). Further, diffuse large-cell lymphoma risk was elevated among men who were homozygous variant allele carriers for SNP7 (OR, 2.3; 95% CI, 1.0-4.9). Although 95% CIs overlapped unity, in men SNP3 (OR, 1.9; 95% CI, 0.88-4.1), SNP5 (OR, 2.3; 95% CI, 0.94-5.8), and SNP9 (OR, 2.3; 95% CI, 0.94-5.7) followed the same trend of increased ORs observed for all non-Hodgkin lymphoma.

For *COMT*, SNP1 was inversely associated with non-Hodgkin lymphoma (heterozygotes: OR, 0.85; 95% CI, 0.63-1.1; homozygous variants: OR, 0.60; 95% CI, 0.36-1.0) and with follicular lymphoma (heterozygotes: OR, 0.85; 95% CI, 0.56-1.3; homozygous variants: OR, 0.37; 95% CI, 0.14-0.97; Table 1). In women, SNP1 was inversely associated with non-Hodgkin lymphoma (heterozygotes: OR, 0.57; 95% CI, 0.36-0.91; homozygous variants: OR, 0.36; 95% CI, 0.15-0.89; Table 2) and follicular lymphoma (heterozygotes: OR, 0.50; 95% CI, 0.26-0.94; Table 3), but not in men. Furthermore, increased risk estimates for non-Hodgkin lymphoma and follicular lymphoma approached statistical significance among women who were homozygous variant carriers for SNP3 (OR, 1.6; 95% CI, 0.86-3.1; OR, 2.0; 95% CI, 0.84-4.9, respectively).

***PRL*, *CYP17A1*, and *COMT* Haplotypes and Non-Hodgkin Lymphoma Risk.** Common haplotypes for *PRL*, *CYP17A1*, and *COMT* are listed in Table 4. Linkage disequilibrium measures between SNPs for each gene studied are presented in Fig. 2. *PRL* haplotypes were estimated excluding SNP4 due to its low allele frequency (2.4%) and because all major haplotypes contained only the wild-type allele, rendering SNP4 uninformative to the haplotype analysis. Using *PRL* SNP1 to SNP3, four common haplotypes were predicted. Using the highest-frequency haplotype HapA (all wild-type alleles) as the reference group, HapB-D were inversely associated with non-Hodgkin lymphoma, although the global test for association was not statistically significant ($P = 0.12$). Notably, 59% of non-Hodgkin lymphoma cases were predicted to carry HapA compared with 55% of controls. HapA was associated with non-Hodgkin lymphoma (OR, 1.2; 95% CI, 1.0-1.5) when compared with all other haplotypes.

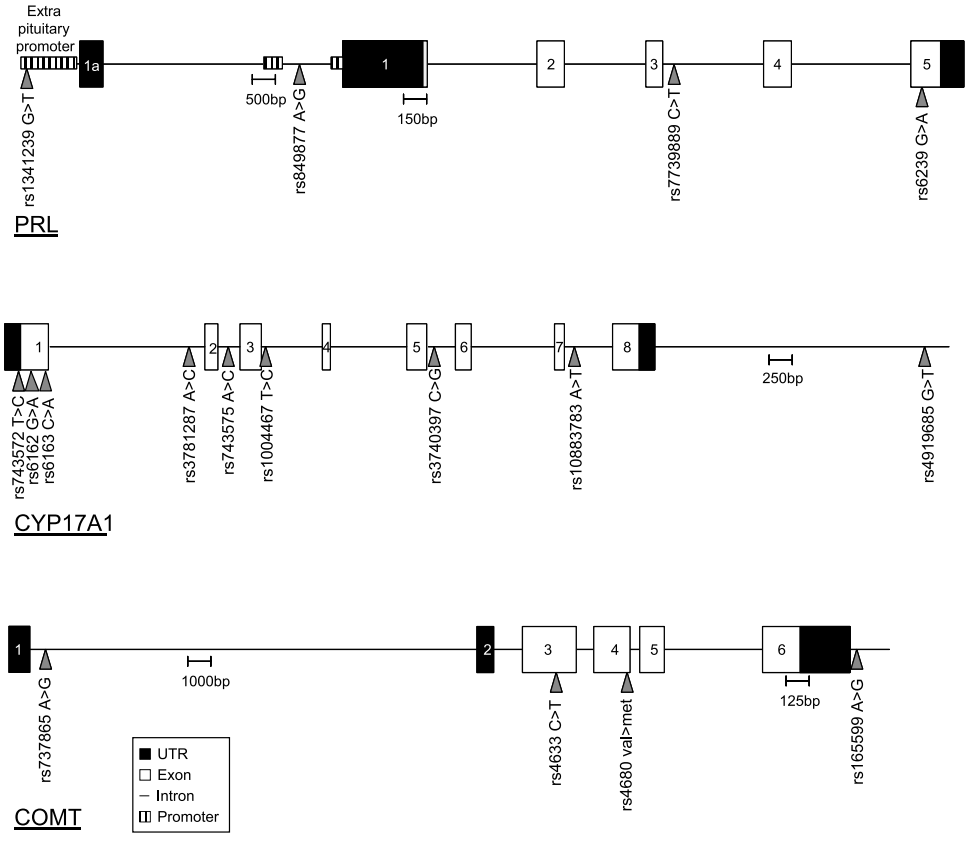

Figure 1. A diagrammatic representation of the SNPs investigated in the *PRL, CYP17A1*, and *COMT* genes.

Table 2. ORs and 95% CIs for all non-Hodgkin lymphoma associated with SNPs in *PRL*, *CYP17A1*, and *COMT* genes among San Francisco Bay Area HIV-negative white non-Hispanics, stratified by sex

