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Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case–control studies

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Background: The two most common forms of non-Hodgkin lymphoma (NHL) exhibit different sex ratios: diffuse large B-cell lymphoma (DLBCL) occurs more frequently in men and follicular lymphoma (FL) more frequently in women. Looking among women alone, this pooled analysis explores the relationship between reproductive histories and these cancers.

Materials and methods: Self-reported reproductive histories from 4263 women with NHL and 5971 women without NHL were pooled across 18 case–control studies (1983–2005) from North America, Europe and Japan. Study-specific odd ratios (ORs) and confidence intervals (CIs) were estimated using logistic regression and pooled using random-effects meta-analyses.

Results: Associations with reproductive factors were found for FL rather than NHL overall and DLBCL. In particular, the risk of FL decreased with increasing number of pregnancies (pooled $OR_{trend} = 0.88$, 95% CI 0.81–0.96). FL was associated with hormonal contraception (pooled OR = 1.30, 95% CI 1.04–1.63), and risks were increased when use started after the age of 21, was used for <5 years or stopped for >20 years before diagnosis. DLBCL, on the other hand, was not associated with hormonal contraception (pooled OR = 0.87, 95% CI 0.65–1.16).

Conclusions: Hormonal contraception is associated with an increased risk of FL but not of DLBCL or NHL overall.

Key words: case–control studies, diffuse large B-cell lymphoma, follicular lymphoma, hormonal contraceptives, non-Hodgkin lymphoma, reproductive history

introduction

Non-Hodgkin lymphoma (NHL) occurs more often in men than women, although within this heterogeneous group of malignancies, some subtypes are more common among women than men [1]. For the two most common NHL subtypes, the sex ratio for diffuse large B-cell lymphoma (DLBCL) is consistent with NHL overall, while follicular lymphoma (FL) has a slight female predominance. The reasons for the differential sex ratios, like the causes of most NHL subtypes, are unclear. NHL has been linked to severe immunosuppression and so factors that affect immune response, such as sex hormones [2], may be involved. For women, a relationship between reproductive history and NHL has been suggested.

Among women, production of sex hormones such as estrogen and progestogen changes with different reproductive stages such as menarche, pregnancy and menopause, or is altered exogenously by the use of hormonal contraception or other hormone treatments. Menstrual and reproductive factors as well as hormonal contraception have been examined with respect to NHL risk, but to date, findings have been equivocal [3–22]. Few studies have reported risks for NHL subtypes [3–7, 11, 22], and generally have been limited by small study size. To investigate the association between NHL and menstrual and reproductive factors, we conducted a pooled analysis of individual data from case–control studies involved in the International Lymphoma Epidemiology Consortium (InterLymph).

materials and methods

Case–control studies with data on reproductive factors were identified through the InterLymph Consortium. Table 1 outlines the studies' designs and more details have been published [4, 7, 11, 13, 15, 23–32]. Eighteen studies conducted between 1983 and 2005 in 10 countries across North America, Europe and Japan contributed data to this pooled analysis. Women with NHL were identified using rapid ascertainment techniques and female controls matched to cases on age were selected from population registers or from among hospital or clinic patients. The appropriate ethical committees approved each study and participants gave their informed consent.

NHL diagnoses were confirmed by pathology reports or samples. Lymphoma codes as described in the International Classification of Diseases for Oncology 3rd edition (ICD-O-3) were of interest in this analysis and included B-cell subtypes of NHL (DLBCL: ICD-O-3 codes 9679/3, 9680/3, 9684/3; FL: 9690/3, 9691/3, 9695/3, 9698/3; chronic lymphocytic leukaemia/small lymphocytic lymphoma: 9670/3, 9823/3; marginal zone lymphoma: 9689/3, 9699/3; mantle cell lymphoma: 9673/3; Burkitt lymphoma: 9687/3, 9826/3; and other unspecified B-cell lymphoma: 9671/3, 9728/3), and T-cell lymphomas as a whole (9700/3, 9701/3, 9702/3, 9705/3, 9708/3, 9709/3, 9714/3, 9716/3, 9717/3, 9718/3, 9719/3, 9729/3, 9827/3) as well as NHL in total (defined by the above ICD-O-3 codes and 9591/3, 9675/3 and 9727/3). These groupings have been used in other InterLymph pooled analyses, and methods to incorporate other classification schemes such as the Working Formulation (used in Connecticut, UCSF, Los Angeles and Northern Italy studies) have been described [33]. The majority of studies did not recruit cases with HIV-associated lymphoma, Hodgkin lymphoma or multiple myeloma, and so these exclusion criteria were applied across the pooled dataset.

