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Oral contraceptives, menopausal hormone therapy use and risk of B-cell non-Hodgkin lymphoma in the California Teachers Study

Yani Lu, **Sophia S. Wang**, **Jane Sullivan-Halley**, **Ellen T. Chang**, **Christina A. Clarke**, **Katherine D. Henderson**, **Huiyan Ma**, **Lei Duan**, **James V. Lacey Jr.**, **Dennis Deapen**, and **Leslie Bernstein**
Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, CA (YL, SSW, JSH, KDH, HM, LD, JVL, LB), Cancer Prevention Institute of California, Fremont, CA (ETC, CAC), Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA (DD)

Abstract

We examined oral contraceptive (OC) and menopausal hormonal therapy (MHT) use in relation to risk of B-cell non-Hodgkin lymphoma (NHL). Women under age 85 years participating in the California Teachers Study with no history of hematopoietic cancer were followed from 1995 through 2007. 516 of 114,131 women eligible for OC use analysis and 402 of 54,758 postmenopausal women eligible for MHT use analysis developed B-cell NHL. Multivariable adjusted and stratified Cox proportional hazards models were fit to estimate relative risks (RR) and 95% confidence intervals (95% CI). Ever versus never OC use was marginally associated with lower B-cell NHL risk, particularly among women first using OCs before age 25 years (RR=0.72, 95%CI=0.51-0.99); yet, no duration-response effect was observed. No association was observed for ever versus never MHT use among postmenopausal women (RR=1.05, 95%CI=0.83-1.33) overall, or by formulation (estrogen alone, ET, or estrogen plus progestin, EPT). Among women with no MHT use, having bilateral oophorectomy plus hysterectomy was associated with greater B-cell NHL risk than having natural menopause (RR=3.15, 95%CI=1.62-6.13). Bilateral oophorectomy plus hysterectomy was not associated with risk among women who used ET or EPT. These results indicate that exogenous hormone use does not strongly influence B-cell NHL risk.

Keywords

non-Hodgkin lymphoma; oral contraceptives; menopausal hormonal therapy; hysterectomy; bilateral oophorectomy

Introduction

Non-Hodgkin lymphoma (NHL) is the fifth most commonly diagnosed cancer among US men and women.[1] While the causes of NHL remain elusive, the lower rates of NHL among women compared to men suggest that sex steroid hormones influence NHL etiology.[2] Biological evidence from animals and humans shows that sex steroid hormones, including

Correspondence to: Yani Lu, Ph.D., Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, 1500 East Duarte Road Duarte, CA 91010, Phone: (626) 471-7316; Fax: (626) 471-7308. yalu@coh.org.

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pharmacologic formulations of exogenous hormones, modulate the immune system.[3-6] This evidence suggests that exogenous hormone use may influence lymphomagenesis. Previous studies investigating the effects of exogenous hormone use on NHL risk have yielded inconsistent results that vary by type of exposure and NHL subtype.[7-20]

Four of six case-control studies assessing use of oral contraceptives (OCs) reported a reduced risk of NHL among ever users,[7,9,17,19] but two case-control [12,15]and two cohort studies[8,20] found no association. Reported associations with menopausal hormone therapy (MHT) are also inconsistent and complicated by the secular changes in the formulation of available MHT and patterns of use over the last several decades.[21] Before 1980, almost all MHT use consisted of unopposed estrogen therapy (ET), but MHT use decreased sharply from 1975 to 1980 due to the reports of increased endometrial cancer risk associated with ET.[22,23] The use of ET (among women with hysterectomy) and combined estrogen-plus-progestin therapy (EPT) (among women with an intact uterus) then steadily increased from 1982, with evidence of protective effects of progestin on estrogen-induced endometrial changes, until 2002, when the Women's Health Initiative clinical trial documented an unfavorable risk-benefit profile for MHT use among post-menopausal women.[24] Thereafter, use of both ET and EPT declined precipitously.[25] In addition to the changing patterns of use, different formulations of MHT have been available over time. The separate effects of ET and EPT and differential usage by hysterectomy status are important aspects for investigation but have been pursued in few studies.[17,20]

The California Teachers Study (CTS), a large prospective cohort of women, collected detailed information on MHT use, including formulations used and how estrogen and progestin were combined, as well as detailed information on OC use. We used the CTS data to investigate whether OC use and MHT use, as well as characteristics of menopause, are associated with risk of B-cell NHL overall or with risk of any of the three main B-cell NHL subtypes (diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)).[26]

Material and Methods

Study Population

A detailed description of the CTS has been published elsewhere.[27] Briefly, this prospective study enrolled 133,479 female public school professionals in California in 1995. All participants completed a self-administered baseline questionnaire, which collected information on demographic factors, menstrual and reproductive events, family and personal history of cancer and other diseases, OC and MHT use, and lifestyle factors such as recreational physical activity, diet, smoking, and alcohol use. Use of human subjects in this study was approved by institutional review boards at each participating institution.

