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Menopausal estrogen therapy and non-Hodgkin's lymphoma: A *post-hoc* analysis of women's health initiative randomized clinical trial

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Estrogens are important immunomodulators, exerting significant effects on cell proliferation, apoptosis, cytokine production and differentiation of hematopoietic cells. Estrogen receptors are expressed on normal B and T lymphocytes, bone marrow and in leukemia and lymphoma cell lines. Epidemiologic evidence for the association of menopausal hormone use with risk of non-Hodgkin's lymphoma (NHL) has been mixed; however, all of the investigations have been observational. We analyzed the data from Women's Health Initiative hormone therapy trials where conjugated equine estrogens (CEE; 0.625 mg/d) plus medroxyprogesterone acetate (MPA; 2.5 mg/d) ($n = 16,654$) or CEE alone (women with prior hysterectomy) ($n = 10,685$) were tested against placebos and the intervention lasted a median of 5.6 years in the CEE + MPA trial and 7.2 years in the CEE alone trial. During 13 years of follow-up through September 20, 2013 383 incident NHL cases were identified. We used the intent-to-treat approach to calculate incidence rates of NHL, hazards ratios (HR) and 95% confidence intervals (CI) by treatment group. Incidence of NHL was virtually the same in the treatment and placebo groups. The HR was 1.02 (95%CI 0.74–1.39) for CEE alone, 0.98 (95% CI 0.76–1.28) for CEE+MPA, and 1.00 (95% CI 0.82–1.22) for both combined. There were no specific NHL subtypes associated with either type of the treatment, except a marginally decreased risk of plasma cell neoplasms (HR= 0.53 95% CI 0.27–1.03) in the CEE-alone group. These results do not support a role of estrogen alone or combined with progestin in the development of NHL among postmenopausal women.

Lymphoid neoplasms, including lymphoma, myeloma and lymphocytic leukemia, comprise the 5th most commonly diagnosed cancer in the United States,[1] following breast, prostate, lung and colorectal cancers. Although lymphoid neoplasms are clinically and etiologically heterogeneous, to a large extent, severe disruption of immune function has been

Key words: Estrogen, Progestogen, Randomized clinical trial, Lymphoma

Abbreviations: CEE: conjugated equine estrogens; CI: confidence intervals; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HR: hazard ratio; HT: hormone therapy; MPA: medroxyprogesterone acetate; NHL: non-Hodgkin's lymphoma; PCN: plasma cell neoplasm; PLL: prolymphocytic leukemia; RCT: randomized clinical trial; SLL: small lymphocytic lymphoma; WHI: Women's Health Initiative

Conflict of Interest.

Dr. R. Chlebowski reports consultant services for Novartis, Genentech, Amgen, Pfizer, Novo Nordisk and Genomic Health and received honoraria from Novartis and Genentech. Other authors declare no conflicts of interest.

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What's new?

Non-Hodgkin lymphoma (NHL) is linked etiologically to disrupted immune function, and in women, that disruption may be attributed in part to the immunomodulatory activities of estrogens. Here, the relationship between estrogen and NHL was explored in a randomized clinical trial of postmenopausal women on hormone therapy that consisted of either estrogen alone or estrogen plus progesterone. NHL incidence rate was about the same for women taking either form of hormone therapy. Women taking only estrogen experienced a modest reduction in risk of plasma cell neoplasm. Overall, the findings suggest that NHL risk is largely unaffected by estrogens.

found to be a significant risk factor for most subtypes of this malignancy.[2–4]