Women were asked about their reproductive histories during in-person or telephone interviews, or through self-completed questionnaires. An anonymized dataset was supplied for each study and was checked for inconsistencies before harmonizing variables and coding data uniformly across studies. Details of reproductive histories collected varied by study: the number of children or births was asked in all 18 studies; whether women had ever been pregnant (13 studies); number of pregnancies (7); ages when periods started and stopped (8). Parity was defined as having one or more full-term pregnancies (Los Angeles), live births (Connecticut) or children (all other studies). The woman's age at first birth and the number of years between the last birth and date of diagnosis for cases and date of interview for controls were derived from the children's dates of birth or woman's age at her children's births. When examining the risk of NHL related to parity, analyses were restricted to women aged 40 or older, a group likely to have completed their families. Information on hormonal contraception was collected in 14 studies with all collecting years of use, 13 requested age or year at first use and 11 requested age at last use. Analysis of hormonal contraception was limited to women born in 1925 or later who would be of reproductive age when hormonal contraception first became available [34]. Control distributions of reproductive variables followed the patterns expected; for example, women in southern Europe and Ireland had a greater number of children, and Japanese women tended to be older at menarche than elsewhere. Accordingly, variable categories

Table 1. Characteristics of case–control studies included in the pooled analysis

Study (reference)	Location	Year of diagnosis	Age range	Cases (n = 4263)		Controls (n = 5971)		
				n	Participation (%)	Source	n	Participation (%)
NCI-SEER [23]	Detroit, MI; Iowa; Los Angeles, CA; Seattle, WA, USA	1998–2001	20–70	327	76	If age <65 years selection by RDD; if age ≥ 65 years, random selection from Centers for Medicare and Medicaid Services, stratified by study area, age, sex and race	269	52
Connecticut [11]	Connecticut, USA	1996–2000	21–84	600	72	if age <65 years selection by RDD; if age ≥ 65 years, random selection from Centers for Medicare and Medicaid Services, stratified by age	717	age <65: 69; age ≥65: 47
Nebraska NHL Study [24]	Nebraska, USA	1999–2002	20–75	172	74	RDD, frequency matched by age and sex	254	78
Mayo Clinic Phase 1 [25]	Iowa, Wisconsin, Minnesota, USA	2002–2005	20+	310	66	Random selection from patients at Mayo general medicine clinic, frequency matched by 5-year age group, sex and county of residence	486	70
UCSF [7]	San Francisco, CA, USA	1988–1995	21–74	581	72	RDD, frequency matched by age, sex and county of residence	836	78
Los Angeles Study [13]	Los Angeles County, CA, USA	1989–1992	18–75	177	45	Random neighbourhood control, individually matched on age, race and language	177	~69
British Columbia Study [26]	Vancouver and Victoria, Canada	2000–2004	20–82	346	78	Random selection from Client Registry of the Ministry of Health, frequency matched by age, sex and region	397	46
UK [4]	Yorkshire, Lancashire, South Lakeland and parts of Southwest England	1998–2003	16–69	393	70	Random selection from general practice lists, individually matched by age, sex and region of residence	397	69
EpiLymph [27]	Parts of Ireland, Germany, France, Czech Republic, Spain and Italy	1998–2004	18–80	744	88	Population or hospital controls matched by age (±5 years), sex and study region	1141	63
Ireland [27]	Six hospitals on the east coast of the Republic of Ireland	2001–2003	18–80	55	90	Hospital controls matched by age (±5 years), sex and study region	84	75
Germany [28]	Ludwigshafen/Upper Palatinate, Heidelberg/Rhine-Neckar County, Würzburg/Lower Frankonia, Hamburg, Bielefeld and Munich	1999–2002	18–80	232	88	Random selection from population register, individually matched by sex, age and study region	320	44
France [27]	Amiens, Dijon and Montpellier	2000–2003	18–80	96	91	Hospital controls matched by age (±5 years), sex and study region	139	74
Czech Republic [27]	One centre in Czech Republic	2001–2003	18–80	87	90	Hospital controls individually matched by age (±5 years), sex and study region	138	60
Spain [29]	Barcelona, Tortosa, Reus and Madrid	1998–2002	18–80	181	82	Hospital controls matched by age (±5 years), sex and study region	302	96