We sequentially excluded participants who, at cohort entry, were not California residents (n=8,867), had an unknown cancer history (n=663), had limited their participation to breast cancer research (n=18), had a prior history of a hematologic malignancy (n=536), or were 85 years of age or older (n=2,179). For the analysis of OC use, we further excluded participants with missing information on OC use at cohort entry (n=4,437) and participants who were older than 45 years old when OCs first became commercially available in the market in 1961 (n=2,648). For the analysis of MHT use and characteristics of menopause, we further excluded participants who, at cohort entry, were premenopausal (n=47,928) or perimenopausal (n=6,410), or had unknown menopausal status (n=4,939) or MHT use status (n=6,191). Women reporting progestin use only were also excluded (n=990), as only 4 NHL cases were in this category and much of this use appeared to occur during the women's reproductive years. Thus, a final cohort of 114,131 women was available for the analysis of

OC use and a final cohort of 54,758 women was available for the analysis of MHT use and menopause.

Case Ascertainment and Follow-up

Incident diagnoses of B-cell NHL (International Classification of Diseases for Oncology, third edition [ICD-O-3],[28] morphology codes: 9590, 9591, 9670-9675, 9678-9699, 9727, 9823, 9832, 9835, 9836) were identified through annual linkages with the population-based California Cancer Registry, which has over 99% complete data on new cancer diagnoses statewide. Follow-up of each woman started on the date that she completed her baseline questionnaire and ended on the first of the following events: death; relocation outside of California; diagnosis of B-cell NHL; diagnosis of a T-cell NHL, Hodgkin lymphoma, multiple myeloma, or leukemia other than CLL and prolymphocytic leukemia or December 31, 2007.

During the follow-up period, 516 women were diagnosed with incident B-cell NHL among the 114,131 women eligible for the OC use analysis; this included 137 with DLBCL (ICD-O-3 9678-9680, 9684), 108 with FL (ICD-O-3 9690-9698), and 110 with CLL/SLL (ICD-O-3 codes 9670, 9823). Among 54,758 women eligible for the MHT use analysis, 402 women were diagnosed with incident B-cell NHL; this included 111 with DLBCL, 77 with FL, and 93 with CLL/SLL.

Exposure Assessment

Women were asked whether they had ever taken OCs for one month or longer, whether they were currently taking OCs at cohort entry, their ages at first and last OC use, and the total number of years of OC use (excluding any periods of time when they temporarily stopped OC use). Data were similarly collected for MHT use with additional questions asked on formulation of MHT (estrogen alone or estrogen and progestin combined), days per month of progestin and the method by which MHT was administered (pill, patch, or other). For the purposes of this study we limited exposure to administration by pill or patch.

Information on menopausal status at cohort entry was collected by asking participants if their menstrual periods had stopped permanently and, if so, when the last period occurred and why their periods stopped. Women were then asked whether they had had a hysterectomy or ovary removal surgery (oophorectomy) and, if so, their ages at each procedure. Furthermore, women with oophorectomy were asked to report if part of one, one, or both ovaries were removed. Postmenopausal women were defined as women whose menstrual periods had stopped naturally more than 6 months before cohort entry, or due to bilateral oophorectomy, medication, chemotherapy, or radiation therapy. Women who were older than 55 years and not considered premenopausal or perimenopausal were classified as postmenopausal. Women 55 years or younger at baseline who reported having had a hysterectomy but without bilateral oophorectomy while still premenopausal were classified as having unknown menopausal status and were excluded from MHT analyses.

