Original Contribution

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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The role of hormonal factors in the etiology of lymphoid neoplasms remains unclear. Previous studies have yielded conflicting results, have lacked sufficient statistical power to assess many lymphoma subtypes, or have lacked detailed information on relevant exposures. Within the European Prospective Investigation Into Cancer and Nutrition cohort, we analyzed comprehensive data on reproductive factors and exogenous hormone use collected at baseline (1992–2000) among 343,458 women, including data on 1,427 incident cases of B-cell non-Hodgkin lymphoma (NHL) and its major subtypes identified after a mean follow-up period 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 undergone surgical menopause had a 51% higher risk of B-cell NHL (based on 67 cases) than women with natural menopause (hazard ratio = 1.51, 95% confidence interval: 1.17, 1.94). Given that this result may have been due to chance, our results provide little support for the hypothesis that sex hormones play a role in lymphomagenesis.

cohort studies; hormone therapy; hysterectomy; lymphoma; menopause; menstrual factors; oophorectomy; parity

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation Into Cancer and Nutrition; HR, hazard ratio; ICD-O-2, *International Classification of Diseases for Oncology, Second Edition*; NHL, non-Hodgkin lymphoma.

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of hematological 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 few 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 α and estrogen receptor β , lymphoid neoplasms express and up-regulate estrogen receptor β (6, 7). Furthermore, estrogen receptor β agonists have been shown to strongly inhibit the growth of lymphoma and leukemia cells 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 with NHL risk have been inconsistent, probably because of study limitations (10), including lack of detailed data on hormonal factors and limited statistical power to examine these associations for different NHL subtypes, which may have different etiologies (11). We therefore investigated the roles of reproductive factors and exogenous hormone use in risk of B-cell NHL using detailed data from a large cohort study, the European Prospective Investigation Into Cancer and Nutrition (EPIC).

METHODS

EPIC is an ongoing multicenter cohort study that recruited 521,324 participants between 1992 and 2000 from 23 research centers in 10 European countries. Participants were generally recruited from the general population residing in a geographic area. Exceptions were the cities of Utrecht, the Netherlands, and Florence, Italy (women participating in breast cancer screening programs); parts of the Italian and Spanish cohorts (blood donors); most of the Oxford, United Kingdom, cohort (vegetarian volunteers); and participants from France and Germany (health care insurance organizations). In France, Norway, Utrecht, and Naples, Italy, only women were enrolled (12). At recruitment, participants signed a consent form and provided information on diet and lifestyle, and anthropometric measurements were taken. Data collection procedures were centralized as those of 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 nonmelanoma skin cancer) and those with missing follow-up information were excluded ($n = 29,332$). Men ($n = 148,007$) and persons with incomplete information on lifestyle factors ($n = 527$) were excluded from the present analysis.

Incident lymphoma cases were identified through population cancer registries and active follow-up (through 2015), including use of health insurance records, hospital registries, and direct contacts with participants or next of kin. Lymphoid neoplasms were initially classified according to the *International Classification of Diseases for Oncology, Second Edition* (ICD-O-2), and were then later recoded to the *International Classification of Diseases for Oncology, Third Edition*, from the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues (13). The conversion was made using an algorithm available on the Surveillance, Epidemiology, and End Results web page (<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 World Health Organization 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 World Health Organization classification (13). We refer here to “B-cell NHL,” which is equivalent to “mature B-cell neoplasms” as defined by the

World Health Organization and which includes multiple myeloma and chronic lymphocytic leukemia/small lymphocytic leukemia in its definition. The total number of cases included 1,849 lymphomas, of which 1,427 were B-cell NHL, 73 were T-cell NHL, 80 were Hodgkin lymphoma, and 269 were other unclassified subtypes of lymphoma. The 1,427 B-cell NHL cases were further categorized into 302 cases of diffuse large-cell lymphoma, 264 cases of follicular lymphoma, 289 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma, 387 cases of multiple myeloma, and 185 cases of other subtypes of B-cell NHL. Analyses of Hodgkin lymphoma, T-cell NHL, and other unclassified subtypes of lymphoma were not performed owing to small numbers. Thus, the present analyses were based on 343,458 women and 1,427 cases of B-cell NHL.