Italy [27]	Sardinia	1998–2004	18–80	93	93	Random selection from population census list, matched by age (±5 years), sex and study region	158	66
Northern Italy [15]	Aviano and Milan	1983–1992	17–79	181	>97	Patients admitted for acute, non-neoplastic, non-immunological conditions in the hospitals where cases diagnosed	448	>97
Italy [30]	Aviano and Naples	1999–2002	18–84	105	97	Hospital controls, frequency matched by age (in 5-year bands), sex and study centre to cases of lymphohematopoietic neoplasms	163	91
HERPACC1 [31, 32]	Aichi Cancer Centre, Nagoya, Japan	1988–2000	18–79	173	~99	Random sample of patients not diagnosed with cancer, individually matched by age and sex	364	~99
HERPACC2 [32]	Aichi Cancer Centre, Nagoya, Japan	2001–2004	18–79	154	~99	Random sample of patients not diagnosed with cancer, individually matched by age and sex	322	~99

RDD, random digit dialling.

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Table 2. Characteristics of women included in the pooled analysis

	Cases, *n* (%)	Controls, *n* (%)
NHL subtype	4263 (100)	–
Diffuse large B-cell lymphoma	1354 (32)	–
Follicular lymphoma	1055 (25)	–
Chronic lymphocytic lymphoma/small lymphocytic lymphoma	432 (10)	
Marginal zone B-cell lymphoma	388 (9)	
Other B-cell lymphoma	232 (5)	–
T-cell lymphoma	221 (5)	–
Unclassified	581 (14)	–
Age	4263 (100)	5971 (100)
≤55	1640 (38)	2473 (41)
56–65	1177 (28)	1513 (25)
>65	1446 (34)	1985 (33)
Year of birth	4263 (100)	5971 (100)
Before 1920	234 (5)	324 (5)
1920–1929	933 (22)	1260 (21)
1930–1939	1133 (27)	1493 (25)
1940–1949	979 (23)	1347 (23)
1950–1959	589 (14)	784 (13)
1960 or later	395 (9)	763 (13)
Ethnicity	4263 (100)	5971 (100)
Caucasian	3698 (87)	4974 (83)
Asian	384 (9)	765 (13)
Afro-Caribbean	103 (2)	147 (2)
Mixed, other or not known	78 (2)	85 (1)
Socioeconomic status[a]	3336 (100)	4568 (100)
High	849 (25)	1293 (28)
Medium	1138 (34)	1642 (36)
Low	1338 (40)	1625 (36)
Not known	11 (0.3)	8 (0.2)

[a]Socioeconomic status data were collected from 15 studies (NCI-SEER, Nebraska, Mayo, UCSF, Los Angeles, British Columbia, UK, EpiLymph studies, North Italy and Italy).

were initially defined by the interquartile ranges within each study, but since findings were similar to those based upon uniform categories across all studies, the latter are reported.