Statistical Analyses

We used multivariate Cox proportional hazards regression models to compute the hazard rate ratio as a measure of relative risk (RR) with 95% confidence intervals (95% CI), using age in days from cohort entry and age in days at the end of follow-up to define the time scale. All models were stratified by age in years at cohort entry and adjusted for race (non-Hispanic white or other races). We assessed potential confounding risk factors such as family history of lymphoma, prior diagnosis of diabetes, residential neighborhood-level socioeconomic status,[29] smoking status at cohort entry, alcohol consumption one year before cohort entry, age at menarche, height, body mass index (kg/m^2), and number of full-

term pregnancies for all exposures of interest. None of these factors altered risk estimates by >5% and therefore, none were included in the final models. For the analysis of OC use, we examined if menopausal status and MHT use were confounders; in the analysis of MHT use, we examined if OC use and age at first OC use were confounders. These potential confounders were not included in the respective final models because the additional adjustment for the other hormonal exposures did not materially alter the risk estimates.

We examined the effects of age at menopause and type of menopause both by including them as separate variables in the same model and by using a single variable that classified natural menopause and surgical menopause (i.e., bilateral oophorectomy) according to whether menopause occurred before or after age 50 years. The latter variable was included in all models for the analysis of MHT use. All models were further adjusted for formulation of MHT use (never use, ET use only, EPT use only, or both ET and EPT use).

About 80% of women who never used MHT or used only EPT reported having had natural menopause. Among women who used ET only, a high percentage had bilateral oophorectomy (41.6%) or hysterectomy without removal of both ovaries (26.5%)). In our study, almost all women (99.3%) who had bilateral oophorectomy also had hysterectomy. We assessed whether exclusion of women who reported bilateral oophorectomy but did not report hysterectomy (0.7% of women with bilateral oophectomy) affected risk estimate. We found no differences in risk and present risk estimates for all women, but, refer to these women as having had bilateral oophorectomy plus hysterectomy in the results and discussion sections. To disentangle the effect of type of menopause from that of MHT use, we stratified analyses by type of menopause (natural, bilateral oophorectomy plus hysterectomy, or hysterectomy without bilateral oophorectomy) to evaluate the effects of different MHT formulations; we also examined associations with type of menopause stratified by MHT formulation. Age at menopause was assessed in these stratified models as a potential confounder but was not included in the final models as it did not materially alter the risk estimates.

Tests for trend were conducted by fitting ordinal values corresponding to exposure categories and testing whether the slope coefficient differed from zero. Two-sided P-values are reported. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

The mean age at cohort entry was 52.0 years for women in the analytic cohort for evaluation of OC use and 63.1 years for postmenopausal women in the analytic cohort for evaluation of MHT use (Table 1). The average length of follow-up was 11 years for both cohort groups. The mean age at diagnosis ± standard deviation was 68.2 ±11.1 years in the OC cohort (range, 33-89) and 72.9 ± 8.9 years in the MHT cohort (range, 47-92). In the OC use analytic cohort, 62% of the participants were past OC users and 6% were current OC users at the time of cohort entry. In the analytic cohort of MHT use, 57% of the participants were current MHT users and 17% were past MHT users. Women who reported past OC use or current MHT use at cohort entry were more likely to be non-Hispanic white, younger, taller, to have consumed alcohol in the year prior to cohort entry, and to have lower body mass index at cohort entry (Table 1). Even after adjusting for age at cohort entry, women who used OCs in the past were more likely to have ever used MHT and to currently use MHT compared to women who never used OCs. Furthermore, women who were current MHT users were more likely to have started using OCs at an earlier age (data not shown).

Compared to women who reported never using OCs, women who ever used OCs had a marginally decreased risk of B-cell NHL (RR=0.86, 95% CI=0.69-1.06) (Table 2). The decreased risk was more pronounced among women who started OC use at an earlier age (<25 years) (RR=0.72, 95% CI=0.51-0.99), but no trend was observed between risk and duration of use. NHL risk did not differ between women who started OC use before 1970 and those who started thereafter. OC use was not associated with risk of any specific B-cell NHL subtype.

Age at menopause was not associated with risk of B-cell NHL (Table 3). Women who reported having had a bilateral oophorectomy plus hysterectomy had elevated B-cell NHL risk compared to women with natural menopause (RR=1.37, 95% CI= 1.04-1.80); however, this increased risk was attenuated after adjustment for formulation of MHT used (RR=1.20, 95% CI=0.88-1.64). No significant association with age at or type of menopause was observed for the three NHL subtypes evaluated.