Information on variables included in the analysis was collected at baseline using standardized questionnaires. These variables included reported age at menarche, number of full-term pregnancies, age at first birth, breastfeeding, duration of breastfeeding, history and duration of oral contraceptive use and postmenopausal hormone therapy, menopausal status, reported age at natural menopause, oophorectomy, and hysterectomy. For the hormone therapy variables, participants were asked whether they had ever used these drugs and about the timing of use, age at starting use, total duration of use, and type of formulation (estrogen alone, progestin alone, or 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 fewer than 9 menstrual cycles in the past 12 months), and premenopausal (regular menses or at least 9 menstrual cycles in the past 12 months).

Proportional hazards modeling was used to estimate hazard ratios and 95% confidence intervals for reproductive factors and risk of B-cell NHL and its major subtypes. Age was used as the underlying time scale, and all models stratified by age at recruitment (1 year-categories) and study center and adjusted for educational 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 hazards assumption was checked using graphical methods and a goodness-of-fit test. Additional analyses were performed by means of the Wald test statistic to assess the homogeneity of the risk between lymphoma subtypes, using the SAS macro %SUBTYPE (SAS Institute, Inc., Cary, North Carolina) (14). All analyses were performed with SAS, version 9.4.

RESULTS

The analytical 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 (available at <https://academic.oup.com/aje>). Overall, age at menarche, parity, and breastfeeding (Table 1), as well as oral contraceptive use 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 as compared with natural menopause (hazard ratio (HR) = 1.51, 95% confidence interval (CI): 1.17, 1.94; Table 2).

Table 1. Risk of B-Cell Non-Hodgkin Lymphoma According to Baseline Menstrual and Reproductive Characteristics, European Prospective Investigation Into Cancer and Nutrition, 1992–2000

Characteristic	No. of Person-Years	No. of Cases ^a	HR ^b	95% CI	P for 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 data		46			
Parity (no. of full-term pregnancies)					0.82
0 (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 data		70			
Age at first full-term pregnancy ^c , 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 data		4			
Breastfeeding ^c					
Never breast-fed	541,260	138	1.00	Referent	
Ever breast-fed	3,058,525	984	1.16	0.97, 1.39	
Missing data		81			
Duration of breastfeeding ^d , months					0.41
≤2 (T1)	976,473	304	1.00	Referent	
3–8 (T2)	1,005,212	304	0.91	0.77, 1.07	
≥9 (T3)	1,044,614	370	1.06	0.90, 1.26	
Missing data		6			

Abbreviations: CI, confidence interval; HR, hazard ratio; T, tertile.

^a Numbers may not sum to totals because of missing values.^b All models stratified the data by center and age and adjusted the results for educational level.^c Among parous women ($n = 1,203$ cases).^d Among parous women who had ever breast-fed ($n = 984$ cases).

Accordingly, women who had undergone both hysterectomy and oophorectomy had a 26% higher risk of B-cell NHL compared with women who had not (HR = 1.26, 95% CI: 1.01, 1.56). Associations were more pronounced among women who had undergone bilateral oophorectomy (HR = 1.51, 95% CI: 1.19, 1.91) than among women who had undergone unilateral oophorectomy (HR = 0.81, 95% CI: 0.59, 1.10), as 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 a 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 Tables 2 and 3). No significant heterogeneity was observed by subtype for any of the potential risk factors evaluated (data not shown). Results of analyses combining B-cell and T-cell subtypes and censoring multiple myeloma from the definition of lymphoma are provided in Web Tables 4 and 5 for comparability with previous studies; results were similar.

DISCUSSION

In this analysis of women from a large prospective cohort study, we generally observed null associations with reproductive

Table 2. Risk of B-Cell Non-Hodgkin Lymphoma According to Baseline Exogenous Hormone Use and Menopausal Factors, European Prospective Investigation Into Cancer and Nutrition, 1992–2000