A two-stage meta-analysis was carried out. The first stage was to conduct logistic regression to estimate study-specific odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age as a continuous variable and ethnicity grouped as Caucasian or other as potential confounders. In order to include all studies, exact methods were employed where the number of cases and controls in any cell was five or less, and where there were no cases or controls, risks were estimated by adding a half to all cell frequencies. Study-specific risk estimates were then pooled in a meta-analysis using a fixed-effects model where there was no evidence of heterogeneity and a random-effects model when heterogeneity was present. Heterogeneity was tested using Cochrane's *Q* test, statistically significant at $P_{\text{heterogeneity}} < 0.10$, and the amount of heterogeneity was described by the I^2 statistic. Pooled risk estimates for trend were calculated by pooling the study-specific ORs for trend and were based upon the ordinal variables. Sensitivity analyses stratified by covariates such as study design were conducted; meta-analyses were repeated, including risks estimated from cell frequencies of more than five to confirm the stability of the pooled risk estimates. To assess whether findings were influenced by confounding factors, analyses were conducted adjusting study-specific risk estimates for socioeconomic status (high, medium, low), smoking status (never, ever), consumption of alcohol (never, ever) and body mass index (underweight, normal weight-for-height, overweight, obese [35]). Individuals with missing values for reproductive variables were excluded from the relevant analysis. All analyses were conducted using Stata 11.1 (StataCorp LP, College Station, TX, 2010).

results

Data on reproductive factors were pooled from 18 case–control studies and totalled 4263 women with NHL and 5971 controls. The majority of NHLs were B-cell in origin ($n = 3461$, 81%) and 5% ($n = 221$) were T-cell; for 14% ($n = 581$), immunophenotype was unknown (Table 2). DLBCL (32%) and FL (25%) were the most common subtypes, while chronic lymphocytic lymphoma/small lymphocytic lymphoma, marginal zone B-cell lymphoma and other specific subtypes each comprised ≤10% of all NHLs. Almost 85% of cases were Caucasian, ∼70% were born between 1920 and 1949 and the median age at diagnosis was 60 years. Compared with controls, cases tended to be older in age, of white race and of lower socioeconomic status.

Table 3 shows the findings for age at menarche, whether menstrual periods had stopped and the age when periods stopped. Compared with women who reached menarche between the ages of 12 and 14, women who were younger or older at menarche did not have an increased risk of NHL. Pooled risks of NHL were also close to 1 for periods having stopped compared with not, and for periods stopping at younger or older ages relative to stopping between the ages of 45 and 51. Similarly, no associations were found for the two most common subtypes DLBCL and FL (Table 3).

The majority of women aged ≥40 had had at least one pregnancy, and NHL was not associated with ever having been pregnant (pooled risk estimate = 0.97, 95% CI 0.80–1.17) or the number of pregnancies (pooled risk estimate for trend = 0.97, 95% CI 0.91–1.03) when compared with women who had never been pregnant (Table 4). Parity, number of children, age at birth of their first child and number of years since their last birth were also not associated with total NHL. Heterogeneity in risks associated with the number of children was due to two studies showing significant trends in opposite directions; the majority of studies showed no trend. Findings for DLBCL and FL were on the whole similar to those for NHL, although some statistically significant risks of FL were found. For instance, FL risks decreased with increasing number of pregnancies (pooled risk estimate for trend = 0.88, 95% CI 0.81–0.96); however, there was no trend with increasing number of children either in all 18 studies or in the 7 studies which also had data on the number of pregnancies (pooled risk estimate for trend = 0.97, 95% CI 0.91–1.03; pooled risk estimate for trend = 0.95, 95% CI 0.88–1.03, respectively). FL risk was increased among women who had had a child in the 10 years before diagnosis when compared with women who had never had a child (pooled risk estimate = 1.87, 95% CI 1.02–3.40). The risk estimates for gravidity and parity changed little when adjusted for contraception use, socioeconomic status, smoking status, alcohol consumption and body mass index.

Table 3. Associations between non-Hodgkin lymphoma, diffuse large B-Cell Lymphoma, and follicular lymphoma and menstrual histories