MHT users had a similar risk of B-cell NHL when compared to women who had never used MHT (Table 4). No associations with duration of use, formulation, or pattern of MHT use were observed. In analyses by NHL subtype, increased risk of FL was suggested for all MHT use exposures, although none of these associations were statistically significant (Table 4). For DLBCL, risk was marginally elevated; this was most pronounced among ET users, especially current ET users (RR=1.73, 95% 0=0.97-3.07). There was no consistent association between MHT use and the risk of CLL/SLL.

Table 5 shows results from the stratified analyses among women by each type of menopause and each formulation of MHT use. Among women who never used MHT, women with bilateral oophorectomy plus hysterectomy had three-fold greater risk for B-cell NHL than those with natural menopause (RR=3.15, 95% CI=1.62-6.13). However, bilateral oophorectomy plus hysterectomy was not associated with risk among women who ever used MHT. Among women with a bilateral oophorectomy plus hysterectomy, ET users had decreased risk for B-cell NHL compared to women who never used any MHT (RR=0.41, 95% CI=0.21-0.82). Neither ET use alone nor EPT use alone was associated with NHL risk among women with natural menopause (Table 5).

Discussion

In this large cohort of female public school professionals, OC use was associated with a decreased risk of B-cell NHL among women who started OC use before age 25 years. However, the risk did not decline with increasing duration of OC use. We observed no overall association between either ET or EPT and risk of B-cell NHL. We observed a consistently, albeit statistically non-significant elevated risk for FL with all MHT use exposure measures. The risk of B-cell NHL increased by three-fold for women whose menopause was due to bilateral oophorectomy plus hysterectomy and who had never used any MHT; however, no increased risk was observed among women who had ever used ET only or EPT. Among women with a bilateral oophorectomy plus hysterectomy, ET use was associated with a 60% reduced risk. Neither ET nor EPT use was associated with B-cell NHL risk among women with natural menopause.

Our results for the association between OC use and overall B-cell NHL risk are consistent with some, 7,9,17,19 but not all studies.12,15 The only study that examined age at first use of OCs also reported a decreased risk for younger age of OCs initiation.[19] Two studies examined OC use in relation to risk of NHL subtypes; in agreement with our study, no statistically significant association was observed for any subtype.[19,20]

Consistent with previous studies,[9,10,15,19,20] age at menopause was not associated with B-cell NHL risk in our study. However, no prior studies have separated women with bilateral oophorectomy as the cause of menopause from those who had hysterectomy without bilateral oophorectomy prior to menopause. We consider this an important distinction, as the former group of women has no circulating hormones of ovarian origin after the surgery, whereas the latter group of women has at least some ovarian production of hormones after hysterectomy. Results from our study, although based on small numbers of cases, suggest that bilateral oophorectomy plus hysterectomy may be a strong risk factor for NHL among women who never used MHT, and that estrogen supplementation with ET may counter this increased risk.

The association between MHT use and NHL risk has been less consistent in prior studies. The substantial changes in the formulations of available MHT and patterns of use over the last several decades,[21] together with the differences in distributions of types of menopause in different studies may account, in part, for the observed inconsistencies in risk estimates. In the Iowa Women's Health Study Cohort, MHT use increased NHL risk, particularly for nodal, follicular lymphoma.[11] Our data are also suggestive of an increased risk of FL among MHT users.

Of studies on NHL and MHT use conducted to date, only the National Institutes of Health (NIH)–American Association of Retired People (AARP) Diet and Health Study Cohort provided information on MHT formulation (ET and EPT) and hysterectomy status,[20] and few others could account for hysterectomy status or oophorectomy status.[17] The NIH-AARP study, carried out contemporaneously with our study, reported null associations for women with an intact uterus who only used EPT and for women with hysterectomy who only used ET.[20] In a comparable analysis, we assessed the association of ET use with B-cell NHL risk, restricting to women reporting a hysterectomy as the reason for cessation of menses, regardless of whether or not they had bilateral oophorectomy, and observed similar null results (RR=0.80, 95% CI=0.49-1.32) (data not shown). In our study, stratified analyses further demonstrated the null association between MHT use and NHL risk among women with natural menopause or those with hysterectomy defining last menstrual period.

One limitation of our study is the limited number of B-cell NHL cases available for some subgroup analyses such as those by menopausal status or by NHL subtype. Although we observed a decreased risk of B-cell NHL among women with bilateral oophorectomy plus hysterectomy who used ET-only formulations, this finding was based on a small number of NHL patients (n=68), only 10 of whom had not used any MHT. Another limitation of our study is that we considered MHT use up to a single point in time, the date of completion of the baseline survey, and did not consider changes in use or formulation after that time.