SNP	Genotype	Controls		All non-Hodgkin lymphoma			
		Men (N = 463)	Women (N = 221)	Men (N = 174)		Women (N = 134)	
		n (%)*	n (%)*	n (%)*	OR (95% CI)†	n (%)*	OR (95% CI)†
PRL							
SNP1	−1149GG	176 (38)	77 (35)	74 (43)	1.0	64 (49)	1.0
	−1149GT	216 (47)	110 (50)	82 (47)	0.93 (0.63-1.4)	48 (37)	0.51 (0.32-0.83)
	−1149TT	69 (15)	33 (15)	18 (10)	0.66 (0.36-1.2)	19 (15)	0.63 (0.32-1.2)
SNP2	−1488AA	179 (39)	88 (40)	76 (44)	1.0	57 (43)	1.0
	−1488AG	217 (47)	102 (46)	82 (47)	0.95 (0.65-1.4)	58 (43)	0.84 (0.52-1.3)
	−1488GG	67 (14)	31 (14)	16 (9)	0.62 (0.33-1.2)	19 (14)	0.86 (0.44-1.7)
SNP3	214CC	279 (61)	122 (55)	109 (63)	1.0	78 (58)	1.0
	214CT	155 (34)	87 (40)	59 (34)	1.0 (0.70-1.5)	50 (37)	0.81 (0.51-1.3)
	214TT	25 (5)	11 (5)	5 (3)	0.51 (0.19-1.4)	6 (4)	0.80 (0.28-2.3)
SNP4	570GG	443 (96)	209 (95)	172 (99)	1.0	128 (96)	1.0
	570GA/AA	20 (4)	12 (5)	2 (1)	0.27 (0.06-1.2)	6 (4)	0.80 (0.29-2.2)
CYP17							
SNP1	−34TT	167 (36)	82 (37)	64 (37)	1.0	49 (37)	1.0
	−34TC	228 (49)	113 (51)	78 (45)	0.90 (0.60-1.3)	59 (44)	0.86 (0.54-1.4)
	−34CC	68 (15)	26 (12)	32 (18)	1.3 (0.76-2.2)	26 (19)	1.7 (0.87-3.2)
SNP2	137GG	157 (34)	80 (36)	58 (33)	1.0	41 (31)	1.0
	137GA	229 (50)	110 (50)	84 (48)	0.99 (0.66-1.5)	65 (49)	1.2 (0.71-1.9)
	137AA	76 (16)	30 (14)	32 (18)	1.2 (0.71-2.1)	28 (21)	1.8 (0.94-3.4)
SNP3	195CC	161 (35)	83 (38)	65 (37)	1.0	49 (37)	1.0
	195CA	231 (50)	112 (51)	75 (43)	0.81 (0.54-1.2)	57 (43)	0.85 (0.53-1.4)
	195AA	69 (15)	26 (12)	34 (20)	1.3 (0.76-2.2)	28 (21)	1.8 (0.96-3.5)
SNP4	−270AA	150 (32)	76 (34)	52 (30)	1.0	44 (33)	1.0
	−270AC	234 (51)	119 (54)	88 (51)	1.1 (0.71-1.6)	61 (46)	0.87 (0.53-1.4)
	−270CC	79 (17)	26 (12)	34 (20)	1.3 (0.75-2.2)	29 (22)	1.9 (0.99-3.6)
SNP5	105AA	225 (49)	113 (52)	79 (46)	1.0	70 (52)	1.0
	105AC	198 (43)	89 (41)	74 (43)	1.1 (0.75-1.6)	50 (37)	0.93 (0.58-1.5)
	105CC	36 (8)	16 (7)	20 (12)	1.6 (0.83-2.9)	14 (10)	1.4 (0.64-3.1)
SNP6	35TT	373 (81)	183 (83)	145 (84)	1.0	102 (76)	1.0
	35TC	85 (18)	34 (15)	27 (16)	0.85 (0.52-1.4)	29 (22)	1.5 (0.87-2.7)
	35CC	5 (1)	3 (1)	1 (0.6)	0.50 (0.06-4.5)	3 (2)	1.5 (0.29-7.6)
SNP7	75CC	171 (37)	82 (37)	59 (34)	1.0	48 (36)	1.0
	75CG	229 (49)	114 (52)	82 (47)	1.0 (0.67-1.5)	60 (45)	0.89 (0.55-1.4)
	75GG	63 (14)	25 (11)	33 (19)	1.5 (0.90-2.7)	26 (19)	1.8 (0.92-3.4)
SNP8	114AA	212 (46)	98 (44)	78 (45)	1.0	69 (51)	1.0
	114AT	189 (41)	95 (43)	75 (43)	1.1 (0.75-1.6)	49 (37)	0.76 (0.48-1.2)
	114TT	61 (13)	28 (13)	21 (12)	1.1 (0.60-1.9)	16 (12)	0.85 (0.42-1.7)
SNP9	2930GG	228 (49)	112 (51)	80 (46)	1.0	68 (51)	1.0
	2930GT	193 (42)	92 (42)	74 (43)	1.1 (0.76-1.6)	50 (37)	0.91 (0.57-1.4)
	2930TT	41 (9)	17 (8)	19 (11)	1.4 (0.77-2.7)	16 (12)	1.5 (0.71-3.2)
COMT							
SNP1	701AA	208 (45)	101 (46)	75 (44)	1.0	82 (62)	1.0
	701AG	204 (43)	96 (43)	82 (48)	1.1 (0.74-1.6)	44 (33)	0.57 (0.36-0.91)
	701GG	49 (11)	24 (11)	15 (9)	0.78 (0.40-1.5)	7 (5)	0.36 (0.15-0.89)
	701AG/GG	253 (55)	120 (54)	97 (56)	1.0 (0.71-1.5)	51 (38)	0.53 (0.34-0.82)
SNP2	186CC	140 (30)	54 (25)	53 (30)	1.0	27 (21)	1.0
	186CT	205 (45)	109 (50)	78 (45)	1.1 (0.69-1.6)	66 (51)	1.3 (0.74-2.3)
	186TT	115 (25)	54 (25)	43 (25)	1.0 (0.62-1.7)	37 (28)	1.5 (0.80-2.9)
	186CT/TT	320 (70)	163 (75)	121 (70)	1.0 (0.70-1.5)	103 (79)	1.4 (0.80-2.3)
SNP3	108/158 VV	139 (30)	54 (25)	49 (28)	1.0	26 (20)	1.0
	108/158 VM	208 (45)	115 (52)	84 (49)	1.2 (0.79-1.9)	69 (52)	1.3 (0.75-2.3)
	108/158 MM	112 (24)	51 (23)	40 (23)	1.0 (0.61-1.7)	37 (28)	1.6 (0.86-3.1)
	108/158 VM/MM	320 (70)	166 (75)	124 (72)	1.1 (0.76-1.7)	106 (80)	1.4 (0.83-2.4)
SNP4	6731AA	214 (47)	104 (47)	85 (49)	1.0	67 (50)	1.0
	6731AG	194 (42)	91 (41)	69 (40)	0.90 (0.61-1.3)	55 (41)	0.91 (0.57-1.4)
	6731GG	52 (11)	26 (12)	19 (11)	0.98 (0.53-1.8)	12 (9)	0.71 (0.33-1.5)
	6731AG/GG	246 (53)	117 (53)	88 (51)	0.91 (0.63-1.3)	67 (50)	0.87 (0.56-1.3)

*Numbers may not add to 308 cases and 684 controls due to missing genotypes.
†ORs and 95% CIs calculated using unconditional logistic regression, adjusted for age.