Investigators have found extensive interactions between the immune and endocrine systems in mammals. Estrogens are important immunomodulators, exerting significant effects on cell proliferation, apoptosis, cytokine production and differentiation of hematopoietic cells.[5–7] Estrogen receptors (both alpha and beta) are expressed on normal B and T lymphocytes, bone marrow, and in leukemia and lymphoma cell lines.[7,8] A consistent clinical observation is that women develop autoimmune diseases much more frequently than men.[7,9,10] Furthermore, epidemiologic studies have demonstrated that a history of autoimmune diseases is a significant risk for the subsequent development of lymphoma and multiple myeloma.[11–13] The sexually distinct patterns of autoimmune diseases have been, at least in part, attributed to sex hormones, particularly estrogens.[5,7,10] Estrogens induce activation-induced deaminase, leading to somatic hypermutation and production of autoantibodies.[5] However, progesterone exert opposite effects to estrogens *in vitro*, particularly at lower physiological levels, whereas the vivo effect of progesterone seems to be more complex, depending on hormone concentrations and other gonadal factors.[14]

Epidemiologic research, both case-control and cohort studies thus far, have generated conflicting results concerning the associations between lymphoid malignancy and exogenous hormone use.[15–23] Results from WHI hormone therapy (HT) trials have revealed differentially increased or decreased risks depending on the types of endpoints assessed.[24] While CEE + MPA and CEE alone treatments have shown similar effects on the conditions in which estrogen has a predominant role, such as bone fractures and gallbladder disease, the addition of progestin made a clear difference in the incidence of several cancers.[24] Herein, we analyzed data from the Women's Health Initiative (WHI) hormonal therapy clinical trials to investigate whether use of exogenous estrogens for an extended period of time increases the risk of non-Hodgkin's lymphoma (NHL) in postmenopausal women and to gain insights concerning the effects of added progestin.

Methods

Study design

Details of the two WHI HT trial designs and outcome adjudication procedures have been published.[24–26] Briefly, 27,347 postmenopausal women aged 50 to 79 years were recruited from 1993 to 1998 at 40 US clinical centers; 16,608 women with a uterus were randomized to oral CEE (0.625 mg/d) plus MPA (2.5 mg/d) (Prempro) or placebo and 10,739 women with a prior hysterectomy were randomized to oral CEE (0.625 mg/d) alone (Premarin) or placebo. The intervention ended on July 7, 2002 for the former and February 24, 2004 for the latter studies, resulting in 3.5–8.5 years (median 5.6 years) and 5–10 years (median 7.2 years) of treatment, respectively. The primary efficacy and safety outcomes of the trial were CHD and invasive breast cancer, respectively. The sample sizes were based on the power to detect these outcomes.[24] Institutional review board approval was obtained at each clinical center and all participants provided written informed consent. For this analysis, women with a history of hematologic malignancies prior to the baseline evaluation ($N = 26$) as well as those with no follow-up data ($N = 92$) were excluded, leaving a total of 27,229 women. Classification of NHL was based on ICDO3 histology codes according to the system proposed by Morton *et al.*[27] and nodal/extra nodal classification was based on ICDO topology codes. Each person's time at risk was calculated as time from randomization to the last documented follow-up as of September 20, 2013, date of their first event of NHL, death, or withdrawal from the study, whichever came first.

Statistical analysis

The primary statistical analysis was performed using time-to-event methods based on the intent-to-treat principle for both treatment groups combined as well as for each hormone treatment. Additional analyses were conducted for major NHL subtypes as well as according to selected patients' characteristics which may affect female hormone levels. Inference on these subgroup analyses rely primarily on tests for interaction. Tests were based on a 1 degree of freedom test for an interaction term of randomization group × dichotomized baseline characteristic. In addition to cumulative analysis through the end of follow-up including the post-intervention period, we performed analysis limited to the intervention phase to rule out dilution of exposure effects.

Kaplan-Meier plots were used to illustrate NHL events over time for each randomized group. Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models that included a minimal set of

Table 1. Clinical and cytological characteristics of incident NHL diagnosed in participants in Hormone Therapy Trials of WHI as of September 20, 2013