Major strengths of our study include its prospective design, an extensive evaluation of OC and MHT use duration and formulation, detailed information on hysterectomy and oophorectomy, comprehensive follow-up procedures, virtually complete ascertainment of cancer outcomes, and the use of the most current WHO Classification system for NHL subtypes.

In summary, we found a modest inverse association of OC use at younger age, and an overall null association of MHT use with B-cell NHL risk. Future research with larger sample sizes and detailed information on hysterectomy and oophorectomy status and MHT formulation will help clarify the role of ET among women with surgical-defined menopause and EPT among women with natural menopause in the development of NHL, and may lead to new insights into the etiology of this disease.

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Table 1

Selected baseline characteristics among eligible women in relation to oral contraceptives (OC) and menopausal hormone therapy (MHT) use at cohort entry in the California Teachers Study, 1995-2007

Characteristic		OC use (%)				MHT use (%)		
	Total n=114,131	Never n=36,244	Past n=71,239	Current n=6,648	Total n=54,758	Never n= 14,077	Past n=9,381	Current n=31,300
Age at cohort entry (years: mean± SD)	52.0±13.2	60.9±13.7	49.0±10.0	34.1±7.1	63.1±9.6	65.3±9.7	67.0±9.5	60.9±8.9
Age-adjusted percentages:								
Race								
Non-Hispanic white	98,690	25.0	71.0	4.0	48,939	23.8	16.1	60.1
All other races/ethnicities	15,441	28.9	66.5	4.6	5,819	33.3	16.7	49.9
First-degree family history of lymphoma								
No	107,697	25.4	70.6	4.0	51,493	24.7	16.2	59.0
Yes	2,983	26.3	70.5	3.2	1,696	22.4	16.7	60.9
Unknown/adopted	3,451	28.3	67.2	4.6	1,569	28.9	14.0	57.1
Alcohol consumption (grams/day								
None	36,104	30.3	66.4	3.4	17,361	29.4	17.3	53.2
< 15	54,153	22.5	73.0	4.5	24,343	22.3	15.3	62.5
≥15	18,203	24.1	72.4	3.5	10,277	22.7	15.9	61.4
Unknown	5,671	30.3	63.9	5.8	2,777	27.1	18.9	54.0
Smoking status								
Never	75,028	26.1	68.9	4.9	31,855	25.8	16.0	58.3
Former	32,610	24.4	73.4	2.4	19,105	22.0	16.5	61.6
Current	5,850	25.2	72.9	2.0	3,474	31.4	16.6	52.0
Unknown	643	28.2	68.2	3.6	324	27.9	15.5	56.6
Height (inches)								
54-61	11,193	32.7	64.4	3.3	6334	27.6	17.7	54.8
62-63	25,197	27.1	69.4	3.5	13047	25.8	17.0	57.2
64-65	33,322	25.1	71.0	3.9	16150	24.0	16.0	60.0
66-67	27,598	24.1	71.6	4.3	12491	23.8	15.8	60.4
>67	16,461	21.7	73.2	5.8	6453	23.4	14.4	62.2

Characteristic		OC use (%)				MHT use (%)		
	Total n=114,131	**Never n=36,244**	**Past n=71,239**	**Current n=6,648**	**Total n=54,758**	**Never n= 14,077**	**Past n=9,381**	**Current n=31,300**
Unknown	360	45.3	51.6	3.1	283	43.9	16.5	39.7
Body mass index (kg/m^2)								
16-24.9	67,048	22.8	72.3	4.9	29,019	22.2	15.1	62.7
25-29.9	27,389	28.2	68.8	3.0	14,861	24.7	17.2	58.1
30-54.9	15,608	28.9	68.6	2.5	7,863	31.2	17.4	51.3
Unknown	4,086	41.2	56.5	2.3	3,015	34.0	18.2	47.8
Number of full-term pregnancies (FTP)								
Never pregnant	23,175	37.8	54.7	7.5	9,479	29.4	16.1	54.4
Pregnant, but no FTP	6,973	16.0	77.6	6.4	2,001	21.8	15.1	63.2
1 FTP	17,661	18.9	76.2	4.9	7,141	25.6	16.0	58.4
2 FTP	37,405	18.4	78.6	3.1	16,539	22.0	15.8	62.2
≥3 FTP	28,012	32.7	65.8	1.5	18,442	24.7	16.6	58.6
Unknown	905	51.6	46.4	2.0	1,156	29.3	17.3	53.5