According to the additive model for the single imputation approach to modeling HapA, those predicted to carry one copy had an OR for non-Hodgkin lymphoma of 1.2, whereas those predicted to carry two copies had an OR of 1.5. Similar results were observed for follicular lymphoma with ORs of 1.5 and 2.4 for those predicted to carry one or two copies, respectively. There was no evidence of sex-specific associations with any of the *PRL* haplotypes (Supplementary Table 2).

Strong pairwise linkage disequilibrium was observed among all *CYP17A1* SNPs (Fig. 2) that resulted in three common haplotypes (Table 4). The estimated haplotype structure and the low haplotype diversity across *CYP17A1* were comparable to what has been reported for Caucasian populations (28, 30). A global test for association between these common *CYP17A1* haplotypes and non-Hodgkin lymphoma was not statistically significant (P = 0.34). HapB (composed of variant alleles for all SNPs except SNP6) was found in 32% of diffuse large-cell lymphoma cases and 24% of controls. The global test confirmed an association between *CYP17A1* haplotypes and diffuse large-cell lymphoma (P = 0.002). Using

HapA (all wild-type alleles) as the reference group and assuming an additive model, one copy of HapB conferred a 1.5-fold increased risk for diffuse large-cell lymphoma, whereas two copies conferred a 2.1-fold increased risk. Further, among women, 11% of non-Hodgkin lymphoma patients were predicted to carry HapC compared with 7% of controls, whereas among men, 7% of patients and 8% of controls carried HapC (Supplementary Table 2). However, the global test for association was not significant among women ($P = 0.12$) or among men ($P = 0.66$).

For *COMT*, six haplotypes were predicted with ≥5% frequency. We found an inverse association between HapC (composed of variant alleles at SNP1 and SNP4) and all non-Hodgkin lymphoma and diffuse large-cell lymphoma present in 14% of controls, 11% of all non-Hodgkin lymphoma, and 9% of diffuse large-cell lymphoma cases (Table 4). These

Table 3. ORs and 95% CIs for diffuse large-cell lymphoma and follicular lymphoma associated with SNPs in *PRL*, *CYP17A1*, and *COMT* genes among San Francisco Bay Area HIV-negative white non-Hispanics, stratified by sex

