American Journal of Epidemiology
Published by the Johns Hopkins Bloomberg School of Public Health 2008.

Vol. 168, No. 3
DOI: 10.1093/aje/kwn119
Advance Access publication June 10, 2008

Original Contribution

Non-Hodgkin Lymphoma in Women: Reproductive Factors and Exogenous Hormone Use

Jennifer S. Lee[1,2], Paige M. Bracci[3], and Elizabeth A. Holly[2,3]

[1] Division of Endocrinology, Clinical Nutrition, and Vascular Medicine, Department of Internal Medicine, University of California Davis, Sacramento, CA.
[2] Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA.
[3] Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA.

Received for publication October 17, 2007; accepted for publication April 7, 2008.

Few studies of reproductive hormone exposures and non-Hodgkin lymphoma (NHL) have examined NHL subtypes. Associations between reproductive hormonal factors and risk of all NHL and of two predominant subtypes, diffuse large-cell lymphoma (DLCL) ($n = 233$) and follicular lymphoma ($n = 173$), were investigated among women ($n = 581$) in a large, population-based, case-control study (1,591 cases, 2,515 controls). Controls ($n = 836$) identified by random digit dialing were frequency matched by age and county to incident NHL cases ascertained in the San Francisco Bay Area of California in 1988–1993. Adjusted unconditional logistic regression was used to obtain odds ratios. More than four pregnancies indicated a possible lower risk of all NHL (odds ratio (OR) = 0.81, 95% confidence interval (CI): 0.55, 1.2; p-trend = 0.06) and of DLCL (OR = 0.53, 95% CI: 0.31, 0.90; p-trend = 0.01). Exclusive use of menopausal hormone therapy for $\geq$5 years was associated with a reduced risk of all NHL (OR = 0.68, 95% CI: 0.48, 0.98) and of DLCL (OR = 0.50, 95% CI: 0.30, 0.85). Oral contraceptive use indicated a lower risk of all NHL (OR = 0.68, 95% CI: 0.49, 0.94), and perhaps DLCL (OR = 0.79, 95% CI: 0.51, 1.2), and of follicular lymphoma (OR = 0.75, 95% CI: 0.46, 1.2). Results suggest that endogenous and exogenous reproductive hormones confer different risks by NHL subtype and are associated with a reduced risk of DLCL in women.

case-control studies; contraception; estrogens; hormone replacement therapy; lymphoma, non-Hodgkin; menopause; pregnancy; reproduction

Abbreviations: DLCL, diffuse large-cell lymphoma; HT, menopausal hormone therapy; NHL, non-Hodgkin lymphoma.

The incidence of non-Hodgkin lymphoma (NHL) is increasing, while determinants in the pathogenesis remain unclear (1). NHL comprises a complex and heterogeneous set of lymphoma subtypes that are likely to differ etiologically, ranging from indolent follicular lymphoma to aggressive diffuse large-cell lymphoma (DLCL). Compared with men, women have a 30 percent lower overall incidence of NHL. However, sex differences in incidence across NHL subtypes exist; women have a lower incidence of DLCL and a comparable incidence of follicular lymphoma (2). Estrogen and other reproductive hormone exposures may confer a reduced risk of some NHL subtypes such as DLCL in women by influencing the immune system via numerous mechanisms (3). For example, estrogen and other reproductive hormones mediate immune responses, release of relevant cytokines, B-cell differentiation and proliferation, and multiple stages of lymphomagenesis (4–8).

Reproductive hormone exposures in women include menstrual factors, pregnancy, and use of exogenous hormones such as oral contraceptives and menopausal hormone therapy (HT). Prior reports are mixed about the relation between these hormonal factors in women and the risk of NHL, and

Correspondence to Dr. Paige M. Bracci, Department of Epidemiology and Biostatistics, University of California San Francisco, 3333 California Street, Suite 280, San Francisco, CA 94118-1944.

few studies have explored whether such inconsistent findings are due, at least in part, to the heterogeneity among NHL subtypes (3, 9, 10). In our earlier analyses restricted to White non-Hispanic women, several variants in genes involved in reproductive hormone metabolism were associated with NHL in the subset of women for whom DNA was available; the corresponding exposure data showed a decreased risk of NHL associated with ever use of oral contraceptives or of non-oral-contraceptive hormones (11).

Here, we present results from more detailed analyses of the risk of NHL and common NHL subtypes associated with reproductive factors and use of exogenous female hormones among all women in our population-based case-control study in the San Francisco Bay Area of California.

MATERIALS AND METHODS

There were 1,591 eligible cases and 2,515 eligible controls who were interviewed in a large, population-based, case-control study of NHL in the San Francisco Bay Area. Eligibility criteria for incident NHL cases identified by the Northern California Cancer Center's rapid case ascertainment system were 1) diagnosis between 1988 and 1993, 2) aged 21–74 years, 3) a resident of one of six Bay Area counties at diagnosis, 4) no physician-indicated contraindications to contact, and 5) able to complete an interview in English. Controls were identified by random digit dialing and were frequency matched to cases by 5-year age group, sex, and county of residence. Eligibility criteria for controls were the same as those for cases with the exception of NHL diagnosis. No proxy interviews were conducted. Results from our earlier analyses showed that noninterviewed NHL cases were younger, more likely to be homosexual men infected with human immunodeficiency virus, and more likely to have high-grade and not-otherwise-specified NHL (12). Response rates were 72 percent for eligible cases and 78 percent for eligible controls. Information collected from the 1,417 women study participants (581 cases, 836 controls) was used in these analyses.