	E-alone Trial		E+P Trial		Total	
	Active *N*	Placebo *N*	Active *N*	Placebo *N*	*N*	%
Non-Hodgkin's lymphoma (NHL)	80	80	113	110	383	100.0
Nodal	29	25	41	34	129	33.7
Extra-nodal	49	54	66	73	242	63.2
Unknown	2	1	6	3	12	3.1
B-cell	69	75	102	102	348	90.9
Precursor B-acute lymphoblastic leukemia/lymphoma (B-ALL)	1	2	0	1	4	1.0
CLL/SLL/PLL	13	17	23	23	76	19.8
Mantle cell lymphoma (MCL)	4	0	1	1	6	1.6
Lymphoplasmacytic lymphoma (LPL)/Waldenstrom Macroglobulinemia (WM)	4	1	1	4	10	2.6
Burkitt lymphoma (BL)	0	1	0	1	2	0.5
Follicular lymphoma (FL)	7	11	15	10	43	11.2
Marginal zone lymphoma (MZL)	4	2	6	8	20	5.2
Hairy cell leukemia (HCL)	0	0	1	0	1	0.3
Diffuse large B-cell (DLBCL)	20	14	20	20	74	19.3
Plasma cell neoplasm (PCN)	13	25	32	27	97	25.3
B-NHL, not otherwise specified (NOS)	3	2	3	7	15	3.9
T-cell lymphoma	5	3	2	3	13	3.4
Precursor T-acute lymphoblastic leukemia/lymphoma (T-ALL)	0	0	1	0	1	0.3
Mycosis Fungoides (MF)/Sezary syndrome (SS)	1	2	1	1	5	1.3
Peripheral T cell lymphoma (PTCL)	3	0	0	2	5	1.3
T-prolymphocytic lymphoma (T-PLL)	1	1	0	0	2	0.5
Unknown lineage	6	2	9	5	22	5.7
Precursor acute lymphoblastic leukemia/lymphoma (U-ALL)	0	0	1	0	1	0.3
Lymphoid neoplasm, unknown lineage (U-NHL)	6	2	8	5	21	5.5

WHI: Women's Health Initiative; E: conjugated equine estrogens; P: medroxyprogesterone acetate; SLL: small lymphocytic lymphoma; CLL: chronic lymphocytic leukemia; PLL: prolymphocytic leukemia.

basic covariates, that is, age, randomization status in the WHI dietary modification trial and participation status in the after intervention (extension) phase. Because previous publications from this study clearly demonstrated that the treatment and placebo groups are very well balanced in terms of major risk factors for hormone-related cancer,[25,26] we assessed a limited number of additional covariates specific to NHL, including a past history of rheumatoid arthritis and/or Lupus, corticosteroid use and antiviral and antibiotic use. None of these showed differential distribution over treatment assignment, and thus only the basic covariates were kept in the model. All statistical tests were two-sided and nominal p values of 0.05 or less were regarded as significant. The p values were not adjusted for multiple outcomes, sequential monitoring, or multiple subgroup comparisons due to the large number of tests conducted; therefore, the p values should be interpreted cautiously.

Results

During an average 13 years of follow up, a total of 383 incident cases of NHL were identified, yielding an annual incidence rate of 106 per 100,0000. About one third of the tumors were nodal, arising from lymph nodes, 91% were B-cell origin, 3% were T cell origin, and the rest of unknown lineage. The top three most common subtypes of B-cell lymphoma were plasma cell neoplasm (PCN), small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL)/prolymphocytic leukemia (PLL) and diffuse large B-cell