	Genotype	Controls		Diffuse large-cell lymphoma				Follicular lymphoma			
		Men ($N = 463$)	Women ($N = 221$)	Men ($N = 57$)		Women ($N = 41$)		Men ($N = 55$)		Women ($N = 57$)	
		n (%)*	n (%)*	n (%)*	OR (95% CI)†	n (%)*	OR (95% CI)†	n (%)*	OR (95% CI)†	n (%)*	OR (95% CI)†
PRL											
SNP1	−1149GG	176 (38)	77 (35)	20 (35)	1.0	18 (44)	1.0	29 (53)	1.0	22 (39)	1.0
	−1149GT	216 (47)	110 (50)	29 (51)	1.3 (0.69-2.4)	17 (41)	0.65 (0.31-1.3)	22 (40)	0.62 (0.34-1.1)	26 (46)	0.82 (0.43-1.6)
	−1149TT	69 (15)	33 (15)	8 (14)	1.1 (0.47-2.7)	6 (15)	0.73 (0.26-2.0)	4 (7)	0.39 (0.13-1.2)	8 (14)	0.73 (0.29-1.8)
SNP2	−1488AA	179 (39)	88 (40)	24 (42)	1.0	18 (44)	1.0	30 (55)	1.0	21 (37)	1.0
	−1488AG	217 (47)	102 (46)	27 (47)	1.0 (0.56-1.9)	17 (41)	0.77 (0.37-1.6)	22 (40)	0.63 (0.35-1.1)	28 (49)	1.1 (0.57-2.1)
	−1488GG	67 (14)	31 (14)	6 (11)	0.76 (0.29-2.0)	6 (15)	0.87 (0.31-2.4)	3 (5)	0.30 (0.09-1.0)	8 (14)	0.98 (0.39-2.5)
SNP3	214CC	279 (61)	122 (55)	38 (67)	1.0	25 (61)	1.0	35 (64)	1.0	30 (53)	1.0
	214CT	155 (34)	87 (40)	17 (30)	0.89 (0.48-1.6)	14 (34)	0.72 (0.35-1.5)	18 (33)	0.99 (0.54-1.8)	25 (44)	1.1 (0.58-2.0)
	214TT	25 (5)	11 (5)	2 (4)	0.56 (0.13-2.5)	2 (5)	0.83 (0.17-4.0)	2 (4)	0.65 (0.15-2.9)	2 (4)	0.67 (0.14-3.2)
SNP4	570GG	443 (96)	209 (95)	57 (100)	1.0	40 (98)	1.0	55 (100)	1.0	55 (96)	1.0
	570GA/AA	20 (4)	12 (5)	0 (0)	—	1 (2)	0.42 (0.05-3.3)	0 (0)	—	2 (4)	0.63 (0.14-2.9)
CYP17											
SNP1	−34TT	167 (36)	82 (37)	19 (33)	1.0	16 (39)	1.0	24 (44)	1.0	21 (37)	1.0
	−34TC	228 (49)	113 (51)	26 (46)	1.0 (0.56-2.0)	13 (32)	0.59 (0.27-1.3)	24 (45)	0.76 (0.41-1.4)	27 (47)	0.93 (0.49-1.8)
	−34CC	68 (15)	26 (12)	12 (21)	1.7 (0.78-3.8)	12 (29)	2.4 (1.0-5.7)	7 (13)	0.82 (0.33-2.0)	9 (16)	1.4 (0.56-3.4)
SNP2	137GG	157 (34)	80 (36)	16 (28)	1.0	16 (39)	1.0	21 (38)	1.0	18 (32)	1.0
	137GA	229 (50)	110 (50)	29 (51)	1.3 (0.66-2.4)	13 (32)	0.60 (0.27-1.3)	25 (46)	0.82 (0.44-1.5)	30 (53)	1.2 (0.62-2.3)
	137AA	76 (16)	30 (14)	12 (21)	1.7 (0.77-3.9)	12 (29)	2.0 (0.85-4.8)	9 (16)	0.99 (0.43-2.3)	9 (16)	1.3 (0.54-3.3)
SNP3	195CC	161 (35)	83 (38)	19 (33)	1.0	16 (39)	1.0	24 (44)	1.0	21 (37)	1.0
	195CA	231 (50)	112 (51)	24 (42)	0.92 (0.49-1.8)	13 (32)	0.60 (0.27-1.3)	24 (44)	0.73 (0.40-1.3)	25 (44)	0.87 (0.45-1.7)
	195AA	69 (15)	26 (12)	14 (25)	1.9 (0.88-4.1)	12 (29)	2.4 (1.0-5.8)	7 (13)	0.78 (0.32-1.9)	11 (19)	1.7 (0.71-4.0)
SNP4	−270AA	150 (32)	76 (34)	16 (28)	1.0	16 (39)	1.0	21 (38)	1.0	18 (32)	1.0
	−270AC	234 (51)	119 (54)	30 (53)	1.2 (0.63-2.3)	13 (32)	0.52 (0.24-1.2)	24 (44)	0.73 (0.39-1.4)	29 (51)	1.0 (0.52-1.9)
	−270CC	79 (17)	26 (12)	11 (19)	1.4 (0.61-3.2)	12 (29)	2.2 (0.91-5.2)	10 (18)	0.99 (0.44-2.2)	10 (18)	1.6 (0.66-4.0)
SNP5	105AA	225 (49)	113 (52)	24 (42)	1.0	22 (54)	1.0	26 (47)	1.0	31 (54)	1.0
	105AC	198 (43)	89 (41)	25 (44)	1.3 (0.69-2.3)	13 (32)	0.76 (0.36-1.6)	25 (45)	1.2 (0.64-2.1)	20 (35)	0.85 (0.45-1.6)
	105CC	36 (8)	16 (7)	8 (14)	2.3 (0.94-5.8)	6 (14)	1.9 (0.68-5.5)	4 (7)	1.1 (0.35-3.3)	6 (11)	1.3 (0.47-3.7)
SNP6	35TT	373 (81)	183 (83)	48 (84)	1.0	30 (73)	1.0	50 (91)	1.0	44 (77)	1.0
	35TC	85 (18)	34 (15)	9 (16)	0.84 (0.39-1.8)	10 (24)	1.8 (0.79-4.0)	5 (9)	0.47 (0.18-1.2)	12 (21)	1.5 (0.69-3.1)
	35CC	5 (1)	3 (1)	0 (0)	—	1 (2)	1.8 (0.18-18)	0 (0)	—	1 (2)	1.2 (0.12-12)
SNP7	75CC	171 (37)	82 (37)	18 (32)	1.0	16 (39)	1.0	24 (44)	1.0	22 (39)	1.0
	75CG	229 (49)	114 (52)	25 (44)	1.0 (0.55-2.0)	13 (32)	0.59 (0.27-1.3)	24 (44)	0.77 (0.42-1.4)	26 (46)	0.84 (0.44-1.6)
	75GG	63 (14)	25 (11)	14 (25)	2.3 (1.0-4.9)	12 (29)	2.5 (1.0-5.9)	7 (13)	0.88 (0.36-2.2)	9 (16)	1.4 (0.56-3.4)
SNP8	114AA	212 (46)	98 (44)	24 (42)	1.0	22 (54)	1.0	26 (47)	1.0	31 (54)	1.0
	114AT	189 (41)	95 (43)	25 (44)	1.2 (0.67-2.3)	13 (32)	0.63 (0.30-1.3)	25 (45)	1.15 (0.64-2.1)	19 (33)	0.67 (0.35-1.3)
	114TT	61 (13)	28 (13)	8 (14)	1.5 (0.62-3.6)	6 (15)	1.0 (0.37-2.8)	4 (7)	0.65 (0.22-2.0)	7 (12)	0.84 (0.33-2.1)
SNP9	2930GG	228 (49)	112 (51)	24 (42)	1.0	21 (51)	1.0	26 (47)	1.0	31 (54)	1.0
	2930GT	193 (42)	92 (42)	25 (44)	1.3 (0.72-2.4)	13 (32)	0.76 (0.36-1.6)	25 (45)	1.2 (0.68-2.2)	20 (35)	0.82 (0.44-1.5)
	2930TT	41 (9)	17 (8)	8 (14)	2.3 (0.94-5.7)	7 (17)	2.2 (0.81-6.0)	4 (7)	1.0 (0.34-3.2)	6 (10)	1.3 (0.45-3.5)
COMT											
SNP1	701AA	208 (45)	101 (46)	25 (44)	1.0	25 (61)	1.0	22 (40)	1.0	38 (67)	1.0
	701AG	204 (43)	96 (43)	28 (49)	1.1 (0.61-2.0)	14 (34)	0.60 (0.29-1.2)	29 (53)	1.3 (0.74-2.4)	18 (32)	0.50 (0.26-0.94)
	701GG	49 (11)	24 (11)	4 (7)	0.63 (0.21-1.9)	2 (5)	0.35 (0.08-1.6)	4 (7)	0.78 (0.25-2.4)	1 (2)	0.11 (0.01-0.82)
	701AG/GG	253 (55)	120 (54)	32 (56)	1.0 (0.57-1.8)	16 (39)	0.55 (0.28-1.1)	33 (60)	1.23 (0.69-2.2)	19 (33)	0.42 (0.23-0.78)
SNP2	186CC	140 (30)	54 (25)	18 (32)	1.0	6 (15)	1.0	18 (33)	1.0	12 (21)	1.0
	186CT	205 (45)	109 (50)	24 (42)	0.94 (0.49-1.8)	24 (60)	2.1 (0.80-5.5)	25 (45)	0.97 (0.50-1.9)	27 (48)	1.3 (0.58-2.7)
	186TT	115 (25)	54 (25)	15 (26)	1.1 (0.50-2.2)	10 (25)	1.8 (0.60-5.4)	12 (22)	0.79 (0.36-1.7)	17 (30)	1.6 (0.70-3.8)
	186CT/TT	320 (70)	163 (75)	39 (68)	0.98 (0.54-1.8)	34 (85)	2.0 (0.79-5.1)	37 (67)	0.90 (0.49-1.7)	44 (79)	1.4 (0.67-2.8)
SNP3	108/158 VV	139 (30)	54 (25)	17 (30)	1.0	6 (15)	1.0	16 (29)	1.0	10 (18)	1.0
	108/158 VM	208 (45)	115 (52)	25 (44)	1.0 (0.52-2.0)	23 (59)	1.9 (0.71-4.9)	29 (53)	1.2 (0.64-2.4)	30 (53)	1.6 (0.70-3.5)
	108/158 MM	112 (24)	51 (23)	15 (26)	1.1 (0.52-2.4)	10 (26)	1.8 (0.62-5.5)	10 (18)	0.73 (0.32-1.7)	17 (30)	2.0 (0.84-4.9)
	108/158 VM/MM	320 (70)	166 (75)	40 (70)	1.1 (0.57-1.9)	33 (85)	1.9 (0.73-4.8)	39 (71)	1.1 (0.56-2.0)	47 (82)	1.7 (0.80-3.7)
SNP4	6731AA	214 (47)	104 (47)	28 (50)	1.0	24 (59)	1.0	32 (58)	1.0	27 (47)	1.0
	6731AG	194 (42)	91 (41)	23 (41)	0.91 (0.50-1.6)	15 (37)	0.71 (0.35-1.4)	17 (31)	0.60 (0.32-1.1)	27 (47)	1.1 (0.60-2.0)
	6731GG	52 (11)	26 (12)	5 (9)	0.78 (0.28-2.1)	2 (5)	0.33 (0.07-1.5)	6 (11)	0.81 (0.32-2.1)	3 (5)	0.43 (0.12-1.5)
	6731AG/GG	246 (53)	117 (53)	28 (50)	0.88 (0.50-2.1)	17 (41)	0.63 (0.32-1.2)	23 (42)	0.64 (0.36-1.1)	30 (53)	0.96 (0.53-1.7)