Characteristic	No. of Person-Years	No. of Cases ^a	HR ^b	95% CI	P for Trend
Oral contraceptive use					
Never use	1,919,675	687	1.00	Referent	
Ever use	2,731,051	706	0.93	0.83, 1.05	
Missing data		34			
Duration of oral contraceptive use, years					0.16
0 (never use)	1,919,675	687	1.00	Referent	
0.2–3.9 (T1)	759,811	222	1.02	0.87, 1.20	
4.0–9.9 (T2)	879,090	206	0.90	0.76, 1.07	
≥10.0 (T3)	833,513	220	0.91	0.77, 1.07	
Missing data		92			
Menopausal status					
Premenopausal	1,693,207	256	1.19	0.92, 1.54	
Perimenopausal	918,876	249	0.93	0.77, 1.13	
Postmenopausal					
Natural	2,058,663	855	1.00	Referent	
Surgical	121,690	67	1.51	1.17, 1.94	
Missing data		0			
Age at natural menopause (<i>n</i> = 855), years					0.83
≤45	331,008	132	1.00	Referent	
46–50	661,418	274	1.03	0.83, 1.27	
>50	595,101	256	1.00	0.80, 1.23	
Missing data		193			
Oophorectomy and hysterectomy status					
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 data		314			
PHT status ^c					
Never use	1,797,159	657	1.00	Referent	
Ever use	1,001,200	427	1.03	0.91, 1.18	
Missing data		87			
Duration of PHT, years					0.11
0 (never use)	1,797,159	657	1.00	Referent	
0.10–1.25 (T1)	330,183	115	0.98	0.80, 1.20	
1.26–4.00 (T2)	345,001	123	1.01	0.83, 1.24	
>4.00 (T3)	317,805	136	1.00	0.82, 1.22	
Missing data		53			
Type of PHT ^c					
Never use	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 data		241			

Abbreviations: CI, confidence interval; HR, hazard ratio; PHT, postmenopausal hormone therapy; T, tertile.

^a Numbers may not sum to totals because of missing values.^b All models stratified the data by center and age and adjusted the results for educational level.^c Among peri- and postmenopausal women (including women with surgical menopause) (*n* = 1,171 cases).

factors and exogenous hormone use and B-cell NHL, except for a moderately increased risk among women who at baseline reported having had a surgical menopause as 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 subject of the role of reproductive factors in lymphomagenesis has been controversial. Evidence for a 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 Clinical Trial (15). In summary, regarding observational data, 7 cohort studies (16–25), 13 case-control studies (26–39), and pooled analysis of 2 consortia of case-control studies (40–42) found associations between reproductive factors or hormone use and incident lymphoma. Several studies lacked detailed data on hormonal exposures and used heterogeneous definitions of lymphoma and hormonal exposures that hampered the performance of a meta-analysis (10). The present analysis was based on detailed hormonal assessments, and it was the third largest individual study in terms of number of cases after 2 registry-based studies carried out in Sweden and Denmark, which assessed pregnancy variables and included 1,744 and 1,573 cases, respectively (20, 28).

Our finding of no association with parity is consistent with findings from the pooled analyses of the International Lymphoma Epidemiology Consortium (InterLymph), which included 3,816 cases and 5,151 controls from 18 studies (40). We observed null results for 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). Additionally, in a systematic review of the literature, we concluded that the association between NHL and postmenopausal hormone therapy probably depends on the formulation used and oophorectomy status, which have been rarely assessed (10). When these data were available, associations were derived from unopposed estrogen use, rather than use of estrogen + progestin, although there were still 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 in disentangling the role of hormone use in lymphoma risk and help to avoid biases commonly observed in observational studies (43). In the Women's Health Initiative Clinical 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 that study, incidence of NHL was similar in the treatment and placebo groups. Together with our data and other cohort data, this suggests that hormone therapy is not associated with NHL.

We observed that women with surgical menopause, particularly women with hysterectomy and bilateral oophorectomy, showed a significantly higher risk of B-cell NHL. The ovaries secrete sex hormones, and several studies have suggested 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, 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. (25) observed that women with bilateral oophorectomy had a significant 37% increased risk of NHL compared with women with natural menopause, in accordance with our results. In a case-control study evaluating risk factors for multiple myeloma, surgical menopause by hysterectomy with bilateral oophorectomy was statistically significantly associated with an 85% increased risk of multiple myeloma (38). However, Lee et al. (31) found null results for NHL in a population-based case-control study, although women with oophorectomy and hysterectomy alone (without oophorectomy) were analyzed together and relevant misclassification of the surgical menopause may occurred. Considering our results and the 2 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 1, which hampered the biological interpretation of this exposure. Therefore, this result could simply reflect type 1 error, given the large number of factors evaluated 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 data set with a prospective design and detailed information on reproductive factors and exogenous hormone use, including formulations. In spite of our relatively large sample size, associations for less common exposures among specific lymphoma subtypes relied on small numbers of cases. We had the ability to control for a variety of potential confounders, including education and body mass index, which biased previous studies of hormone therapy and disease because of 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). In addition, information on hormone therapy was not periodically updated; therefore, we could not evaluate incident use. Importantly, the reported association between B-cell NHL and surgical menopause may have been due to chance, because we 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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