Diagnostic pathology slides were rereviewed and classified by using the working formulation for 97 percent of NHL patients. To reflect the more recent Revised European American Lymphoma Classification (REAL)/World Health Organization classification system, diffuse large-cell and large-cell immunoblastic subtypes were combined to represent DLCL, and all follicular subtypes were combined to represent follicular lymphoma for these analyses (13).

All participants provided informed consent prior to interview and venipuncture. Procedures and protocols were approved by the University of California San Francisco Committee on Human Research. Further details of the study design and methods have been published in previous manuscripts (12, 14–20).

Interviews

Trained interviewers used a standard questionnaire to collect exposure and risk factor data from study participants during in-person interviews. Interviews were conducted at a place and time convenient to participants, with most taking place in participants' homes. Data collected included demographic characteristics, personal and family medical histories, travel and other lifestyle factors, occupational history, and chemical exposures.

Participants also were asked about reproductive history and use of exogenous hormones. Reproductive history questions included age at menarche, number of pregnancies, number of births, sex of each child in birth order, and age at birth of the first child. Questions on exogenous hormone use pertained to the use of oral contraceptives and of other non-oral-contraceptive hormones. For oral contraceptive use, women were asked whether they had ever used birth control pills, the total number of months and years they were used, the brand(s) used (assisted by photographs and cue cards), age at which they were first used, and duration of use for each type. Data were similarly collected for use of non-oral-contraceptive hormones, primarily HT, and hormones to inhibit lactation or to treat morning sickness.

Statistical analyses

All statistical analyses for women (581 cases, 836 controls) were conducted by using SAS v.9 software (SAS Institute, Inc., Cary, North Carolina). Odds ratios and 95 percent confidence intervals were computed as estimates of relative risks (hereafter called risk) using unconditional logistic regression adjusted for age group. For analyses of exogenous hormone use, women who never had used any exogenous hormones constituted the referent group. Duration of hormone use was computed for oral contraceptive use only, HT use only, and any exogenous hormone use. Duration was categorized as <1 year, 1–<5 years, 5–<10 years, and ≥ 10 years of use for easy comparison with published data on exogenous hormone use. Time since first and last use was computed as the difference between age at first (or last) use and age at diagnosis (or interview for controls). Continuous variables, other than duration of use, were grouped on the basis of quartiles of the frequency distribution among controls. If the odds ratios for contiguous categories of a factor were not different from one another or if cell numbers were small, these categories were collapsed for the final analyses.

Information on age at menopause was not collected in the study questionnaire. However, analyses that used average age at menopause for US women (age 51 years (21)) showed results for HT use to be similar for postmenopausal women and all women. Therefore, data for all women are presented in the tables in this article. Oral contraceptive use was dichotomized as first use before 1970 versus 1970 or later to assess the effect of the highest-dose-estrogen oral contraceptives prescribed prior to recommendations resulting from the 1970 US Senate hearings (http://www.fda.gov/bbs/topics/CONSUMER/CON00027.html). We also chose this cutpoint for comparability with already published studies of oral contraceptive use and risk of NHL (9, 22).

Factors considered in the analyses as potential confounders or effect modifiers included race, marital status, years of education, lifetime average number of alcoholic drinks consumed per week, lifetime number of sexual partners, and obesity (based on usual adult weight, body mass index

(weight (kg)/height (m)^2) ≥30) (16). Potential confounding factors were retained in the final models if their inclusion modified the main effect estimate by more than 10 percent. Linear trends in odds ratios were determined from adjusted unconditional logistic models and were based on the beta estimate for the factor of interest when included in the model as an ordinal variable. When appropriate, p values for linear trend are presented here.

All statistical tests were two sided and were considered significant for $p \leq 0.05$ ($p \leq 0.10$ for interaction). Results were considered borderline significant for $p > 0.05$ to $p \leq 0.10$.

RESULTS

Median age at diagnosis or interview for both cases and controls was 61 years (interquartile range, 19). Lifestyle factors associated with disease status that also may be associated with reproductive hormone exposures included educational level, weekly alcohol consumption, body mass index, marital status, and lifetime number of sexual partners (table 1).

Reproductive factors

Menstrual and pregnancy factors were not consistently associated with risks of all NHL (table 2). However, an increasing number of pregnancies (p-trend = 0.01) and of livebirths (p-trend = 0.04) were associated with a decreasing trend in the risk of DLCL (table 2). Sex of the first child, total number of boys, total number of girls, and percentage of boys relative to family size were not associated with NHL risk (data not shown in table, $p > 0.24$ for all factors).

Exogenous hormone use

Approximately 70 percent of women with NHL had ever used oral contraceptives, HT, or other hormones (table 3). Slightly more NHL patients had ever used HT alone, whereas fewer women with NHL, compared with controls, had ever used oral contraceptives alone (table 3). Among women who had used HT alone, 13 percent had used oral estrogen plus progestin and 55 percent had used oral estrogen alone. The remainder of these women had used menopausal hormones administered by injection, cream, or patch. One percent of women reported having used other hormones to inhibit lactation, to treat menstrual disorders, or to treat morning sickness as their only exogenous hormone exposure.