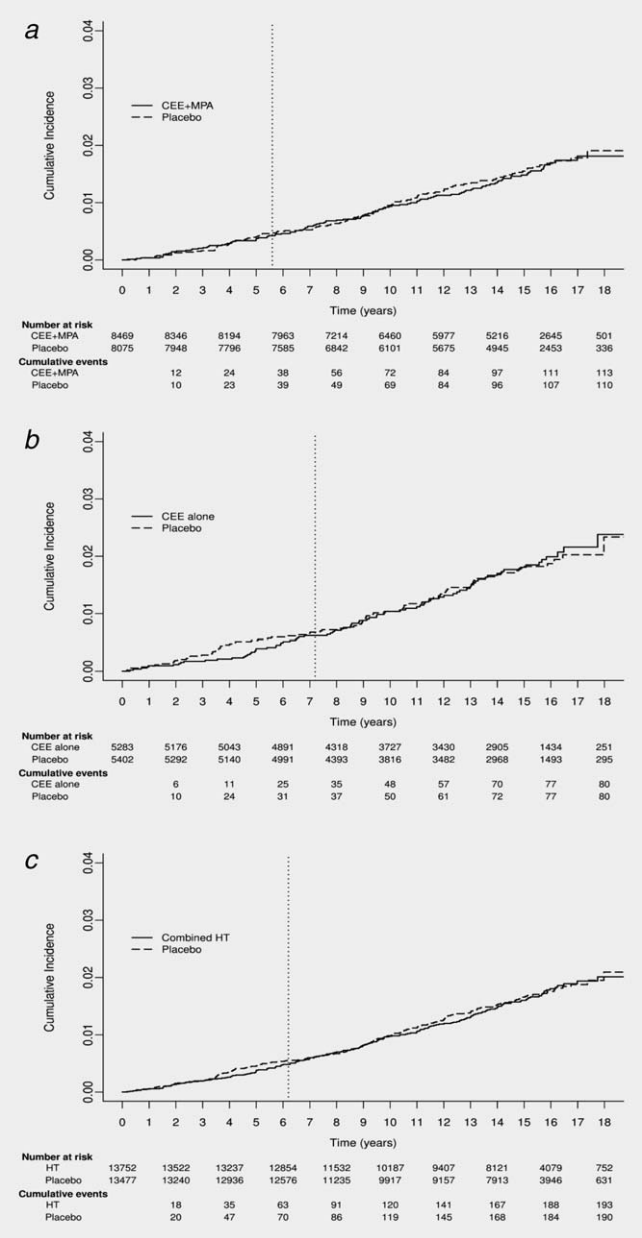

Figure 1. Kaplan-Meier curves for cumulative incidence of NHL by treatment assignment in hormone therapy trials in WHI (solid line: active treatment, broken line: placebo, dotted vertical line: median treatment end time). (*a*) CEE+ MPA trial (median treatment 5.6 years); (*b*) CEE alone trial (median treatment 7.2 years) and (*c*) Combined trial (median treatment 6.2 years).

lymphoma (DLBCL), which comprised approximately two thirds of B-cell lymphoma (Table 1). Among these 383 cases, 144 cases were diagnosed within the intervention period (71 cases from the CEE alone trial and 73 cases from the CEE + MPA trial), resulting in an annual incidence of 85 per 100,000.

For all NHL combined, two cumulative incidence curves for active treatment and placebos were virtually non-separable, regardless of types of treatments, as illustrated in Figure 1, throughout the intervention and post-intervention periods. A minor exception was a transient decrease in the incidence of NHL associated with CEE-alone treatment in the middle of the intervention period (years 4–5). As shown in Figure 2, further analysis to evaluate personal characteristics associated with estrogen exposure did not identify any subgroups with significantly increased or decreased risk of NHL and, therefore, we concluded there were no significant interactions.

HRs adjusted for age, randomization status in the WHI dietary modification trial and participation status in the after intervention (extension) phase were nearly 1.00 for either type of the treatment or both (Table 2). We also estimated the HR for hormonal therapy for each of the major subtypes of B-cell lymphoma, although the number of women with T-cell lymphoma was too small for a separate analysis. When both treatments were combined, there was little variation in the risk associated with NHL subtype. CEE-alone treatment showed a somewhat greater variation in risk by NHL subtypes, that is, a decreased risk of plasma cell neoplasms (HR= 0.53) and an increased risk for diffuse large B-cell lymphoma (HR =1.48), however, these relationships were not statistically significant.

Additional analysis limited to the intervention phase revealed that the HRs for all NHL combined were slightly lower than those from the cumulative analysis, 0.89 (95% CI: 0.56–1.42) for CEE alone, 0.81 (95% CI: 0.51–1.29) for CEE+ MPA and 0.85 (95% CI: 0.61–1.18) for both treatments combined. This slight decrease was primarily accounted for by a decreased risk of plasma cell neoplasms, exclusively seen in the CEE-alone group (HR=0.28, 95% CI 0.09–0.83), whereas the risk of other B-cell lymphoma was not altered by either treatment or both treatments combined (HR = 1.00).