Table 2

Relative risk (RR) estimates (and 95% confidence intervals (CI)) for the association between oral contraceptives (OC) use and B-cell NHL risk in the California Teachers Study, 1995-2007

		B-cell NHL (n=516)	DLBCL (n=137)	FL (n=108)	(CLL/SLL (n=110)				
OC use	**Person-years**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**
Never use	388,640	273	1.00	68	1.00	49	1.00	58	1.00
Ever use	873,546	243	0.86 (0.69-1.06)	69	1.02 (0.68-1.55)	59	0.87 (0.55-1.38)	52	1.08 (0.69-1.70)
Age at first use (years)									
<25	585,929	105	0.72(0.51-0.99)	29	0.85 (0.44-1.61)	32	0.95 (0.49-1.84)	18	0.99 (0.44-2.20)
≥25	267,491	134	0.92(0.73-1.15)	39	1.08 (0.71-1.66)	25	0.80 (0.47-1.33)	34	1.15 (0.73-1.83)
Duration of use (years)									
<5	396,051	118	0.91 (0.71-1.17)	26	0.82 (0.49-1.38)	29	0.94 (0.55-1.59)	29	1.35 (0.81-2.25)
5-9	270,262	63	0.79 (0.58-1.07)	26	1.35 (0.80-2.28)	13	0.67(0.34-1.31)	13	1.01 (0.52-1.96)
≥10	186,085	57	0.88(0.64-1.19)	14	0.88 (0.48-1.64)	16	1.04(0.56-1.93)	10	0.90 (0.44-1.83)
P-trend			0.21		0.80		0.76		0.77
Year began OC use									
Before 1970	454,875	182	0.86 (0.69-1.08)	54	1.10(0.72-1.68)	38	0.77 (0.47-1.27)	44	1.10(0.69-1.76)
1970 and after	398,544	57	0.87 (0.60-1.26)	14	0.71 (0.34-1.50)	19	1.12(0.55-2.27)	8	1.34(0.58-3.13)

Abbreviations: DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma.

All models adjusted for race.

Table 3

Relative risk (RR) estimates (and 95% confidence intervals (CI)) for the association between menopause and B-cell NHL risk in the California Teachers Study, 1995- 2007

		B-cell NHL (n=402)			DLBCL (n=111)	FL (n=77)		CLL/SLL (n=93)		
Menopause variables	**Person-years**	**n**	**RR (95% CI)**	**RR†(95% CI)**	**n**	**RR†(95% CI)**	**n**	**RR†(95% CI)**	**n**	**RR†(95% CI)**
Age at menopause (years)*										
<44	69,861	37	1.00	1.00	12	1.00	7	1.00	6	1.00
44-46	61,981	32	0.91 (0.56-1.47)	0.91 (0.56-1.47)	9	0.78 (0.33-1.87)	8	1.14(0.41-3.17)	3	0.53 (0.13-2.14)
47-49	93,363	72	1.44(0.95-2.17)	1.45 (0.96-2.19)	14	0.95 (0.43-2.12)	9	0.76 (0.27-2.09)	22	2.59 (1.02-6.52)
50-52	128,544	79	1.08 (0.71-1.64)	1.10(0.72-1.67)	28	1.28 (0.61-2.67)	13	0.75 (0.28-1.97)	15	1.25 (0.47-3.38)
≥53	116,018	86	1.13 (0.75-1.70)	1.15 (0.76-1.75)	26	1.10(0.52-2.32)	18	1.04 (0.41-2.67)	21	1.72 (0.66-4.48)
P-trend			0.75	0.67		0.53		0.90		0.21
Type of menopause*										
Natural	340,200	217	1.00	1.00	63	1.00	42	1.00	48	1.00
Bilateral oophorectomy	116,875	81	1.37 (1.04-1.80)	1.20 (0.88-1.64)	23	1.19(0.66-2.15)	14	0.82 (0.39-1.75)	20	1.59 (0.84-3.01)
Hysterectomy§	70,996	66	1.40 (0.79-2.47)	1.25 (0.70-2.24)	13	1.09 (0.33-3.59)	16	0.68(0.19-2.44)	17	0.91 (0.31-2.66)
Others	49,014	34	1.34(0.85-2.11)	1.34(0.85-2.11)	9	1.45 (0.61-3.42)	5	0.55 (0.16-1.84)	8	0.99 (0.38-2.62)
Type and age (years) at menopause										
Natural, age <50	131,078	69	1.00	1.00	18	1.00	12	1.00	15	1.00
Natural, age ≥50	206,877	146	1.19(0.89-1.59)	1.23 (0.91-1.67)	43	1.37 (0.79-2.40)	30	1.35 (0.69-2.67)	33	1.24(0.67-2.31)
Bilateral oophorectomy, age<50	81,477	59	1.66(1.17-2.36)	1.45 (0.98-2.15)	13	1.17(0.54-2.54)	11	1.33 (0.54-3.27)	14	1.86(0.84-4.10)
Bilateral oophorectomy, age≥50	25,850	14	0.93 (0.52-1.66)	0.82 (0.45-1.51)	9	2.01 (0.87-4.66)	1	0.28 (0.04-2.23)	3	0.89 (0.25-3.17)
Hysterectomy§	70,996	66	1.38 (0.98-1.95)	1.30 (0.90-1.88)	13	0.88 (0.42-1.88)	16	1.53 (0.67-3.51)	17	1.67 (0.79-3.53)
Others	49,014	34	1.38 (0.92-2.09)	1.35 (0.87-2.08)	9	1.41 (0.63-3.15)	5	1.03 (0.36-2.93)	8	1.51 (0.64-3.59)