The observed decreased risk of all NHL with exogenous hormone use was found for mainly those women who had used oral contraceptives. In models adjusted for age group and total years of oral contraceptive use, increasing number of years since first use of oral contraceptives was associated with a reduced risk of all NHL (p-trend = 0.005, table 3). First oral contraceptive use before 1970 also was associated with a lower risk (p-trend = 0.03), although, after adjustment for age group, age at first use, duration of use, and lifetime number of sexual partners, individual confidence intervals included unity. Analyses of types of hormones by NHL subtype suggested that oral contraceptive use was associated with a reduced risk of DLCL and follicular lymphoma, although the associations did not differ from chance (table 4). Analyses by first use before 1970 versus 1970 or

TABLE 1. Lifestyle and demographic characteristics of women with non-Hodgkin lymphoma and of controls participating in a population-based case-control study, San Francisco Bay Area, California, 1988–1993

Characteristic	NHL* cases (n = 581)		Controls (n = 836)	
	No.	%	No.	%
Age group† (years)				
<40	71	12	105	13
40–<50	79	14	117	14
50–<60	115	20	170	20
60–<70	210	36	292	35
70–74	106	18	152	18
White non-Hispanic				
No	129	22	158	19
Yes	452	78	678	81
Education				
<12 years	76	13	72	9
High school graduate	208	36	265	32
Some college	130	22	232	28
College graduate	84	15	154	18
>16 years	83	14	113	14
Cigarette smoking status				
No tobacco use	284	49	407	49
Former smoker	172	30	265	32
Current smoker	125	22	164	20
Weekly alcohol consumption				
No alcohol consumption	221	38	255	30
<2 drinks	124	21	197	24
2–<5.5 drinks	121	21	198	23
≥5.5 drinks	115	20	185	22
Body mass index‡				
Lean to normal (<25)	405	70	623	75
Overweight (25–<30)	129	22	166	20
Obese (≥30)	45	8	46	6
Marital status				
Married, living as married, widowed	442	76	543	65
Separated, divorced, single, never married	139	24	293	35
Lifetime no. of sexual partners				
0–1	284	50	303	37
2–4	144	25	248	30
≥5	143	25	274	33

* NHL, non-Hodgkin lymphoma.
† Age at diagnosis for cases and age at interview for controls.
‡ Usual adult weight in kilograms divided by height in meters squared.

TABLE 2. Age-adjusted odds ratios and 95% confidence intervals for reproductive factors associated with all non-Hodgkin lymphoma and with the subtypes follicular lymphoma and diffuse large-cell lymphoma among women in a population-based case-control study, San Francisco Bay Area, California, 1988–1993

Reproductive factor	Controls ($n = 836$)		All NHL* cases ($n = 581$)				FL* cases ($n = 173$)				DLCL* cases ($n = 233$)			
	No.	%	No.	%	OR*	CI*	No.	%	OR†	CI	No.	%	OR‡	CI
Age at menarche (years)														
≤11	167	20	110	19	1.0§		35	21	1.0§		46	20	1.0§	
12–13	415	50	308	53	1.1	0.85, 1.5	83	49	0.96	0.62, 1.5	130	56	1.1	0.78, 1.7
14	128	15	87	15	1.0	0.72, 1.5	29	17	1.1	0.63, 1.9	32	14	0.91	0.55, 1.5
>14	123	15	72	12	0.89	0.61, 1.3	23	14	0.90	0.51, 1.6	25	11	0.74	0.43, 1.3
p-trend						0.43				0.90				0.17
No. of pregnancies														
Never pregnant¶	116	15	80	14	1.0§		20	12	1.0§		38	17	1.0§	
1–3	410	50	317	55	1.1	0.81, 1.5	104	60	1.4	0.79, 2.4	122	53	0.67	0.43, 1.0
4	125	15	78	14	0.90	0.60, 1.4	22	13	0.89	0.44, 1.8	27	12	0.43	0.24, 0.78
>4	174	21	98	17	0.81	0.55, 1.2	26	15	0.77	0.39, 1.5	43	19	0.53	0.31, 0.90
p-trend						0.06				0.05				0.01
No. of livebirths														
0	55	7	28	5	0.74	0.43, 1.3	6	3	0.77	0.29, 2.1	12	5	0.64	0.31, 1.3
1–2	299	36	238	41	1.2	0.82, 1.6	85	49	1.6	0.88, 2.8	85	36	0.63	0.40, 1.0
3	173	21	123	21	1.0	0.71, 1.5	35	20	1.0	0.54, 2.0	47	20	0.58	0.34, 0.99
≥4	191	23	112	19	0.85	0.58, 1.2	27	16	0.73	0.37, 1.4	51	22	0.56	0.33, 0.94
p-trend						0.44				0.14				0.04
Age at birth of first child (years)														
≤21	189	24	141	26	1.1	0.76, 1.6	37	22	1.2	0.64, 2.3	54	24	0.70	0.42, 1.2
22–24	179	23	119	22	1.0	0.67, 1.4	35	21	1.1	0.56, 2.0	52	24	0.69	0.41, 1.2
25–28	158	20	118	21	1.1	0.75, 1.6	38	23	1.3	0.70, 2.6	47	21	0.70	0.41, 1.2
>28	135	17	95	17	1.0	0.70, 1.5	37	22	1.5	0.80, 3.0	30	14	0.51	0.29, .91
p-trend						0.92				0.17				0.06
Hysterectomy/ oophorectomy														
No	555	66	381	66	1.0		116	67	1.0		154	66	1.0	
Yes	281	34	200	34	1.0	0.81, 1.3	57	33	1.1	0.75, 1.6	79	34	1.0	0.74, 1.4

* NHL, non-Hodgkin lymphoma; FL, follicular lymphoma; DLCL, diffuse large-cell lymphoma; OR, odds ratio; CI, confidence interval.

† Number of pregnancies, number of livebirths, and age at birth of first child were also adjusted for marital status and lifetime number of sexual partners.