Discussion

The results of the present analysis did not support any appreciable role for female sex hormones at lower physiologic levels (as opposed to higher physiological levels found during pregnancy) in the development of lymphoid malignancies in women. We anticipated that treatment effects should persist even several years after the cessation of the treatment as immune dysregulation was the primary postulated biological mechanism,[2–4] which is likely to act on earlier stages of carcinogenesis rather than as a direct growth stimulatory effect, that is, found for endometrial and breast cancer. Subgroup analyses did not reveal any particular groupings of women who may experience increased or reduced risks of NHL associated with CEE + MPA or CEE alone.

Biologically, effects of estrogens and progestogens on immunological functions are complex. Both exert biphasic effect depending on their concentrations *in vitro*.[10,27] Their effects are generally opposite, particularly at lower physiological levels, on lymphocyte differentiation, survival and proliferation levels.[14] Also, the prescribed hormones in the WHI

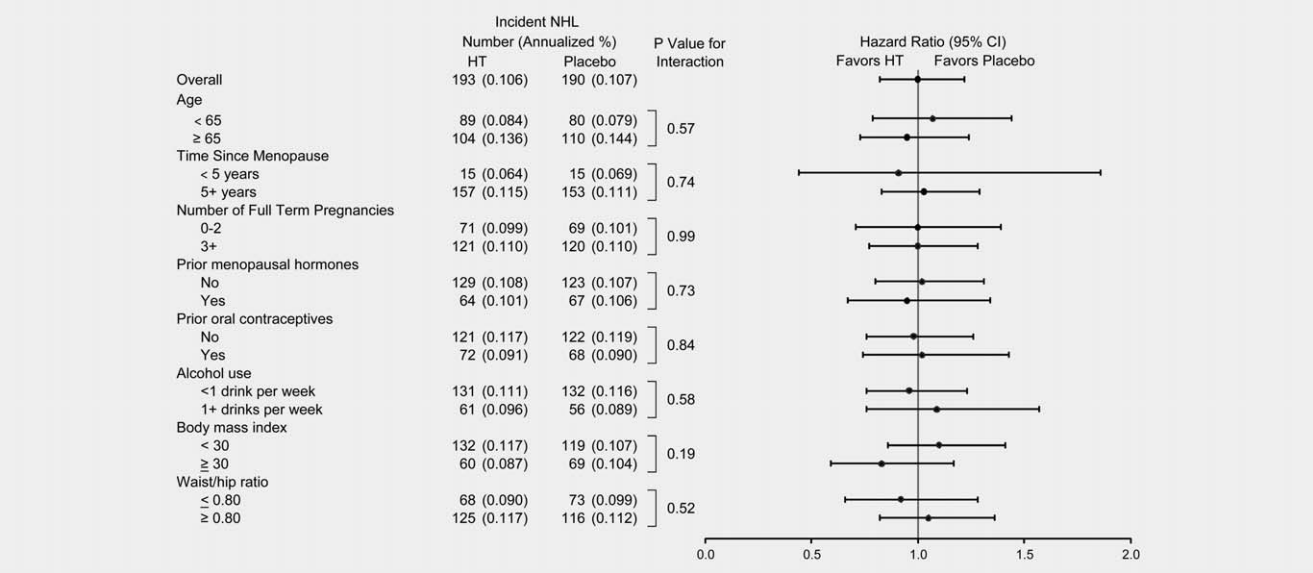

Figure 2. NHL annualized incidence rates (percentages), hazard ratios (HR) and 95% confidence intervals (CI) associated with hormone therapy (HT) combined in subgroups of women in WHI RCT. HRs were adjusted for age, randomization status in the WHI dietary modification trial and participation status in the after intervention (extension) phase.

trials were synthetic or non-human and thus different pharmacological properties were anticipated than what one would expect for endogenous hormone levels. MPA displays higher potencies as androgen and glucocorticoid agonists[28,29] and equine specific estrogens show different affinities to estrogen receptor subtypes,[30] which could complicate the net effect of the intervention.