	Controls	NHL	Pooled OR[a]	95% CI	I^2	P_{het}	DLBCL	Pooled OR[a]	95% CI	I^2	P_{het}	FL	Pooled OR[a]	95% CI	I^2	P_{het}
Age at menarche[b]	Number of studies = 8															
Total[c]	3733	2497					847					647				
<12	627	424	0.96	0.83–1.10	0%	0.45	159	1.04	0.85–1.28	0%	0.62	114	1.02	0.81–1.28	0%	0.86
12–14	2417	1627	1	ref			555	1	ref			426	1	ref		
≥15	639	408	1.00	0.87–1.16	0%	0.49	122	0.84	0.67–1.06	0%	0.44	96	0.98	0.76–1.27	4%	0.40
Periods stopped[b]	Number of studies = 8															
Total[c]	3074	2091					674					493				
No	918	555	1	ref			189	1	ref			144	1	ref		
Yes	2126	1511	1.15	0.91–1.44	21%	0.26	479	1.18	0.78–1.77	41%	0.11	345	1.02	0.61–1.70	49%	0.06
Age at which periods stopped[b]	Number of studies = 8															
Total[c]	2126	1511					479					345				
<45	512	420	1.16	0.98–1.37	0%	0.90	144	1.28	1.00–1.65	0%	0.81	101	1.28	0.96–1.72	0%	0.77
45–51	980	651	1	ref			203	1	ref			143	1	ref		
≥52	550	380	1.05	0.89–1.24	0%	0.91	115	1.05	0.81–1.36	0%	0.87	87	1.13	0.84–1.52	0%	0.90

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

[a]Pooled ORs adjusted for age and ethnicity were estimated in meta-analysis using a random-effects model; pooled ORs and CIs were similar from a fixed-effects model where the amount of between-study variation in risk (I^2) was low.

[b]Studies with data on periods starting and stopping were Connecticut, Mayo, UK, North Italy, Italy, HERPACC1 and HERPACC2; UCSF had data on age at menarche only, while Los Angeles had information on periods stopping.

[c]Frequencies do not sum to the total due to missing values.

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Table 4. Associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma and reproductive histories among women aged ≥40

	Controls	NHL	Pooled OR[a]	95% CI	I^2	P_{het}	DLBCL	Pooled OR[a]	95% CI	I^2	P_{het}	FL	Pooled OR[a]	95% CI	I^2	P_{het}
Ever pregnant[b]	Number of studies = 13															
Total[c]	3531	2396					793					537				
No	307	199	1	ref			73	1	ref			41	1	ref		
Yes	3163	2137	0.97	0.80–1.17	0%	0.59	702	0.81	0.59–1.13	15%	0.29	481	0.94	0.66–1.33	0%	0.78
Number of pregnancies[d]	Number of studies = 7															
Total[c]	2609	1736					590					417				
None	209	116	1	ref			41	1	ref			28	1	ref		
1	249	166	1.01	0.65–1.56	28%	0.22	60	1.25	0.70–2.22	14%	0.32	46	1.07	0.59–1.92	0%	0.95
2	605	438	1.20	0.91–1.58	0%	0.97	131	0.95	0.63–1.44	0%	0.93	130	1.49	0.94–2.36	0%	0.85
3	585	398	1.09	0.82–1.44	0%	0.80	139	1.00	0.64–1.58	6%	0.38	79	0.93	0.57–1.52	0%	0.64
≥4	885	547	0.98	0.75–1.28	0%	0.72	195	0.92	0.62–1.36	0%	0.52	117	0.82	0.51–1.31	0%	0.97
Trend			0.97	0.91–1.03	20%	0.28		0.95	0.89–1.03	0%	0.68		0.88	0.81–0.96	0%	0.89
Parous[e]	Number of studies = 18															
Total[c]	5151	3816					1162					985				
No	681	489	1	ref			160	1	ref			126	1	ref		
Yes	4463	3322	1.04	0.92–1.18	0%	0.58	1000	0.88	0.71–1.08	14%	0.29	859	1.06	0.86–1.31	0%	0.76
Number of children[e]	Number of studies = 18															
Total[c]	5151	3816					1162					985				
None	681	489	1	ref			160	1	ref			126	1	ref		
1	603	510	1.20	0.99–1.45	12%	0.32	147	0.97	0.71–1.33	22%	0.19	137	1.33	1.00–1.77	0%	0.89
2	1665	1225	1.06	0.92–1.22	0%	0.56	348	0.84	0.65–1.08	18%	0.24	343	1.13	0.90–1.42	0%	0.51
3	1136	833	1.03	0.88–1.20	0%	0.66	251	0.90	0.72–1.14	0%	0.59	200	0.97	0.76–1.25	0%	0.90
≥4	1055	749	1.00	0.82–1.22	28%	0.13	254	0.99	0.78–1.26	0%	0.55	179	1.02	0.78–1.33	0%	0.80
Trend			0.98	0.93–1.02	37%	0.06		0.98	0.93–1.04	0%	0.72		0.97	0.91–1.03	0%	0.90
Age at first child[f]	Number of studies = 15															
Total[c]	4341	3039					982					745				
Nulliparous	563	374	1	ref			132	1	ref			90	1	ref		
<25	2069	1533	1.10	0.94–1.27	0%	0.48	483	0.91	0.70–1.20	24%	0.19	372	1.08	0.83–1.39	0%	0.82
25–29	1161	776	1.02	0.87–1.21	0%	0.54	245	0.86	0.67–1.10	0%	0.60	185	1.05	0.79–1.38	0%	0.83
≥30	506	330	0.96	0.75–1.23	31%	0.12	113	0.87	0.60–1.24	24%	0.19	92	1.16	0.84–1.61	0%	0.57
Trend			0.98	0.91–1.05	31%	0.12		0.95	0.86–1.05	20%	0.24		1.03	0.94–1.13	0%	0.52
Years since last child[g]	Number of studies = 11															
Total[c]	2946	2057					667					521				
Nulliparous	410	260	1	ref			96	1	ref			63	1	ref		
≥30	1427	997	1.11	0.88–1.41	26%	0.20	302	0.83	0.62–1.10	4%	0.41	222	1.10	0.79–1.54	0%	0.63
10–29	990	717	1.10	0.84–1.44	37%	0.10	240	0.90	0.56–1.43	51%	0.02	211	1.23	0.90–1.68	0%	0.91