*Numbers may not add to 308 cases and 684 controls due to missing genotypes.
† ORs and 95% CIs calculated using unconditional logistic regression, adjusted for age.

Table 4. ORs and 95% CIs for non-Hodgkin lymphoma associated with haplotypes in *PRL*, *CYP17A1*, and *COMT* genes among HIV-negative, white non-Hispanic men and women, San Francisco Bay Area, 1988-1995

	Haplotype*,†	Controls	All non-Hodgkin lymphoma		Diffuse large-cell lymphoma		Follicular lymphoma	
		N = 684	*N* = 308	OR (95% CI)‡	*N* = 98	OR (95% CI)‡	*N* = 112	OR (95% CI)‡
PRL								
A	0-0-0	0.55	0.59	1.0 (reference)	0.60	1.0 (reference)	0.63	1.0 (reference)
B	1-1-1	0.20	0.17	0.78 (0.60-1.0)	0.18	0.88 (0.59-1.3)	0.20	0.94 (0.65-1.4)
C	1-1-0	0.13	0.11	0.85 (0.61-1.2)	0.14	1.2 (0.75-1.9)	0.09	0.66 (0.39-1.1)
D	0-1-0	0.06	0.05	0.81 (0.52-1.3)	0.05	0.80 (0.39-1.6)	0.03	0.41 (0.18-0.96)
Other§	Pooled (low frequency)	0.07	0.08	1.2 (0.84-1.8)	0.03	0.40 (0.16-1.0)	0.05	0.67 (0.34-1.3)
CYP17A1								
A	0-0-0-0-0-0-0-0-0	0.51	0.50	1.0 (reference)	0.50	1.0 (reference)	0.57	1.0 (reference)
B	1-1-1-1-1-0-1-1-1	0.24	0.27	1.2 (0.95-1.5)	0.32	1.6 (1.1-2.2)	0.28	1.2 (0.90-1.7)
C	1-1-1-1-0-1-1-0-0	0.08	0.09	1.1 (0.79-1.6)	0.10	1.3 (0.80-2.2)	0.08	1.0 (0.59-1.7)
Other§	Pooled (low frequency)	0.16	0.14	0.91 (0.71-1.2)	0.07	0.46 (0.27-0.79)	0.07	0.48 (0.29-0.78)
COMT								
A	0-1-1-0	0.37	0.40	1.0 (reference)	0.41	1.0 (reference)	0.42	1.0 (reference)
B	1-0-0-0	0.14	0.13	0.89 (0.65-1.2)	0.12	0.86 (0.52-1.4)	0.12	0.87 (0.54-1.4)
C	1-0-0-1	0.14	0.11	0.74 (0.53-1.0)	0.09	0.54 (0.30-0.97)	0.11	0.72 (0.44-1.2)
D	0-0-0-1	0.12	0.13	1.2 (0.87-1.7)	0.14	1.3 (0.77-2.1)	0.11	0.93 (0.56-1.5)
E	0-0-0-0	0.12	0.12	0.93 (0.66-1.3)	0.13	1.1 (0.64-1.7)	0.14	1.2 (0.76-1.9)
F	0-1-1-1	0.06	0.05	0.84 (0.53-1.3)	0.04	0.58 (0.24-1.4)	0.04	0.63 (0.29-1.4)
Other§	Pooled (low frequency)	0.06	0.05	1.0 (0.65-1.6)	0.07	1.2 (0.64-2.3)	0.05	0.97 (0.48-2.0)

*Jointly adjusted haplotypes estimated using tagSNPs implementation of the EM algorithm. *CYP17A1* haplotypes are described left to right: SNP1-SNP9, wild-type allele designated "0" and variant allele designated "1".

† *PRL* haplotypes are described left to right: SNP1-SNP3, wild-type allele designated "0" and variant allele designated "1". SNP4 is not included because only the wild-type allele cosegregates with haplotypes ≥0.05.

‡ Haplotype ORs and 95% CIs estimated using a single-imputation approach, modeled using unconditional logistic regression adjusted for age and sex. All haplotype categories for a gene are included in the same model using the highest-prevalence haplotype as the reference category.

§ Haplotypes with estimated frequencies <0.05 are pooled into a single category.

associations seemed to be due to the difference in haplotype frequencies in women, but the global test of association was not statistically significant for women (P = 0.20) or men (P = 0.41; Supplementary Table 2).

Oral Contraceptive and Non-Oral Contraceptive Hormone Use and Non-Hodgkin Lymphoma Risk among Women. Among all white non-Hispanic women in our study population, non-Hodgkin lymphoma risk was reduced by 35% among those who ever had used oral contraceptives compared with never users (Table 5). There also was a decreasing trend in ORs with increasing years of oral contraceptive use (P for trend = 0.001). Postmenopausal status and ever use of non-oral contraceptive hormones were not associated with non-Hodgkin lymphoma. Because long-term use of non-oral-contraceptive hormones may be related to hysterectomy, analyses were stratified by history of hysterectomy or oophorectomy. Among women with no history of hysterectomy/oophorectomy, ORs decreased with increasing years of use, whereas among women who had a history of hysterectomy/oophorectomy, the OR was increased for shorter duration of use. In general, risk estimates from analyses restricted to genotyped women were only somewhat consistent with results from analyses among all women. In this restricted group of women, ORs for non-Hodgkin lymphoma associated with use of exogenous estrogens were imprecise and were consistently less than unity, but not different from a chance occurrence. The small number of exposed patients restricted more detailed analyses of duration of hormone use in this group. Due to sparse data, we also did not evaluate duration of use by non-Hodgkin lymphoma subtype or gene-environment interactions.