‡ Age at birth of first child was adjusted for age group and marital status. Number of pregnancies and number of livebirths were also adjusted for marital status and education.

§ Referent.

¶ Referent group for all subsequent reproductive factors in this table.

later showed a decreasing trend in odds ratios with earlier use for risk of DLCL (p-trend = 0.02), although individual effects were not different from unity (table 4). No associations were observed for follicular lymphoma risk.

A decreasing trend in NHL risk was observed with increasing total years of use of HT (table 3, p-trend = 0.05). When analyses were restricted to women who used HT alone, those who reported 5 or more total years of use had a reduced NHL risk, although there was little evidence of a linear trend in risk (p-trend = 0.09). Further analyses of total years of use and years since last use of HT combined showed that recent long-term users of HT had a nearly 40 percent reduced risk of NHL compared with women who had never used exogenous hormones (table 3). An association was suggested between long-term and more recent use of HT and risk of all NHL and of DLCL (tables 3 and 4). A decreasing risk of DLCL was associated with older age at last use of HT, with more recent use, and with longer duration of use for women who used HT exclusively (table 4). Risk estimates for follicular lymphoma by characteristics of HT use appeared to differ somewhat from those for DLCL, but confidence intervals were wide. Results did not differ by

TABLE 3. Odds ratios and 95% confidence intervals for exogenous hormone use* associated with all non-Hodgkin lymphoma among women in a population-based case-control study, San Francisco Bay Area, California, 1988–1993†

Characteristics of exogenous hormone use	Controls ($n = 836$)		All cases ($n = 581$)		OR	95% CI
	No.	%	No.	%		
Use of exogenous hormones						
No exogenous hormone use‡	211	25	174	30	1.0§	
Type of exogenous hormones¶						
Non-OC, non-HT only	12	1	8	1	0.83	0.33, 2.1
Menopausal HT only	212	25	163	28	0.96	0.72, 1.3
OCs only	231	28	140	24	0.68	0.49, 0.94
Both OCs and HT	168	20	95	16	0.68	0.49, 0.93
OC use						
Age at first use (years)# (quartiles)						
<21	102	12	51	9	0.45	0.21, 0.97
21–<25	82	10	55	10	0.65	0.32, 1.3
25–<33	104	13	59	10	0.60	0.30, 1.2
≥33	105	13	61	11	0.69	0.37, 1.3
p-trend						0.72
Total years of use**						
<1	90	11	49	9	0.44	0.18, 1.1
1–<5	146	18	90	16	0.54	0.25, 1.2
5–<10	89	11	54	10	0.58	0.27, 1.3
≥10	47	6	29	5	0.51	0.22, 1.2
p-trend						0.61
Calendar year of first use††						
≥1970	112	13	79	14	0.62	0.22, 1.8
<1970	281	34	147	25	0.43	0.15, 1.3
p-trend						0.03
Years since first use (quartiles)#						
<20	89	15	67	17	0.82	0.42, 1.6
20–<25	104	17	67	17	0.67	0.35, 1.3
25–<28	94	16	46	12	0.50	0.24, 1.0
≥28	106	18	46	12	0.43	0.21, .89
p-trend						0.005
Years since last use (quartiles)#						
<14	96	16	71	18	1.5	0.66, 3.4
14–<19.5	87	15	60	15	1.3	0.61, 2.9
19.5–<24	99	17	51	13	0.93	0.46, 1.9
≥24	100	17	41	10	0.68	0.36, 1.3
p-trend						0.005

Table continues

type of HT for the relatively few women who used estrogen alone or who used estrogen plus progestin.

DISCUSSION

This study focused on whether reproductive factors among women and exogenous hormone use are related to risk of NHL and of its common subtypes, DLCL and follicular lymphoma. Our results are consistent with data showing that follicular lymphoma incidence is similar in women and men, whereas DLCL is more common in men. Results indicate that greater exposure to female reproductive hormones, particularly from multiple pregnancies and exogenous hormones, may be associated with a reduced risk of NHL, particularly DLCL. Such

TABLE 3. Continued

Characteristics of exogenous hormone use	Controls ($n = 836$)		All cases ($n = 581$)		OR	95% CI
	No.	%	No.	%		
Menopausal hormone use						
Total years of use						
<1	57	7	50	9	1.1	0.69, 1.6
1–<5	105	13	81	14	0.94	0.66, 1.3
5–<10	66	8	35	6	0.64	0.41, 1.0
≥10	145	17	83	14	0.68	0.48, 0.96
p-trend						0.05
Women exclusively using HT						
Age at first use (years) (quartiles)						
≤41	50	12	36	11	0.88	0.55, 1.4
>41–47	52	12	44	13	1.0	0.66, 1.6
>47–52	55	13	43	13	0.97	0.61, 1.5
>52	53	13	39	12	0.92	0.57, 1.5
p-trend						0.79
Age at last use (years) (quartiles)						
<53	50	12	60	18	1.4	0.95, 2.2
53–<62	52	12	43	13	1.0	0.64, 1.6
62–<68	52	12	26	8	0.60	0.36, 1.0
≥68	56	13	31	9	0.67	0.40, 1.1
p-trend						0.04
Years since last use						
≤1.5	110	26	68	20	0.76	0.53, 1.1
>1.5	100	24	92	28	1.2	0.80, 1.6
p-trend						0.63
Total years of use						
<5	79	19	86	26	1.3	0.92, 1.9
≥5	129	31	72	22	0.68	0.48, 0.98
p-trend						0.09
Total years of use, years since last use						
<5, >1.5	61	15	62	19	1.2	0.82, 1.9
<5, ≤1.5	18	4	23	7	1.6	0.81, 3.0
≥5, >1.5	38	9	27	8	0.87	0.51, 1.5
≥5, ≤1.5	90	22	45	14	0.61	0.40, 0.93

* Oral contraceptives (OCs) and non-OC hormones, including menopausal hormone therapy (HT).
† Odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for age group.
‡ Referent for all analyses.
§ Referent.
¶ Includes OC use; hormone use for menstrual problems, to inhibit lactation, to treat morning sickness.
# Adjusted for age group and total number of years of OC use.
** Adjusted for age group, lifetime number of sexual partners, and age at first use of OCs.
†† Adjusted for age group, lifetime number of sexual partners, age at first use of OCs, and total number of years of OC use.

exposure to estrogen and/or other reproductive hormones may alter immunity and hinder the development of NHL in women.