<10	70	51	1.26	0.82–1.94	0%	0.86	15	1.13	0.60–2.12	0%	1.00	19	1.87	1.02–3.40	0%	0.68
Trend			1.04	0.94–1.15	17%	0.28		0.99	0.84–1.17	31%	0.15		1.14	0.99–1.30	0%	0.94

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

[a]Pooled ORs adjusted for age and ethnicity were estimated in meta-analysis using a random-effects model; pooled ORs and CIs were similar from a fixed-effects model where the amount of between-study variation in risk (I^2) was low.

[b]Studies with data on ever being pregnant were Connecticut, UCSF, Los Angeles, EpiLymph-Ireland, EpiLymph-Germany, EpiLymph-France, EpiLymph-Czech Republic, EpiLymph-Spain, EpiLymph-Italy, Northern Italy, Italy, HERPACC1 and HERPACC2.

[c]Frequencies do not sum to the total due to missing values.

[d]Studies with data on the number of pregnancies were Connecticut, UCSF, Los Angeles, Northern Italy, Italy, HERPACC1 and HERPACC2.

[e]All studies collected data on parity and number of children.

[f]Studies with data on age at first child were Connecticut, Mayo, UCSF, Los Angeles, UK, EpiLymph-Ireland, EpiLymph-Germany, EpiLymph-France, EpiLymph-Czech Republic, EpiLymph-Spain, EpiLymph-Italy, North Italy, Italy, HERPACC1 and HERPACC2.

[g]Studies with data on years since the last child were Mayo, UCSF, UK, EpiLymph-Ireland, EpiLymph-Germany, EpiLymph-France, EpiLymph-Czech Republic, EpiLymph-Spain, EpiLymph-Italy, North Italy and Italy.