Discussion

Here we report an association between common genetic variants in the *CYP17A1, PRL*, and *COMT* genes and risk of non-Hodgkin lymphoma. Among both men and women, we observed increased risk for all non-Hodgkin lymphoma and

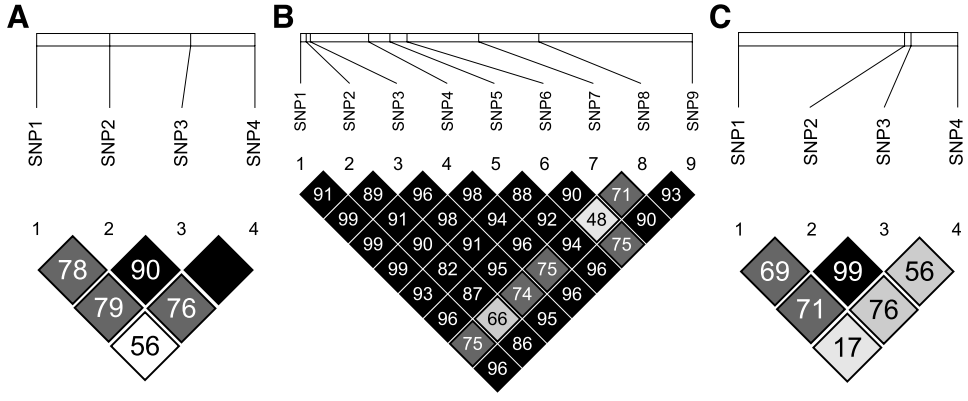

Figure 2. Pairwise measures of linkage disequilibrium ($D' \times 100$) among *PRL* (**A**), *CYP17A1* (**B**), and *COMT* (**C**) loci genotyped in the control population. These linkage disequilibrium plots were generated using Haploview (27).

Table 5. ORs and 95% CIs for non-Hodgkin lymphoma associated with exogenous estrogens among all HIV-negative, white non-Hispanic women and restricted to those for whom DNA was genotyped for hormone-related SNPs, San Francisco Bay Area

Characteristic	All women			Genotyped women		
	Cases (N = 451)	Controls (N = 678)	OR (95% CI)*	Cases (N = 134)	Controls (N = 220)	OR (95% CI)*
	n (%)	n (%)		n (%)	n (%)	
Ever oral contraceptive use						
No	270 (60)	354 (52)	1.0 (reference)	74 (56)	119 (54)	1.0 (reference)
Yes	180 (40)	324 (48)	0.65 (0.49-0.86)	59 (44)	101 (46)	0.93 (0.56-1.6)
Duration of oral contraceptive use in years						
≤5	125 (28)	206 (30)	0.71 (0.52-0.97)	39 (29)	58 (26)	1.1 (0.61-1.4)
>5	55 (12)	118 (17)	0.54 (0.37-0.80)	20 (15)	43 (20)	0.74 (0.38-1.4)
			P_{trend} = 0.001†			P_{trend} = 0.45†
Postmenopausal status						
Premenopausal	100 (22)	155 (23)	1.0 (reference)	24 (18)	50 (23)	1.0 (reference)
Postmenopausal	351 (78)	523 (77)	1.1 (0.69-1.6)	110 (82)	170 (77)	1.8 (0.81-4.2)
Postmenopausal women						
Ever non-oral contraceptive hormone use						
No	124 (35)	176 (34)	1.0 (reference)	43 (39)	54 (32)	1.0 (reference)
Yes	227 (65)	346 (66)	0.93 (0.70-1.2)	67 (61)	116 (68)	0.70 (0.42-1.2)
Duration of non-oral contraceptive hormone use in years						
≤5	116 (33)	139 (27)	1.2 (0.85-1.7)	28 (26)	48 (29)	0.66 (0.35-1.2)
>5	110 (31)	204 (39)	0.77 (0.55-1.1)	38 (35)	66 (39)	0.72 (0.41-1.3)
			P_{trend} = 0.11†			P_{trend} = 0.26†
Duration of non-oral contraceptive hormone use among women without a hysterectomy/oophorectomy						
No use	91 (48)	120 (41)	1.0 (reference)	30 (43)	36 (38)	1.0 (reference)
≤5 y	60 (32)	89 (31)	0.83 (0.53-1.3)	20 (29)	32 (34)	0.63 (0.29-1.4)
>5 y	38 (20)	81 (28)	0.60 (0.37-0.96)	19 (28)	27 (28)	0.81 (0.38-1.7)
			P_{trend} = 0.04†			P_{trend} = 0.53
Duration of non-oral contraceptive hormone use among women with hysterectomy/oophorectomy						
No use	33 (20)	56 (24)	1.0 (reference)	13 (32)	18 (25)	1.0 (reference)
≤5 y	56 (35)	50 (22)	1.9 (1.1-3.4)	8 (20)	16 (22)	0.66 (0.22-2.0)
>5 y	72 (45)	123 (54)	0.95 (0.56-1.6)	19 (48)	39 (53)	0.69 (0.28-1.7)
			P_{trend} = 0.44†			P_{trend} = 0.45

*ORs and 95% CIs computed using unconditional logistic regression adjusted for age. Reference group is never users.
†P_{trend} based on χ^2 statistic for ordinal duration of use from age-adjusted unconditional logistic regression.

for diffuse large-cell lymphoma, particularly with the *CYP17A1* −34CC genotype. In *CYP17A1* haplotype analyses, a high-risk haplotype for diffuse large-cell lymphoma (HapB) was more frequent among cases than controls. These data are consistent with our recent findings in another large non-Hodgkin lymphoma case-control study conducted in the United Kingdom where the *CYP17A1* −34CC genotype was associated with a similar elevated risk (31). The replication of this finding in both men and women in a second study suggests that an association exists between the *CYP17A1* −34CC genotype and non-Hodgkin lymphoma risk. Further, the similar magnitudes of effect in both sexes suggest that testosterone and other cholesterol metabolites downstream of CYP17A1, or other factors common to both sexes, may be involved in the pathogenesis of non-Hodgkin lymphoma. The higher incidence of diffuse large-cell lymphoma among men compared with women (32) is consistent with the notion that steroids in this pathway other than estrogens influence diffuse large-cell lymphoma risk.