Consistent with the null results from this study, earlier epidemiologic studies on NHL have reported mixed inconclusive observations concerning associations with reproductive history, which encompassed ages at menarche and first full term pregnancy, numbers of live births, number of pregnancies, and breast-fed children and history of oophorectomy and oral contraceptive use. For most of these factors, associations have been observed in both directions, and significantly increased or decreased risks of NHL from one study were not replicated by others.[15,17–19,31–33] The only exception is an inverse association between parity and NHL, which was reported by more than two studies.[23]

As far as the associations with menopausal hormone use in observational studies are concerned, case-control studies have generally reported decreased risks of NHL among menopausal hormone users, yielding a pooled odd ratio (OR) of 0.70 (95% CI 0.54–0.90) in an international pooled analysis, InterLymph.[20] Conversely, cohort studies have yielded mixed results. Virtually null associations, relative risks (RR) of 0.99 and 1.05, were reported by a Danish population-based retrospective cohort study[16] and by a prospective cohort study among Californian teachers.[18] Significantly increased risks (RR= 1.4–2.2) of overall or subtypes of NHL were found in the Iowa Women's Health Study[17] and in an American Cancer Society Cancer Prevention II cohort.[22] On the other hand, a significantly reduced risk (RR=0.49) of DLBCL among estrogen-only users was observed in the AARP cohort study.[33]

Some investigators postulate that the effects of female sex hormone may differ by subtypes of NHL which is considered to be the most heterogeneous malignancy.[34] Based on sex ratios and age-specific incidence patterns by subtype, it has been hypothesized that estrogen alone or combined with progestin may be positively associated with follicular lymphoma (FL), but inversely with DLBCL.[17,20] Some studies verified the inverse association for DLBCL,[15,33] but in the others the RRs for both subtypes were almost equally increased[22] or decreased.[19] We did not have an *a priori* hypothesis about specific subtypes of NHL associated with hormone therapies, given the limited number of cases available for this analysis. Besides earlier studies have not provided biological mechanisms through which estrogens modulate specific B-cell differentiation steps which lead to the development of respective subtypes of NHL.

Because subtype analyses increase the number of comparisons, caution should be exercised in interpreting our data showing variations in risk by subtype associated with randomization to CEE-alone. The only finding in our study which may deserve follow-up is the inverse association between PCN and CEE-alone treatment. This effect was specifically pronounced in the late intervention period, suggesting transient suppression of precursor progression to PCN[35] during the course of treatment. Substantially reduced risks of multiple myeloma or PCN associated with menopausal hormone use have also been reported in case-control studies from Italy (OR = 0.2, 95% CI 0.1–1.0)[36] and Connecticut (OR = 0.6, 95% CI 0.4–0.99)[21] as well as by a prospective cohort study in the US for estrogen only users (RR = 0.63, 95% CI 0.29–1.37).[33]

Table 2. NHL and its subtype Annualized Incidence Rates (percentages), Hazard Ratios (HR) and 95% Confidence Intervals (CI) Associated with Hormone Therapy (HT) in WHI RCT, based on follow-up through September 2013

