

Reproductive factors, exogenous hormone use and risk of B-cell non-Hodgkin lymphoma in a cohort of women from the European Prospective Investigation into Cancer and Nutrition

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Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation Into Cancer and Nutrition; HR, hazard ratio; MM, multiple myeloma; NHL, non-Hodgkin lymphoma

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Abstract

The role of hormonal factors in lymphoid neoplasms etiology remains unclear. Previous studies have yielded conflicting results, been underpowered to assess many lymphoma subtypes, or lacked detailed information on relevant exposures. Within the European Prospective Investigation into Cancer and Nutrition cohort, we analyzed comprehensive data collected at baseline (1992–2000) on reproductive factors and exogenous hormone use among 343,458 women, including 1,427 incident B-cell non-Hodgkin lymphomas (NHL) and its major subtypes identified after a mean follow-up of 14 years (through 2015). We estimated hazard ratios and 95% confidence intervals using multivariable proportional hazards modeling. Overall, we observed no statistically significant associations between parity, age at first birth, breastfeeding, oral contraceptive use or ever use of postmenopausal hormone therapy and risk of B-cell NHL or its subtypes. Women who had a surgical menopause had a 51% higher risk of B-cell NHL (based on 67 cases) compared with natural menopause (hazard ratio=1.51, 95% confidence interval=1.17, 1.94). Given that this result may be due to chance, our results provide little support for the hypothesis that sex hormones play a role in lymphomagenesis.

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of hematologic malignancies, the incidence of which has risen in some western countries since the 1970s, although it seems to have reached a plateau during the last decades. Incidence rates of NHL are higher in men than in women for most NHL subtypes (1). Reproductive hormones interact with the immune system in numerous ways (2,3), and women produce a more vigorous cellular and humoral response than men (4). Increasing evidence suggests a role of estrogens in hematological malignancies (5). While normal human peripheral blood cells express both estrogen receptor (ER) α and ER β , lymphoid neoplasms express and up-regulate ER β (6,7). Furthermore, ER β agonists have been shown to strongly inhibit lymphoma and leukemia growth in mice (8,9).

Although the interaction between the endocrine and immune systems is complex, hormonal influences in NHL etiology seem biologically plausible. However, analyses that have examined the association of reproductive factors on NHL risk have been inconsistent, likely due to study limitations (10), including lack of detailed data on hormonal factors and limited statistical power to examine these associations for NHL subtypes, which may have different etiologies (11). We therefore investigated the role of reproductive factors and exogenous hormone use on risk of B-cell NHL using detailed data from the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

MATERIALS AND METHODS

EPIC is an ongoing multicenter cohort study that recruited 521,324 participants between 1992 and 2000 from 23 centers in 10 European countries. Participants were generally recruited from the general population residing in a geographic area. Exceptions were Utrecht and Florence (women attending breast cancer screening programs), parts of the

Italian and Spanish cohorts (blood donors); most of the Oxford cohort (vegetarian volunteers); and France and Germany (health care insurance organizations). In France, Norway, Utrecht and Naples only women were enrolled (12). At recruitment, participants signed a consent form and information on diet, lifestyle, and anthropometric measurements was collected. Data collection procedures were centralized as a single study with multiple centers. Specific questionnaires for women were used to collect information on menstrual factors, reproductive history, and use of exogenous hormones (12). Participants with prevalent cancer (except non-melanoma skin cancer) and those with missing follow-up information, were excluded (n=29,332). Men were excluded in the present analysis (n=148,007), and those with incomplete information on lifestyle (n=527).

Incident lymphoma cases were identified through population cancer registries, and through active follow-up (through 2015), including use of health insurance records, hospital registries, or direct contacts with participants or next of kin. Initially, lymphoid neoplasms were classified according to the second revision of the International Classification of Disease for Oncology (ICD-O-2) and then later recoded to the latest classification, ICD-O-3, from the WHO classification of tumours of hematopoietic and lymphoid tissue (13). The conversion was made using a program available from the Surveillance Epidemiology and End Results (SEER) webpage (<http://www.seer.cancer.gov/>) and involved a pathology expert and local expertise from participating EPIC centers. Cases with ICD-O-2 codes that could not be translated unequivocally into a lymphoid neoplasm diagnosis according to the WHO classification system, were categorized as lymphoid neoplasm unclassified (“nos”). The classification was further revised by participating centers using the InterLymph Pathology Working Group classification, which is based in the 2008 WHO classification (13). We refer to ‘B-

cell NHL' which is equivalent to 'mature B-cell neoplasms' as defined by the WHO and which includes multiple myeloma (MM) and chronic lymphocytic leukemia/small lymphocytic leukemia in its definition. The total number of cases included 1849 lymphomas, of whom 1,427 were B-cell NHL, 73 T-cell NHL, 80 Hodgkin's lymphoma (HL), and 269 other unclassified subtypes of lymphoma. The 1,427 B-cell NHL cases were further categorized into 302 diffuse large cell lymphoma, 264 follicular lymphoma, 289 chronic lymphocytic leukemia/ small lymphocytic lymphoma, 387 MM and 185 other subtypes of B-cell NHL. Analyses of Hodgkin lymphoma, T-cell neoplasms and the other unclassified lymphoma were not performed owing to small numbers. Thus, the present analyses were based on 343,305 women including 1,427 B-cell NHL cases.