Inconsistent results have been reported in previously published investigations of the association between exposure to reproductive hormones and risk of NHL in women (23). In most studies, with a few exceptions (3, 9, 10, 22, 24), pooling heterogeneous NHL subtypes likely contributed to the observed inconsistencies in risk estimates. Consistent with

TABLE 4. Odds ratios and 95% confidence intervals for exogenous hormone use* associated with follicular lymphoma and diffuse large-cell lymphoma among women in a population-based case-control study, San Francisco Bay Area, California, 1988–1993†

Characteristics of exogenous hormone use	Controls ($n = 836$)		FL‡ cases ($n = 173$)				DLCL‡ cases ($n = 233$)			
	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Use of exogenous hormones§										
No exogenous hormone use	211	25	49	28	1.0¶		74	32	1.0¶	
Type of exogenous hormones§										
Non-OC, non-HT only	12	1	4	2	1.5	0.46, 4.8	2	1	0.51	0.11, 2.3
Menopausal HT only	163	28	47	27	1.0	0.64, 1.6	59	25	0.88	0.58, 1.3
OCs only	231	28	45	26	0.75	0.46, 1.2	60	26	0.79	0.51, 1.2
Both OCs and HT#	168	20	28	16	0.70	0.42, 1.2	38	16	0.74	0.47, 1.2
OC use										
Age at first use** (years)										
<21	102	12	14	8	0.59	0.18, 1.9	21	9	0.60	0.22, 1.6
21–<25	82	10	24	14	2.1	0.40, 3.0	21	9	0.68	0.26, 1.7
25–<33	104	13	21	12	0.75	0.29, 2.0	26	11	0.72	0.30, 1.7
≥33	105	13	12	7	0.43	0.16, 1.1	26	11	0.84	0.37, 1.9
p-trend						0.21				0.91
Total years of use††										
<5	236	40	44	36	1.2	0.35, 4.4	60	37	0.50	0.16, 1.5
≥5	136	23	28	23	1.5	0.45, 5.0	30	18	0.52	0.18, 1.5
p-trend						0.67				0.52
Calendar year of first use‡‡										
≥1970	112	13	19	16	1.2	0.34, 4.4	37	22	0.64	0.16, 2.6
<1970	281	34	52	43	1.4	0.44, 4.6	57	34	0.35	0.08, 1.5
p-trend						0.48				0.02
Years since first use§§										
<25	193	32	42	35	0.73	0.31, 1.7	58	34	0.90	0.42, 1.9
≥25	200	33	29	24	0.47	0.18, 1.2	36	21	0.49	0.21, 1.2
p-trend						0.27				0.03
Years since last use¶¶										
<19.5	183	31	36	30	0.82	0.29, 2.3	62	37	1.9	0.76, 4.8
≥19.5	199	34	34	29	0.67	0.28, 1.6	31	19	0.71	0.32, 1.5
p-trend						0.26				0.007
Menopausal hormone use										
Total years of use										
<5	162	19	3	19	0.88	0.54, 1.4	53	23	0.93	0.62, 1.4
≥5	211	25	40	23	0.83	0.52, 1.3	38	16	0.50	0.32, 0.78
p-trend						0.42				0.003

Table continues

several earlier reports (3, 24), we found that risk of NHL was somewhat decreased with increasing parity and was not associated with age at menarche (3, 24) or women's age at the birth of their first child (3, 9, 24–26).

Also similar to several prior reports (9, 10, 22, 27–29), the current results provided some evidence of an inverse relation between HT use and NHL, particularly DLCL. In contrast, we found no consistent association between duration of HT use and follicular lymphoma risk, whereas, in the Iowa Women's Health Study, long-term HT use was associated with an increased risk of follicular lymphoma (10). From our results, higher-dose oral contraceptives may be associated with a decreased risk of NHL, particularly DLCL, possibly accounting for the similar relation for all NHL cases. The relation between oral contraceptive use and follicular lymphoma risk was less clear in this study because of the relatively small number of follicular lymphoma cases. With regard to the use of oral contraceptives, our results are