Abbreviations: ET = unopposed estrogen therapy; EPT = estrogen plus progestin therapy; LBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma

All models adjusted for race.

*Age at menopause and type of menopause were mutually adjusted for each other.

†Models were further adjusted for formulation of MHT use (never use, ET only, EPT only, ET and EPT).

[§]Hysterectomy group includes women had hysterectomy but with part of one, one or both ovaries retained.

Table 4

Relative risk (RR) estimates (and 95% confidence intervals (CI)) for the association between menopausal hormone therapy (MHT) use and B-cell NHL risk in the California Teachers Study, 1995-2007

	B-cell NHL (n=402)			DLBCL (n=111)		FL (n=77)		CLL/SLL (n=93)	
MHT use	**Person-years**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**
Never MHT user	146,753	103	1.00	28	1.00	14	1.00	23	1.00
Ever MHT user	437,188	299	1.05 (0.83-1.33)	83	1.15 (0.73-1.80)	63	1.57 (0.86-2.86)	70	1.06 (0.64-1.74)
MHT use and formulation									
Past ET or EPT	96,456	84	1.15 (0.86-1.55)	17	0.89 (0.49-1.64)	19	1.98 (0.98-3.98)	21	1.21 (0.67-2.21)
Current MHT use	340,732	215	1.02(0.79-1.31)	66	1.30(0.81-2.10)	44	1.41 (0.75-2.66)	49	1.00 (0.59-1.70)
Current ET	166,257	136	1.28 (0.94-1.74)	42	1.73 (0.97-3.07)	25	1.60 (0.74-3.46)	32	1.27 (0.67-2.41)
Current EPT	174,475	79	0.84(0.62-1.13)	24	1.03 (0.59-1.82)	19	1.29 (0.63-2.63)	17	0.80 (0.42-1.53)
Formulation of MHT use									
ET only	184,520	163	1.21 (0.91-1.60)	46	1.35 (0.80-2.29)	33	1.91 (0.94-3.87)	35	1.00 (0.56-1.81)
EPT only	173,279	78	0.88 (0.64-1.20)	21	0.94 (0.52-1.71)	20	1.39 (0.68-2.84)	19	1.01 (0.53-1.92)
ET and EPT	79,390	58	1.07 (0.77-1.49)	16	1.12(0.60-2.11)	10	1.36(0.60-3.13)	16	1.27 (0.66-2.46)
Duration of ET use only (years)									
<5	67,538	57	1.19(0.84-1.67)	14	1.15 (0.59-2.26)	12	2.05 (0.90-4.69)	10	0.88 (0.40-1.91)
5-15	51,260	46	1.24 (0.84-1.83)	14	1.70 (0.83-3.49)	9	1.60(0.61-4.19)	14	1.60 (0.75-3.42)
>15	59,728	56	1.00 (0.67-1.49)	16	1.27 (0.60-2.69)	12	1.94(0.74-5.10)	10	0.68 (0.28-1.63)
P-trend			0.88		0.37		0.25		0.70
Duration of EPT use only (years)									
<5	96,442	42	0.99 (0.67-1.48)	10	0.95 (0.43-2.06)	11	1.78 (0.75-4.25)	10	1.16(0.51-2.66)
≥5	72,817	36	0.80 (0.53-1.20)	11	0.94 (0.45-1.97)	9	1.22 (0.50-2.98)	9	1.05 (0.46-2.41)
P-trend			0.30		0.85		0.61		0.29
Years since last MHT use for past users									
≤5	39,258	25	1.07 (0.68-1.68)	5	0.87 (0.33-2.33)	7	2.06 (0.81-5.24)	5	0.95 (0.35-2.61)
>5	56,844	59	1.17(0.83-1.65)	12	0.89 (0.44-1.81)	12	1.84(0.82-4.13)	16	1.35 (0.68-2.69)