Among women born in 1925 or later, ~40% reported having used hormonal contraception (Table 5). Use was not associated with NHL (pooled risk estimate = 0.98, 95% CI 0.83–1.16). Risks were also not increased among women who used hormonal contraception before or after the age of 22 or the year 1975; who used hormonal contraception for ≤5 years or >5 years; nor whose use was current or in the past 10, 20 or more years ago. Pooled risks for DLBCL were largely consistent with those for NHL overall (Figure 1). For FL, study-specific risk estimates mostly ranged from around one- to twofold, and when pooled, gave an increased risk of 1.30 with hormonal contraception use (95% CI 1.04–1.63). FL risk was also increased among women who were aged >22 years at first use (pooled risk estimate = 1.46, 95% CI 1.10–1.92); who first used contraception before 1975 (pooled risk estimate = 1.28, 95% CI 1.02–1.60); who used it for ≤5 years (pooled risk estimate = 1.56, 95% CI 1.19–2.03); and who last used it ≥20 years ago (pooled risk estimate = 1.55, 95% CI 1.02–2.35). Adjusting for the number of pregnancies, the number of children, socioeconomic status, smoking status, alcohol consumption and body mass index did not alter these findings.

discussion

This pooled analysis of InterLymph case–control studies from 10 countries across North America, Europe and Japan found little evidence to support an association between reproductive factors and NHL. The examination of potential risk factors among women limited the number of subjects for most studies to under half those recruited and so when considering NHL subtypes, study-specific ORs were most robust for the two most common, DLBCL and FL. In general, pooled risk estimates for other subtypes, including other B-cell lymphomas and T-cell lymphoma, were similar to those for NHL overall in finding no effect (data not shown). As for exogenous hormones, hormonal contraception was found to increase the risk of FL, while no association was found for DLBCL or NHL overall. Findings were examined further in sensitivity analyses and were found to be consistent whether pooled by continent or population- or hospital-based study design; restricted to studies where the participation rates were ≥70%, or to Caucasians; or adjusted for socioeconomic status, other lifestyle or reproductive factors.

Four studies included in this meta-analysis have reported their findings for menstrual factors [4, 7, 11, 13], 11 for reproductive histories [4, 7, 11, 13, 15, 22] and 9 for hormonal contraception use [7, 11, 13, 22]; the remaining studies are included here for the first time. This dataset comprises most of the available information arising from case–control studies on NHL risk associated with reproductive histories; only four others have published their findings, two on reproductive histories [17, 18] and two on contraception use [19, 21]. Among cohorts or case–control studies nested within cohorts, findings have been reported for menstrual factors in four cohorts [3, 5, 6, 9, 12], reproductive histories in eight [5, 6, 8–10, 12, 14, 16] and contraception in three [3, 5, 20]. When examining the evidence, our findings are in agreement with those published previously for ages at menarche or menopause in showing no association with NHL overall or its subtypes [3,

Table 5. Associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma and hormonal contraception use among women born in 1925 or later