CYP17A1 exhibits both 17α-hydroxylase and 17,20-lyase enzymatic activities in ovarian theca cells, testicular Leydig cells, and in the adrenal cortex, which are essential for sex steroid and glucocorticoid production (33). Through the δ5 pathway, CYP17A1 converts pregnenolone to dehydroepiandrosterone, the precursor for estrogen and testosterone (Fig. 3; ref. 34). Whereas the *CYP17A1* −34CC genotype has been associated with elevated estrogen levels in women, an association with increased estrogen or testosterone levels in men is uncertain (reviewed in refs. 18, 35). Thus, further studies may be warranted to test whether testosterone or its major metabolite, 5α-dihydrotestosterone, potentiates lymphoma risk. Through the δ4 pathway, CYP17A1 also converts progesterone to 17α-hydroxyprogesterone, a substrate in the production of cortisol (Fig. 3; ref. 34). Cortisol can either suppress or stimulate immune function in a dose-dependent manner, so modulation of its production could potentially influence non-Hodgkin lymphoma risk. Currently, no functional studies have reported whether the *CYP17A1* −34T>C polymorphism alters glucocorticoid production. Additional studies of SNPs in genes involved in glucocorticoid and sex hormone production such as *CYP21A2*, *CYP11B1*, 3β-hydroxysteroid dehydrogenase (*3β-HSD*), *17β-HSD*, *CYP19*, and 5α-reductase type 2 (*SRD5A2*) may clarify this pathway in lymphomagenesis.

We also observed that genetic variants in *COMT* were associated with increased risk of non-Hodgkin lymphoma in women. Specifically, the *COMT* SNP3 variant (108/158Met), which was related to reduced COMT enzyme activity, elevated circulating estradiol (36) and 2-hydroxyestrone levels (37), and increased breast cancer risk (38, 39), was associated with borderline elevated risk of non-Hodgkin lymphoma, particularly follicular lymphoma, in women. Reduced COMT activity decreases the detoxification of catechol estrogens to the less toxic methoxy derivatives (40), notably 2-methoxyestradiol, an anticarcinogen that induces apoptosis and inhibits angiogenesis and tumor cell growth (41). In contrast, the intronic *COMT* SNP1 variant allele was associated with a reduced risk for non-Hodgkin lymphoma in women, which was likely driven by the reduced risk observed for follicular lymphoma. Whether the effect of this SNP is due to a function of enhanced COMT expression or is linked to an unknown causal variant remains to be determined. Nonetheless, these findings suggest a possible role of

catechol estrogens in the pathogenesis of follicular lymphoma in women through genotoxic mechanisms that involve oxidative DNA damage, DNA double-strand breaks, and/or tumor initiation. Alternatively, the increased risk of diffuse large-cell lymphoma associated with the *CYP17* −34CC genotype in women and men suggests enhanced B-cell activation, proliferation, and survival as a possible mechanism through estrogen receptor- or testosterone receptor-mediated effects.

In the haplotype analyses, *COMT* HapC was identified as a low-risk haplotype for non-Hodgkin lymphoma in both men and women. This same haplotype recently was described as a high-risk haplotype for schizophrenia (42), where the population frequency was similar to that for controls in our population. This haplotype was associated with reduced MB-COMT expression and elevated dopamine levels in the brain. Dopamine exerts profound effects on immune function, is produced by lymphocytes (43), and its receptors are found on lymphocytes, macrophages, and neutrophils (44). Thus, it is possible that interactions between the nervous and immune systems that involve dopamine and/or other neurotransmitters alter the risk for non-Hodgkin lymphoma.

Prolactin also regulates lymphocyte function and is synthesized by these cells (45). In the present study, the *PRL* −1149T variant (SNP1) was inversely associated with all non-Hodgkin lymphoma and with follicular lymphoma both in men and in women. Multiple promoters and start sites present in the *PRL* gene modulate pituitary and extrapituitary expression (10). The *PRL* −1149T allele, located in the extrapituitary promoter, is associated with reduced promoter activity and prolactin mRNA levels in lymphocytes (11), whereas the −1149G allele may abrogate the effect of prolactin on lymphoproliferation (46). Prolactin promotes both cell-mediated and humoral immune responses through signaling pathways, including Jak/Stat and mitogen-activated protein kinase, resulting in target gene expression (47), stimulation of B- and T-cell proliferation, proinflammatory cytokine production, and B-cell growth arrest (reviewed in ref. 1). Alternatively, estradiol exerts predominantly a humoral immune response via T-cell suppression and B-cell proliferation, enhanced antibody production, and B-cell survival (1). In animal studies, treatment with either estradiol (48) or prolactin (49) leads to the rescue of autoreactive B-cells from apoptosis by up-regulating BCL-2 expression (50), indicating a role of these hormones in autoimmune disease. Furthermore, testosterone and its major endogenous metabolite 5α-dihydrotestosterone may also exert pleiotropic effects on the immune system. 5α-dihydrotestosterone promotes proliferation of prostate epithelial cells through up-regulation of the BCL-2 and nuclear factor κB pathways (51), but little is known about its proliferative and antiapoptotic effects on B-cells.

Reduced ORs for non-Hodgkin lymphoma in long-term oral contraceptive users in our analyses are somewhat consistent with the results of two other studies (7, 8) but different from that of one study (52). Although the epidemiologic data have been inconsistent, it is biologically plausible that long-term oral contraceptive use and/or women's exposure to exogenous estrogens during the reproductive years may alter non-Hodgkin lymphoma risk. Oral contraceptive use inhibits ovulation and the cyclic fluxes in estrogen and progesterone production during the menstrual cycle. Furthermore, oral contraceptive use is associated with significantly reduced levels of serum testosterone and dehydroepiandrosterone sulfate and elevated levels of serum hormone binding globulin (53), a protein that binds to and restricts the biological action of estradiol and testosterone. It is plausible that long-term oral contraceptive use reduces the overall lifetime exposure to estrogens, thus reducing proliferation and enhanced survival of B-cells and risk for non-Hodgkin lymphoma.