TABLE 4. Continued

Characteristics of exogenous hormone use	Controls ($n = 836$)		FL cases ($n = 173$)				DLCL cases ($n = 233$)			
	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Women exclusively using HT										
Age at first use (years) (quartiles)										
≤41	50	12	12	12	1.0	0.51, 2.1	11	8	0.62	0.31, 1.3
>41–47	52	12	13	14	1.1	0.54, 2.2	14	11	0.76	0.39, 1.5
>47–52	55	13	12	12	0.95	0.47, 1.9	18	14	0.92	0.50, 1.7
>52	53	13	10	10	0.82	0.38, 1.8	15	11	0.80	0.42, 1.5
p-trend						0.69				0.5
Age at last use (years) (quartiles)										
<53	50	12	13	14	1.1	0.57, 2.2	20	15	1.1	0.62, 2.0
53–<62	52	12	11	11	0.92	0.44, 1.9	15	12	0.81	0.43, 1.5
62–<68	52	12	8	8	0.68	0.30, 1.5	11	8	0.59	0.29, 1.2
≥68	56	13	15	16	1.2	0.60, 2.4	10	8	0.49	0.23, 1.0
p-trend						0.92				0.03
Years since last use										
≤1.5	110	26	27	28	1.1	0.62, 1.8	21	16	0.54	0.32, 0.94
>1.5	100	24	20	21	0.87	0.48, 1.6	35	27	1.0	0.61, 1.6
p-trend						0.71				0.71
Total years of use										
<5	79	19	21	22	1.2	0.64, 2.1	33	25	1.2	0.72, 1.9
≥5	129	31	24	26	0.81	0.46, 1.4	23	18	0.50	0.30, 0.85
p-trend						0.51				0.02
Total years of use, years since last use										
<5, >1.5	61	15	11	12	0.77	0.37, 1.6	29	22	1.4	0.79, 2.3
<5, ≤1.5	18	4	10	11	2.4	1.0, 5.5	3	2	0.47	0.14, 1.7
≥5, >1.5	38	9	7	7	0.79	0.33, 1.9	5	4	0.37	0.14, 0.99
≥5, ≤1.5	90	22	17	18	0.81	0.44, 1.5	18	14	0.57	0.32, 1.0

* Oral contraceptives (OCs) and non-OC hormones, including menopausal hormone therapy (HT).
† Odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for age group.
‡ FL, follicular lymphoma; DLCL, diffuse large-cell lymphoma.
§ DLCL data were adjusted for age group and lifetime number of sexual partners. Exogenous hormones includes OC use, HT use, and hormone use to treat menstrual problems, to inhibit lactation, to treat morning sickness.
¶ Referent.
# Includes hormone use for menstrual problems, to inhibit lactation, to treat morning sickness.
** Adjusted for age group, number of years of OC use, and lifetime number of sexual partners.
†† Adjusted for age group, age at first use of OCs, and lifetime number of sexual partners.
‡‡ Adjusted for age group, age at first use of OCs, number of years of OC use, and lifetime number of sexual partners.
§§ Adjusted for age group and age at first use of OCs.
¶¶ FL data were adjusted for age group, number of years of OC use, and lifetime number of sexual partners; DLCL data were adjusted for age group and number of years of OC use.

most consistent with those from a Los Angeles, California, study of women with aggressive intermediate and high-grade NHL, where NHL risk was decreased among women who had ever used oral contraceptives, had used oral contraceptives for 5 years or more, or had used oral contraceptives before 1970 (9). Similar results for ever use of oral contraceptives and with pre–1970 use also have been observed in some (1, 9, 22, 30) but not all (28, 31) studies that evaluated exogenous hormone use among women.

Greater exposure to reproductive hormones during several pregnancies and exogenous hormone use may reduce the risk of NHL by altering several facets of immunity. These include modulating cell-mediated immune (Th1) and antibody-mediated immune (Th2) responses, Th1 and Th2 cytokine production, B-cell lymphopoiesis and survival, and immune cell apoptosis (7). Greater estrogen and progesterone exposures lead to a reduction in B-cell lymphopoiesis, whereas ovariectomy enhances lymphopoiesis

(32–34). Early B-cell precursors appear particularly sensitive to sex steroids, such as estrogen, resulting in decreases in B-cell differentiation and proliferation (5). Oral contraceptives also might reduce lymphomagenesis by altering circulating lymphocytes, including B-cells, and proportions of lymphocyte subsets throughout cycles of oral contraceptive use (35).

Pregnancy represents a complex hormonal state in which nearly every aspect of immune response is modified (36), including sharp increases in estrogen and progesterone, changes in levels of cytokines and growth factors, and modulation of immune cell counts and functions. Estrogen likely has biphasic dose effects; lower levels may enhance, whereas higher levels, such as during pregnancy, may inhibit specific immune activities. These effects are evident in pregnant women with immune disorders, such as lupus and rheumatoid arthritis (37). For example, lupus tends to be predominantly a Th2 response that antagonizes Th1 cells, and lupus tends to flare during pregnancy likely from high estrogen and progesterone levels exacerbating this shift in immune balance (37). In contrast, rheumatoid arthritis tends to be predominantly a Th1 response, and symptoms diminish during pregnancy. Repeated exposure to high levels of estrogen and other reproductive hormones in highly parous women may tip the balance of immune responses to reduce the risk of developing DLCL (7, 37, 38).

To our knowledge, results that showed a reduced NHL risk for recent long-term users of HT are unique to this study and imply a possible detrimental effect of HT on lymphomagenesis. HT may restore Th1/Th2 balance during menopause to reduce NHL risk (39, 40). HT may prevent the menopausal changes in levels of cytokines, such as interleukin-10 (8, 41). It also may lower natural killer cell activity (40) and restore premenopausal proportions of certain subsets of B-cells (42). HT prevents the menopausal increase in interleukin-10, a cytokine that is elevated in NHL patients and is considered a pathogenic factor in NHL. Interleukin-10 suppresses Th1 cytokines and appears to act as an autocrine growth factor that potently stimulates B-cell proliferation and differentiation in B-cell lymphomas (43). Moreover, polymorphisms in the interleukin-10 gene may be associated with NHL risk (44). Interleukin-6 also has garnered much attention, particularly as a potent growth factor cytokine prominent in DLCL and other lymphomas (45). Menopausal estrogen deprivation appears to enhance interleukin-6 production by peripheral blood monocytes (45, 46). Using estradiol also appears to lower interleukin-6 levels substantially in postmenopausal women, compared with premenopausal women or to untreated postmenopausal women (45–47), and may contribute to reduced NHL risk.