Variables included in the analysis were collected at baseline using standardized questionnaires. These included reported age at menarche, number of full-term pregnancies (FTP), age at first birth, breastfeeding, duration of breastfeed, history and duration of oral contraceptive (OC) use and postmenopausal hormone therapy, menopause status, reported age at natural menopause, oophorectomy, and hysterectomy. For the hormone therapy variables, participants were asked if they had ever used these drugs, the timing of use, their age at start, total duration of use and formulations (estrogen alone, progestin alone, and estrogen + progestin). Self-reported baseline menopausal status was defined as menopausal (natural cessation of menses in the last 12 months or surgical menopause due to bilateral ovariectomy), perimenopausal (no longer naturally menstruating at the time of recruitment or <9 menstrual cycles in the past 12 months), and premenopausal (regular menses or 9 cycles in the past 12 months).

Proportional hazards modeling was used to estimate hazard ratios (HRs) and 95% confidence interval (95%CI) for reproductive factors and risk of B-cell NHL and its major subtypes. Age was used as the underlying time scale and all models were stratified by age

at recruitment (1 year-categories) and study center, and adjusted for education level. Body mass index, physical activity, and smoking status were not included as adjustment covariates because they did not change the risk estimates by more than 10%. The proportional Hazard assumption was checked using graphical methods and a goodness-of-fit test. Additional models were performed to assess the homogeneity of the risk between lymphoma subtypes, by means of the Wald test statistic using the SAS macro %subtype (14). All analyses were performed using SAS v.9.4 (Cary, North Carolina, USA).

RESULTS

The analytic cohort was followed for an average of 14 years, for a total of 4,792,436 person-years. Baseline characteristics of participants are presented in [Web Table 1](#). Overall, age at menarche, parity, breastfeeding ([Table 1](#)), as well as oral contraception, and age at natural menopause ([Table 2](#)) were not statistically significantly associated with B-cell NHL risk.

Surgical menopause was significantly associated with B-cell NHL risk compared with natural menopause (HR=1.51, 95%CI=1.17, 1.94; [Table 2](#)). Accordingly, women who had hysterectomy and oophorectomy had a 28% higher risk of B-cell NHL compared with women who did not (HR=1.26, 95%CI=1.01, 1.56). Associations were more pronounced among women who had bilateral oophorectomy (HR=1.51, 95%CI=1.19, 1.91) than unilateral oophorectomy (HR=0.81, 95%CI=0.59, 1.10 compared with women with intact ovaries; data not shown). Postmenopausal hormone therapy was not associated with B-cell NHL (HR=1.03, 95%CI=0.91, 1.18) overall or by formulation (estrogen alone, progestin alone, or estrogen plus progestin). Among women with no postmenopausal hormone therapy use, having a surgical menopause was still associated with greater B-

cell NHL risk than having natural menopause (HR=1.74, 95%CI=1.19-2.49, data not shown).

No consistent associations were found in the analyses by lymphoma subtype ([Web Table 2](#) and [3](#)). No significant heterogeneity was observed by subtype for any of the potential risk factors evaluated (data not shown). Analyses combining B-cell and T-cell subtypes and censoring MM from the definition of lymphoma are provided in [Web Table 4 and 5](#) for comparability with previous studies, with similar results.

DISCUSSION

In this large prospective cohort analysis, we observed in general null associations with reproductive factors and exogenous hormone use and B-cell NHL, except for a moderate increased risk among women who at baseline reported having had a surgical menopause compared with women who did not. Hysterectomy alone was not associated with B-cell NHL risk, while women with hysterectomy plus oophorectomy (especially bilateral oophorectomy) showed a higher risk of B-cell NHL.