Although imprecise, the magnitude of the ORs associated with history of non-oral contraceptive hormone use among the genotyped and nongenotyped postmenopausal women tended to be consistent with the borderline reduced estimates published in most studies (7, 8, 52, 54). Exceptions to these results that show a somewhat inverse relationship are the increased risks for follicular lymphoma associated with hormone therapy among postmenopausal women in the Iowa Women's Health study (6) and for all non-Hodgkin lymphomas among women in Los Angeles County (5). The estimates from these two studies were somewhat similar to our results among women who had had a hysterectomy or oophorectomy and used non-oral-contraceptive hormones for 5 or fewer years. In general, the estimates from most previous studies and our study were imprecise and based on a small number of exposed patients. Studies that include a large number of exposed women and detailed information about hormone use are required to determine whether these observed associations are true. However, given that estrogens influence immune function, these epidemiologic results are biologically plausible and are consistent with our genetic data.

As with all exposure data collected in case-control studies, these data are subject to recall bias and exposure misclassification. To address these known problems, hormone-related information was collected from both case and control participants in a consistent manner, with photographs of the hormone types, brands, and manufacturers' packaging shown to all participants to assist recall. Unless patients perceived that oral contraceptive or non-oral contraceptive hormone use was associated with their disease, we would expect the misclassification to be nondifferential and the recall bias to be minimal. Thus, the estimated ORs are likely to be biased

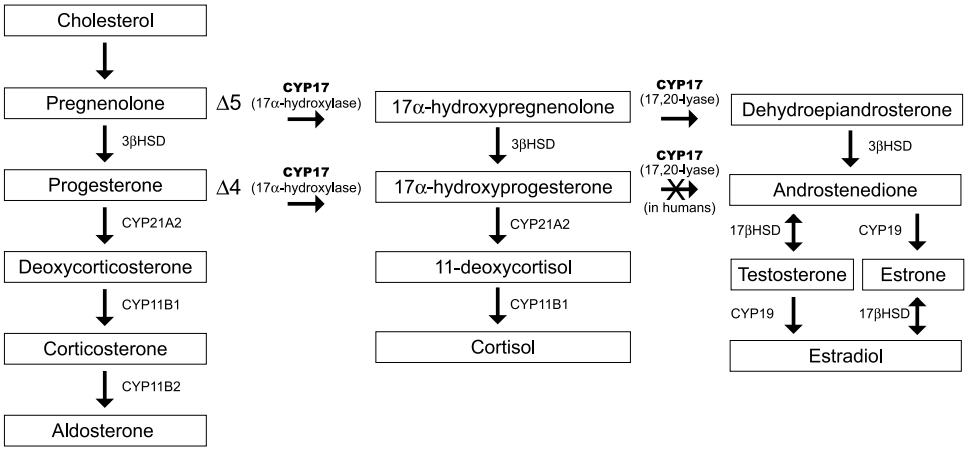

Figure 3. Schematic of the synthesis and metabolism of estradiol and testosterone. *CYP19,* cytochrome *P*450 19; *SRD5A2,* 5α-reductase type 2; *3β-HSD,* 3β-hydroxysteroid dehydrogenase; *17β-HSD,* 17β-hydroxysteroid dehydrogenase; *DHT,* 5α-dihydrotestosterone.

toward the null especially for details about oral contraceptive and non-oral-contraceptive hormone use. Furthermore, the potential heterogeneity of non-oral-contraceptive hormone use related to other characteristics, including reason for use and type of hormone used, may have affected the estimates for these factors. Power to test associations for more detailed analyses in the restricted population of genotyped women was low. Analyses of gene-environment interactions were not pursued because estimates obtained from the analyses of exogenous hormone use in the restricted population of women were not entirely consistent with those obtained for the complete group of women and may have resulted in spurious gene-environment effects. Although these results are consistent with those from some previous epidemiologic investigations of hormone use and non-Hodgkin lymphoma, confirmation in larger studies is required.

Compared with all HIV-negative patients (regardless of eligibility) who did not provide a blood specimen, patients who gave blood were less likely to have had high-grade lymphomas. If treatment or prognosis for patients with high-grade lymphomas was related to blood collection, then our results may be comparable only to patients with better prognosis or less urgent treatment regimens. In addition, compared with noninterviewed patients, patients who were interviewed had a higher proportion of low-grade lymphomas (55). If all HIV-negative patients had been interviewed, the overall proportion of low-grade lymphomas would have been somewhat lower, whereas there would have been little change in the proportion of high-grade lymphomas. Given that low-grade lymphomas are somewhat overrepresented among HIV-negative patients in our overall study population and among those who gave blood, our estimates for all non-Hodgkin lymphoma may be biased slightly away from the null for factors related to low-grade disease.

Additional limitations of this study are similar to other case-control studies of genetic associations and complex diseases. Like many polygenic diseases, the risk alleles studied are not likely to be sufficient to induce non-Hodgkin lymphoma and require replication and confirmation in additional larger studies. However, we have attempted to address some of the shortcomings of genetic association studies by investigating haplotypes in addition to SNPs, assessing the extent of linkage disequilibrium, considering haplotypes and SNPs at loci that function in the same or related biological pathways, restricting analyses to white non-Hispanics, and including epidemiologic measures of estrogen exposure to provide a more comprehensive evaluation of the potential role of estrogen in the development of non-Hodgkin lymphoma.

Overall, our observations suggest *PRL*, *CYP17A1*, and *COMT* as non-Hodgkin lymphoma susceptibility genes and provide support for the role of prolactin, estrogens, and possibly testosterone, cortisol, and/or dopamine in the pathogenesis of lymphoma. Our findings suggest that in both men and women, lymphocyte prolactin and circulating estrogen levels may be inversely associated with follicular lymphoma and diffuse large-cell lymphoma risk, respectively. These effects may be promoted through similar pathways involving enhanced B-cell activation, proliferation, and survival, although prolactin also can elicit a strong proinflammatory cytokine response. Our results among women suggest a role for catechol estrogens, possibly through genotoxic mechanisms, in the initiation of follicular lymphoma. The positive association between diffuse large-cell lymphoma and the *CYP17* −34CC genotype among men and women raises the question of whether this SNP has an effect on testosterone or cortisol production (not measured in this study) and whether these hormones influence lymphoma risk. Functional studies will be needed to address these questions. Finally, the inverse association between diffuse large cell lymphoma and *COMT* HapC, related to elevated dopamine levels, suggests that although lymphoma is not considered a classic endocrinological tumor, interactions involving aberrant cross-talk between the neuroendocrine-immune networks may play a role in non-Hodgkin lymphoma pathogenesis. Further investigation of these ideas is warranted in independent studies, ideally as part of a large consortium such as InterLymph.

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