The complex interactions among female reproductive hormones, immunity, and lymphomagenesis are not well understood. By distinguishing NHL phenotypes, the modulating effects of reproductive hormones of various doses, duration, timing, and type can be better ascertained (8). New molecular techniques such as gene expression assays are being used to recognize gene expression signatures for the many NHL entities (48, 49) and thus may help to differentiate the subtypes affected by reproductive hormones.

Limitations of the current study need to be considered when interpreting these results. Case-control studies are prone to recall bias and misclassification of exposure data; however, in the current study, recall bias was less likely because most risk factors for NHL are unknown to the general public. To minimize potential biases, controls were recruited by using random digit dialing in the same general population from which the cases arose, and data were gathered by in-person interview. No proxy interviews were conducted. Recall of oral contraceptive use may be less accurate than that of menopausal hormone use because oral contraceptives typically were used in the more distant past. However, controls and cases were matched on age to minimize differential bias due to misclassification. In addition, cue cards with photographs of the hormones and their packaging, along with hormone brand and generic names, were used to assist in recall of specific hormones. Rapid case ascertainment was used to identify cases shortly after diagnosis to minimize loss of cases because of death. However, women with follicular lymphoma and other more aggressive NHL subtypes may have been underrepresented in this study because these women were less likely to be interviewed because they were more likely to have died after diagnosis. Only incident validated cases were included in the study. This study does not directly address the possibility that nonestrogen hormones, such as progesterone and prolactin, might help to explain the observed associations, because few women used nonestrogen sex steroids for HT or other reasons. Interpretation of analyses by type of HT was limited by small sample size.

In summary, this large, population-based study shows that multiple pregnancies and, to some extent, use of HT and high-dose oral contraceptives, are associated with a reduced risk of NHL, particularly DLCL. These results support the hypothesis that exposures to estrogen and/or other reproductive hormones in women may induce favorable immunologic responses that reduce the risk of developing certain NHL subtypes and may help to explain sex differences in risk across subtypes. Further investigation is needed to confirm these results, to better characterize the heterogeneous NHL subtypes, and to better ascertain the underlying mechanisms of reproductive hormones in the pathogenesis of NHL. Large, pooled analyses through consortia such as the International Lymphoma Consortium (InterLymph) are warranted to increase the power to test hypotheses of the association between endogenous and exogenous hormone exposures and NHL and to investigate effects within rare NHL subtypes.

ACKNOWLEDGMENTS

J. S. L. was supported by Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR). Financial support was provided by grant CA45614 and in part by grants CA89745, and CA87014 from the National Cancer Institute, National Institutes of Health.

Conflict of interest: none declared.