The role of reproductive factors in lymphomagenesis has been controversial. Evidence for the role of hormonal factors in NHL etiology comes mainly from observational data summarized in a systematic review of the literature (10) and randomized data from the Women's Health Initiative trial (15). In summary, regarding observational data, 7 cohort studies (16–25), 13 case–control studies (26–39), and pooled analysis of two consortia of case-control studies (40–42) reported associations between reproductive factors or hormone use and incident lymphoma. Several studies lacked detailed data on hormonal exposures, and counted with heterogeneous definitions of hormonal exposures and lymphoma definitions that hampered the performance of a meta-analysis (10). The present analysis is based on detailed hormonal assessments and it is the third largest

individual study in number of cases after two registry-based studies in Sweden and Denmark, which assessed pregnancy variables and included 1,744 and 1,573 cases, respectively (20,28). Our finding of no associations with parity is consistent with the findings from the pooled analyses from the International Lymphoma Epidemiology Consortium (InterLymph), which included 3,816 cases and 5,151 controls from 18 studies (40). We observed null results with oral contraception, in accordance with previous studies (16,23,24). Postmenopausal hormone therapy has yielded contradictory findings. The protective role of hormone therapy observed in case-control studies (31–33,36,39,42) has not been replicated in cohort studies (16,19,21,24,25). As well, in a systematic review of the literature, we concluded that the association between NHL and postmenopausal hormone therapy probably depends on the formulation and oophorectomy status, which have been rarely assessed (10). When these data were available, associations were derived from unopposed estrogen use, rather than estrogen + progestin, although still with inconsistencies. However, in the present cohort analyses we did not find associations between B-cell NHL and unopposed estrogen use or combined therapy. Randomized data can help disentangling the role of hormone use and lymphoma risk, and avoid biases commonly observed in observational studies (43). In the Women's Health Initiative trial, conjugated equine estrogens plus medroxyprogesterone acetate or conjugated equine estrogens alone were tested against placebo and incidence rates of NHL were calculated by treatment group (15). During the 13 years of follow-up, 27,229 women were randomized to treatments, and 383 incident NHL cases were identified. In this study, incidence of NHL was similar in the treatment and placebo groups, which altogether with our data and other cohort data suggest that hormone therapy is not associated with NHL.

We observed that women with surgical menopause, in particular women with hysterectomy and bilateral oophorectomy, showed a significantly higher risk of B-cell NHL. The ovaries secrete sex hormones, and several studies suggest that women who undergo bilateral oophorectomy have reduced serum concentrations of androgens, rather than estrogens, compared with postmenopausal women with intact ovaries(44,45). However, the steroid metabolism is very complex and in vitro data suggest that androgens could modulate NHL risk in either direction (46,47). Epidemiologic literature on the role of oophorectomy in NHL risk or its subtypes is scarce. In the California Teachers Study cohort, Lu et al observed that women with bilateral oophorectomy had a significant 37% increased risk of NHL compared with women with natural menopause (25), in accordance with our results. In a case-control study evaluating risk factors for MM, surgical menopause by hysterectomy with bilateral oophorectomy was statistically significantly associated with an 85% increased MM risk (38). However, Lee et al found null results for NHL in a population-based case-control, although women with oophorectomy and hysterectomy alone (without oophorectomy) were analyzed together and relevant misclassification of the surgical menopause may occurred (31). Considering our results and the two previous positive findings (25,38), further assessment of bilateral oophorectomy is therefore warranted. However, the association was based on a small number of subjects, and the estimate for unilateral oophorectomy was below one, which hampered the biological interpretation of this exposure. Therefore, this result could simply reflect a type 1 error, given the large number of evaluated factors in the present analyses. Pooled analyses of cohort studies may provide the statistical power needed to corroborate or rule out these associations.

Our study was based on a large dataset with a prospective design and detailed information on reproductive factors and exogenous hormone use, including formulations. In spite our

relatively large sample size, associations on less common exposures among specific lymphoma subtypes relied on small numbers. We had the ability to control for a variety of potential confounders, including education and body mass index, which biased previous studies of hormonal therapy and disease, due to confounding and a healthy user effect (43). However, these variables may imprecisely measure complex factors such as socioeconomic factors or adiposity, and therefore residual confounding cannot completely be ruled out. A concern in this study is that menstrual and reproductive variables were based on self-reported data. However, the reliability of responses to questions on reproductive history, including self-reported oophorectomy and use of hormones, has been shown to be very high (48). Also, information on hormone therapy was not periodically updated, and therefore, we could not evaluate incident users. Importantly, the reported association between B-cell NHL and surgical menopause may be due to chance because we have performed multiple comparisons. In conclusion, our prospective analysis does not support a strong role for reproductive factors or exogenous hormones in lymphomagenesis.

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Table 1. Menstrual and reproductive characteristics collected at baseline and risk of B-cell NHL in the EPIC cohort, 1992–2000.