Abbreviations: ET = unopposed estrogen therapy; EPT = estrogen plus progestin therapy; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma

All models adjusted for race, type and age at menopause.

Table 5

Relative risk (RR) estimates (and 95% confidence intervals (CI)) for the association between type of menopause, menopausal hormone therapy (MHT) use and B-cell NHL risk in the California Teachers Study, 1995-2007

	Formulation of MHT use								
	Never used MHT			Used ET only			Used both ET and EPT		
Type of menopause	**Non-cases**	**Cases**	**RR (95% CI)**	**Non-cases**	**Cases**	**RR (95% CI)**	**Non-cases**	**Cases**	**RR (95% CI)**
Natural	11,073	76	1.00	4,481	43	1.00	3,465	29	1.00
Bilateral oophorectomy	498	10	3.15(1.62-6.13)	7,274	58	1.12(0.73-1.72)	2,255	12	1.11 (0.55-2.25)
Hysterectomy[§]	1,091	9	1.12(0.56-2.25)	4,616	48	1.20 (0.79-1.84)	883	9	1.37 (0.64-2.92)
Others	1,132	8	1.30 (0.62-2.72)	755	11	1.71 (0.88-3.32)	623	7	1.63 (0.71-3.74)
	Type of menopause								
Formulation of MHT	**Natural menopause**			**Hysteirectomy[§]**			**Bilateral oophorectomy**		
ET use only	Non-cases	cases	RR (95% CI)	Non-cases	cases	RR (95% CI)	Non-cases	cases	RR (95% CI)
Never	11,073	76	1.00	1,091	9	1.00	498	10	1.00
Ever	4,481	43	1.18(0.80-1.74)	4,616	48	1.24 (0.60-2.54)	7,274	58	0.41 (0.21-0.82)
Past	2,899	29	1.21 (0.78-1.89)	1,096	12	1.27 (0.53-3.04)	1,120	8	0.31(0.12-0.79)
Current	1,582	14	1.13 (0.63-2.00)	3,520	36	1.23 (0.58-2.57)	6,154	50	0.44 (0.22-0.89)
Duration									
<5 years	2,657	25	1.23 (0.78-1.95)	1,126	10	1.18(0.47-2.92)	2,201	14	0.40(0.17-0.94)
5-15 years	937	10	1.25 (0.64-2.44)	1,337	16	1.50 (0.65-3.48)	2,185	17	0.44 (0.20-1.01)
>15 years	721	6	0.87 (0.38-2.04)	1,965	21	1.18(0.53-2.59)	2,696	27	0.43 (0.20-0.90)
P-trend			0.74			0.64			0.14
EPT use only	Non-cases	cases	RR (95% CI)						
Never	11,073	76	1.00						
Ever	12,595	69	1.04 (0.73-1.49)						
Past	2,360	16	1.17(0.68-2.03)						
Current	10,235	53	1.01 (0.69-1.47).						
Duration									

	Formulation of MHT use								
	Never used MHT			Used ET only			Used both ET and EPT		
Type of menopause	Non-cases	Cases	RR (95% CI)	Non-cases	Cases	RR (95% CI)	Non-cases	Cases	RR (95% CI)
<5 years	7,321	36	1.13 (0.74-1.74)						
≥5 years	4,973	33	1.03 (0.67-1.58)						
P-trend			0.83						

Abbreviations: ET = unopposed estrogen therapy; EPT = estrogen plus progestin therapy.

All models adjusted for race.

§Hysterectomy group includes women who had hysterectomy but with part of one, one or both ovaries retained.