REFERENCES

1. Hartge P, Wang SS, Bracci PM, et al. Non-Hodgkin lymphoma. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. 3rd ed. New York, NY: Oxford University Press, 2006.
2. Groves FD, Linet MS, Travis LB, et al. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92:1240–51.
3. Zhang Y, Holford TR, Leaderer B, et al. Menstrual and reproductive factors and risk of non-Hodgkin's lymphoma among Connecticut women. Am J Epidemiol 2004;160: 766–73.
4. Preti HA, Cabanillas F, Talpaz M, et al. Prognostic value of serum interleukin-6 in diffuse large-cell lymphoma. Ann Intern Med 1997;127:186–94.
5. Kincade PW, Medina KL, Payne KJ, et al. Early B-lymphocyte precursors and their regulation by sex steroids. Immunol Rev 2000;175:128–37.
6. Medina KL, Strasser A, Kincade PW. Estrogen influences the differentiation, proliferation, and survival of early B-lineage precursors. Blood 2000;95:2059–67.
7. Lang TJ. Estrogen as an immunomodulator. Clin Immunol 2004;113:224–30.
8. Olsen NJ, Kovacs WJ. Gonadal steroids and immunity. Endocr Rev 1996;17:369–84.
9. Nelson RA, Levine AM, Bernstein L. Reproductive factors and risk of intermediate- or high-grade B-cell non-Hodgkin's lymphoma in women. J Clin Oncol 2001;19:1381–7.
10. Cerhan JR, Vachon CM, Habermann TM, et al. Hormone replacement therapy and risk of non-Hodgkin lymphoma and chronic lymphocytic leukemia. Cancer Epidemiol Biomarkers Prev 2002;11:1466–71.
11. Skibola CF, Bracci PM, Paynter RA, et al. Polymorphisms and haplotypes in the cytochrome P450 17A1, prolactin, and catechol-O-methyltransferase genes and non-Hodgkin lymphoma risk. Cancer Epidemiol Biomarkers Prev 2005;14:2391–401.
12. Holly EA, Gautam M, Bracci PM. Comparison of interviewed and non-interviewed non-Hodgkin's lymphoma (NHL) patients in the San Francisco Bay Area. Ann Epidemiol 2002; 12:419–25.
13. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361–92.
14. Holly EA, Lele C. Non-Hodgkin's lymphoma in HIV-positive and HIV-negative homosexual men in the San Francisco Bay Area: allergies, prior medication use, and sexual practices. J Acquir Immune Defic Syndr Hum Retrovirol 1997;15:211–22.
15. Holly EA, Lele C, Bracci P. Non-Hodgkin's lymphoma in homosexual men in the San Francisco Bay Area: occupational, chemical, and environmental exposures. J Acquir Immune Defic Syndr Hum Retrovirol 1997;15:223–31.
16. Holly EA, Lele C, Bracci PM, et al. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. Am J Epidemiol 1999;150:375–89.
17. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol 2003;158:316–27.
18. Bracci PM, Holly EA. Tobacco use and non-Hodgkin lymphoma: results from a population-based case-control study in the San Francisco Bay Area, California. Cancer Causes Control 2005;16:333–46.
19. Bracci PM, Dalvi TB, Holly EA. Residential history, family characteristics and non-Hodgkin lymphoma, a population-based case-control study in the San Francisco Bay Area. Cancer Epidemiol Biomarkers Prev 2006;15:1287–94.
20. Flick ED, Chan KA, Bracci PM, et al. Use of nonsteroidal antiinflammatory drugs and non-Hodgkin lymphoma: a population-based case-control study. Am J Epidemiol 2006; 164:497–504.
21. Nichols HB, Trentham-Dietz A, Hampton JM, et al. From menarche to menopause: trends among US women born from 1912 to 1969. Am J Epidemiol 2006;164:1003–11.
22. Zhang Y, Holford TR, Leaderer B, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004;15:419–28.
23. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer 2007;120(suppl 12):1–39.
24. Cerhan JR, Habermann TM, Vachon CM, et al. Menstrual and reproductive factors and risk of non-Hodgkin lymphoma: the Iowa women's health study (United States). Cancer Causes Control 2002;13:131–6.
25. Adami HO, Tsaih S, Lambe M, et al. Pregnancy and risk of non-Hodgkin's lymphoma: a prospective study. Int J Cancer 1997;70:155–8.
26. Tavani A, Pregnolato A, La Vecchia C, et al. A case-control study of reproductive factors and risk of lymphomas and myelomas. Leuk Res 1997;21:885–8.
27. Altieri A, Gallus S, Franceschi S, et al. Hormone replacement therapy and risk of lymphomas and myelomas. Eur J Cancer Prev 2004;13:349–51.
28. Beiderbeck AB, Holly EA, Sturkenboom MC, et al. No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands). Cancer Causes Control 2003;14:639–44.
29. Fernandez E, Gallus S, Bosetti C, et al. Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies. Int J Cancer 2003;105:408–12.
30. Schiff D, Suman VJ, Yang P, et al. Risk factors for primary central nervous system lymphoma: a case-control study. Cancer 1998;82:975–82.
31. Cerhan JR, Wallace RB, Folsom AR, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst 1997;89:314–18.
32. Medina KL, Kincade PW. Pregnancy-related steroids are potential negative regulators of B lymphopoiesis. Proc Natl Acad Sci U S A 1994;91:5382–6.
33. Kincade PW, Medina KL, Smithson G, et al. Pregnancy: a clue to normal regulation of B lymphopoiesis. Immunol Today 1994;15:539–44.
34. Kincade PW, Medina KL, Smithson G. Sex hormones as negative regulators of lymphopoiesis. Immunol Rev 1994;137: 119–34.
35. Auerbach L, Hafner T, Huber JC, et al. Influence of low-dose oral contraception on peripheral blood lymphocyte subsets at particular phases of the hormonal cycle. Fertil Steril 2002;78: 83–9.
36. Luppi P. How immune mechanisms are affected by pregnancy. Vaccine 2003;21:3352–7.
37. Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. Science 1999;283:1277–8.
38. Beagley KW, Gockel CM. Regulation of innate and adaptive immunity by the female sex hormones oestradiol and progesterone. FEMS Immunol Med Microbiol 2003;38: 13–22.

39. Pietschmann P, Gollob E, Brosch S, et al. The effect of age and gender on cytokine production by human peripheral blood mononuclear cells and markers of bone metabolism. Exp Gerontol 2003;38:1119–27.
40. Stopinska-Gluszak U, Waligora J, Grzela T, et al. 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 2006;69: 65–75.
41. Deguchi K, Kamada M, Irahara M, et al. Postmenopausal changes in production of type 1 and type 2 cytokines and the effects of hormone replacement therapy. Menopause 2001;8: 266–73.
42. Kamada M, Irahara M, Maegawa M, et al. B cell subsets in postmenopausal women and the effect of hormone replacement therapy. Maturitas 2001;37:173–9.
43. Cortes J, Kurzrock R. Interleukin-10 in non-Hodgkin's lymphoma. Leuk Lymphoma 1997;26:251–9.
44. Rothman N, Skibola CF, Wang SS, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol 2006;7:27–38.
45. Rachon D, Mysliwska J, Suchecka-Rachon K, et al. Effects of oestrogen deprivation on interleukin-6 production by peripheral blood mononuclear cells of postmenopausal women. J Endocrinol 2002;172:387–95.
46. Saucedo R, Rico G, Basurto L, et al. Transdermal estradiol in menopausal women depresses interleukin-6 without affecting other markers of immune response. Gynecol Obstet Invest 2002;53:114–17.
47. Berg G, Ekerfelt C, Hammar M, et al. Cytokine changes in postmenopausal women treated with estrogens: a placebo-controlled study. Am J Reprod Immunol 2002;48:63–9.
48. Savage KJ, Gascoyne RD. Molecular signatures of lymphoma. Int J Hematol 2004;80:401–9.
49. Krause JR, Shahidi-Asl M. Molecular pathology in the diagnosis and treatment of non-Hodgkin's lymphomas. J Cell Mol Med 2003;7:494–512.