Characteristic	Person-years	N	HR ^c	95%CI	P-trend
Age at menarche, years					0.65
<12	699,808	191	1.00	Referent	
12	978,186	251	0.92	0.76, 1.11	
13	1,194,471	372	1.06	0.89, 1.27	
14	1,002,365	326	1.02	0.85, 1.23	
>14	741,051	241	0.90	0.74, 1.10	
Missing		46			
Parity, no. of full-term pregnancies					0.82
Nulliparous	706,477	176	1.00	Referent	
1	683,853	207	0.97	0.79, 1.19	
2	1,832,221	516	0.87	0.73, 1.04	
3+	1,244,184	458	1.02	0.85, 1.22	
Missing		70			
Age at first full term pregnancy, years					0.91
<=20	563,887	172	1.00	Referent	
21- 23	1,029,538	319	1.01	0.84, 1.22	
24- 25	760,262	248	1.05	0.86, 1.28	
26- 30	1,112,936	335	0.97	0.80, 1.17	
>30	392,245	125	1.08	0.85, 1.38	
Missing		4			
Breastfeeding ^a					
Never	541,260	138	1.00	Referent	
Ever	3,058,525	984	1.16	0.97, 1.39	
Missing		81			
Duration of breastfeeding ^b					0.41
T1 (≤2 months)	976,473	304	1.00	Referent	
T2 (3- 8 months)	1,005,212	304	0.91	0.77, 1.07	
T3 (≥9 months)	1,044,614	370	1.06	0.90, 1.26	
Missing		6			

a) Among parous women.

b) Among parous women who had ever breastfed.

c) All models were adjusted by center, age and educational level. Numbers do not always add to the total because of missing values.

Abbreviations: CI= confidence interval; EPIC= European Prospective Investigation Into Cancer and Nutrition; HR = hazard ratio; T = Tertile; NHL = non-Hodgkin lymphoma.

Table 2. Exogenous hormone use and menopausal factors collected at baseline and risk of B-cell NHL in the EPIC cohort, 1992–2000.

Characteristic	Person-years	N	HR ^b	95%CI	P-trend
Oral contraceptives use					
Never	1,919,675	687	1.00	Referent	0.16
Ever	2,731,051	706	0.93	0.83, 1.05	
Missing		34			
Duration of oral contraception					
Never	1,919,675	687	1.00	Referent	
T1 (0.2- 3.9 years)	759,811	222	1.02	0.87,1.20	0.16
T2 (4.0- 9.9 years)	879,090	206	0.90	0.76,1.07	
T3 (≥10.0 years)	833,513	220	0.91	0.77,1.07	
Missing		92			
Menopausal status					
Premenopausal	1,693,207	256	1.19	0.92, 1.54	0.83
Perimenopausal	918,876	249	0.93	0.77, 1.13	
Postmenopausal (natural)	2,058,663	855	1.00	Referent	
Surgical postmenopausal	121,690	67	1.51	1.17, 1.94	
Missing		0			
Age at natural menopause, years					
≤45	331,008	132	1.00	Referent	0.83
46- 50	661,418	274	1.03	0.83, 1.27	
>50	595,101	256	1.00	0.80, 1.23	
Missing		193			
Oophorectomy + Hysterectomy ^a					
Neither	3,253,667	885	1.00	Referent	
Oophorectomy	87,407	28	0.97	0.64, 1.42	
Hysterectomy	244,685	105	1.17	0.95, 1.43	
Hysterectomy + oophorectomy	82,879	95	1.26	1.01, 1.56	
Missing		314			
Use of postmenopausal hormone therapy ^a					
Never	1,797,159	657	1.00	Referent	0.11
Ever	1,001,200	427	1.03	0.91, 1.18	
Missing		87			
Duration of postmenopausal hormone therapy					
Never	1,797,159	657	1.00	Referent	
T1 (0.1- 1.25 years)	330,183	115	0.98	0.80, 1.20	0.11
T2 (1.26- 4.0 years)	345,001	123	1.01	0.83, 1.24	
T3 (>4 years)	317,805	136	1.00	0.82, 1.22	
Missing		53			
Type of postmenopausal hormone therapy ^a					
Never	1,797,159	657	1.00	Referent	
Estrogen alone	428,936	137	0.95	0.78, 1.17	
Progestin alone	11,837	5	1.27	0.51, 3.12	
Estrogen + Progestin	290,446	131	1.13	0.92, 1.38	
Missing		241			

a) Among peri- and postmenopausal women (including surgical menopause).

b) All models were stratified by center and age and adjusted by educational level. Numbers do not always add to the total because of missing values.

Abbreviations: CI= confidence interval; EPIC= European Prospective Investigation Into Cancer and Nutrition; HR = hazard ratio; T = Tertile; NHL = non-Hodgkin lymphoma