	CEE-alone trial					CEE+MPA trial					Combined HT trials				
	CEE-alone ($N = 5,283$)		Placebo ($N = 5,402$)			CEE+ M PA ($N = 8,469$)		Placebo ($N = 8,075$)			Active ($N = 13,752$)		Placebo ($N = 13,477$)		
Outcomes	*n*	(%)	*n*	(%)	HR (95% CI)	*n*	(%)	*n*	(%)	HR (95% CI)	*n*	(%)	*n*	(%)	HR (95% CI)
Mean follow-up time, years	12.9		12.9			13.5		13.4			13.3		13.2		
All NHL	80	(0.117)	80	(0.115)	1.02 (0.74, 1.39)	113	(0.099)	110	(0.101)	0.98 (0.76, 1.28)	193	(0.106)	190	(0.107)	1.00 (0.82, 1.22)
Nodal	29	(0.043)	25	(0.036)	1.18 (0.69, 2.02)	41	(0.036)	34	(0.031)	1.13 (0.72, 1.78)	70	(0.038)	59	(0.033)	1.16 (0.82, 1.63)
Extra-nodal	49	(0.072)	54	(0.078)	0.92 (0.62, 1.35)	66	(0.058)	73	(0.067)	0.85 (0.61, 1.19)	115	(0.063)	127	(0.071)	0.89 (0.69, 1.15)
All B-cell lymphoma	69	(0.101)	75	(0.108)	0.94 (0.67, 1.30)	102	(0.089)	102	(0.094)	0.96 (0.73, 1.26)	171	(0.094)	177	(0.099)	0.95 (0.77, 1.17)
B-cell-lymphoma, excluding plasma cell neoplasms	56	(0.082)	50	(0.072)	1.14 (0.78, 1.67)	70	(0.061)	75	(0.069)	0.89 (0.64, 1.24)	126	(0.069)	125	(0.070)	0.99 (0.77, 1.27)
CLL/SLL/PLL	13	(0.019)	17	(0.024)	0.77 (0.37, 1.58)	23	(0.020)	23	(0.021)	0.94 (0.53, 1.68)	36	(0.020)	40	(0.023)	0.87 (0.56, 1.37)
Follicular lymphoma	7	(0.010)	11	(0.016)	0.64 (0.25, 1.67)	15	(0.013)	10	(0.009)	1.41 (0.63, 3.14)	22	(0.012)	21	(0.012)	1.02 (0.56, 1.85)
DLBCL	20	(0.029)	14	(0.020)	1.48 (0.75, 2.93)	20	(0.018)	20	(0.018)	0.96 (0.52, 1.79)	40	(0.022)	34	(0.019)	1.17 (0.74, 1.85)
Plasma cell neoplasms	13	(0.019)	25	(0.036)	0.53 (0.27, 1.03)	32	(0.028)	27	(0.025)	1.14 (0.68, 1.90)	45	(0.025)	52	(0.029)	0.85 (0.57, 1.27)

NHL: non-Hodgkin's lymphoma; WHI: Women's Health Initiative; RCT; Randomized clinical trial; E: conjugated equine estrogens; P: medroxyprogesterone acetate; SLL: small lymphocytic lymphoma; CLL: chronic lymphocytic leukemia; PLL: prolymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma.

To our knowledge, this is the first study to examine associations among CEE alone and CEE plus MPA use and NHL incidence in a randomized clinical trial setting. Randomized clinical trials could eliminate confounding involved in choice of particular treatments by patients and physicians. Study strengths include the large study population, randomized, placebo-controlled study design, long term follow-up, lymphoma diagnosis verified by medical record review, and the availability of detailed NHL subtype information. There are two other Phase III RCT's using anti-estrogens. The Anastrozole trial yielded a non-significantly reduced risk of leukemia/lymphoma/myeloma among women randomized to Anastrzole (HR = 0.58 0.17–1.97),[37] whereas the corresponding HR in the Tamoxifen trial was 1.58 (95% CI 0.86–2.98).[38] Limitations of the current study include the fact that lymphoma was not a primary monitoring endpoint. The number of cases of NLH was also rather limited and precluded reliable subtype analyses and issues of multiple testing apply for additional endpoints. Finally, each trial tested a single hormonal regimen and thus results do apply to other hormonal formulations, and treatment adherence in the WHI was reported to have declined over time.[39]

In summary, this report representing 13 years of cumulative follow-up demonstrates that standard doses of CEE or CEE + MPA treatment for an average of 5 years in postmenopausal women do not either increase or decrease the risk of NHL. The suggestion of a reduced risk of plasma cell neoplasm with CEE only supplements may warrant further investigation, given the favourable role of estrogens in bone metabolism.[40]

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