Hormonal contraception	Controls	NHL	Pooled OR[a]	95% CI	I^2	P_{het}	DLBCL	Pooled OR[a]	95% CI	I^2	P_{het}	FL	Pooled OR[a]	95% CI	I^2	P_{het}
Contraception[b]	Number of studies = 14															
Total[c]	3857	2584					787					631				
Never used	2337	1567	1	ref			502	1	ref			327	1	ref		
Ever used	1495	987	0.98	0.83–1.16	33%	0.11	277	0.87	0.65–1.16	43%	0.04	296	1.30	1.04–1.63	7%	0.38
Age first used[d]	Number of studies = 13															
Total[c]	3536	2431					737					584				
Never used	2036	1426	1	ref			456	1	ref			284	1	ref		
≤22	769	451	0.81	0.62– 1.05	44%	0.05	129	0.72	0.48–1.11	50%	0.02	130	1.09	0.82–1.44	0%	0.89
>22	699	510	1.05	0.86–1.28	32%	0.13	139	0.91	0.70–1.18	9%	0.36	157	1.46	1.10–1.92	13%	0.31
Trend			1.01	0.92–1.10	26%	0.18		0.95	0.83–1.10	20%	0.24		1.18	1.04–1.35	9%	0.36
Year first used[d]	Number of studies = 13															
Total[c]	3536	2431					737					584				
Never used	2036	1426	1	ref			456	1	ref			284	1	ref		
>1975	456	277	1.06	0.84–1.34	14%	0.30	94	1.14	0.80–1.62	13%	0.32	71	1.25	0.80–1.95	22%	0.22
≤1975	1012	684	0.92	0.73–1.18	52%	0.02	174	0.78	0.55–1.10	41%	0.06	216	1.28	1.02–1.60	0%	0.47
Trend			0.96	0.87–1.06	38%	0.08		0.91	0.77–1.08	43%	0.05		1.13	1.01–1.27	2%	0.42
Years of use[b]	Number of studies = 14															
Total[c]	3857	2584					787					631				
Never used	2337	1567	1	ref			502	1	ref			327	1	ref		
≤5	797	581	1.13	0.89–1.43	51%	0.01	161	0.99	0.68–1.45	52%	0.01	175	1.56	1.19–2.03	11%	0.33
>5	663	386	0.86	0.73–1.02	0%	0.49	111	0.83	0.64–1.06	0%	0.60	116	1.12	0.86–1.47	0%	0.72
Trend			0.94	0.87–1.02	0%	0.50		0.91	0.80–1.04	9%	0.36		1.09	0.96–1.24	0%	0.47
Years since last used[e]	Number of studies = 11															
Total[c]	2943	2008					606					488				
Never used	1860	1271	1	ref			377	1	ref			260	1	ref		
≥20	408	312	1.06	0.74–1.51	56%	0.01	77	1.00	0.66–1.53	33%	0.14	110	1.55	1.02–2.35	33%	0.15
10–19	282	205	1.10	0.88–1.36	0%	0.77	65	1.07	0.77–1.48	0%	0.93	63	1.34	0.96–1.88	0%	0.79
1–9	184	118	1.08	0.82–1.42	0%	0.59	48	1.39	0.94–2.05	0%	0.70	31	1.34	0.78–2.31	15%	0.30
Current	170	58	0.68	0.48–0.97	0%	0.84	27	1.04	0.65–1.68	0%	0.71	12	0.71	0.39–1.28	0%	0.93
Trend			0.97	0.91–1.04	0%	0.98		1.04	0.95–1.14	0%	0.88		1.04	0.94–1.16	0%	0.93

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

[a]Pooled ORs adjusted for age and ethnicity were estimated in meta-analysis using a random-effects model; pooled ORs and CIs were similar from a fixed-effects model where the amount of between-study variation in risk (I^2) was low.

[b]Studies with data on hormonal contraception use and number of years hormonal contraception was used were Connecticut, Mayo, UCSF, Los Angeles, British Columbia, EpiLymph-Ireland, EpiLymph-Germany, EpiLymph-France, EpiLymph-Czech Republic, EpiLymph-Spain, EpiLymph-Italy, North Italy, Italy and HERPACC2.

[c]Frequencies do not sum to the total due to missing values.

[d]HERPACC2 did not have data on age or year first used contraception.

[e]Mayo, Los Angeles and HERPACC2 did not have data on number of years since last used contraception.

5, 6, 9, 12]. As for reproductive histories, the gravidity and parity variables investigated here have shown little consistent effect in other independent studies [5, 6, 8–10, 12, 14, 16–18]. In one cohort, NHL risks were found to decrease with increasing gravidity and parity [6], with trends suggested not only for FL—as we found for gravidity—but for DLBCL as well. We also found an increased risk of FL among women who had had a child <10 years before diagnosis; no other data were available for direct comparison with one cohort reporting the risks of NHL overall, finding no association [10].

Hormonal contraception does not appear to be linked with the risk of NHL overall [3, 5, 19–21]; for NHL subtypes, associations have been examined less often [3, 5]. Findings varied, with one cohort suggesting decreasing risks of DLBCL with longer use of hormonal contraception but no association for FL [5], and the other reporting no association with either DLBCL or FL [3]. The US women followed in these cohorts may differ from the women studied here with regard to factors such as birth cohort and socioeconomic status, for instance. In our study, risks were increased for FL, particularly for older age or earlier time period at first use; shorter durations of use; and last use at least 20 years before diagnosis. Findings for shorter durations of use may relate to older women of earlier birth cohorts having started contraceptives at older ages. Unfortunately data on contraception formulation were not available, although the majority of women were probably using

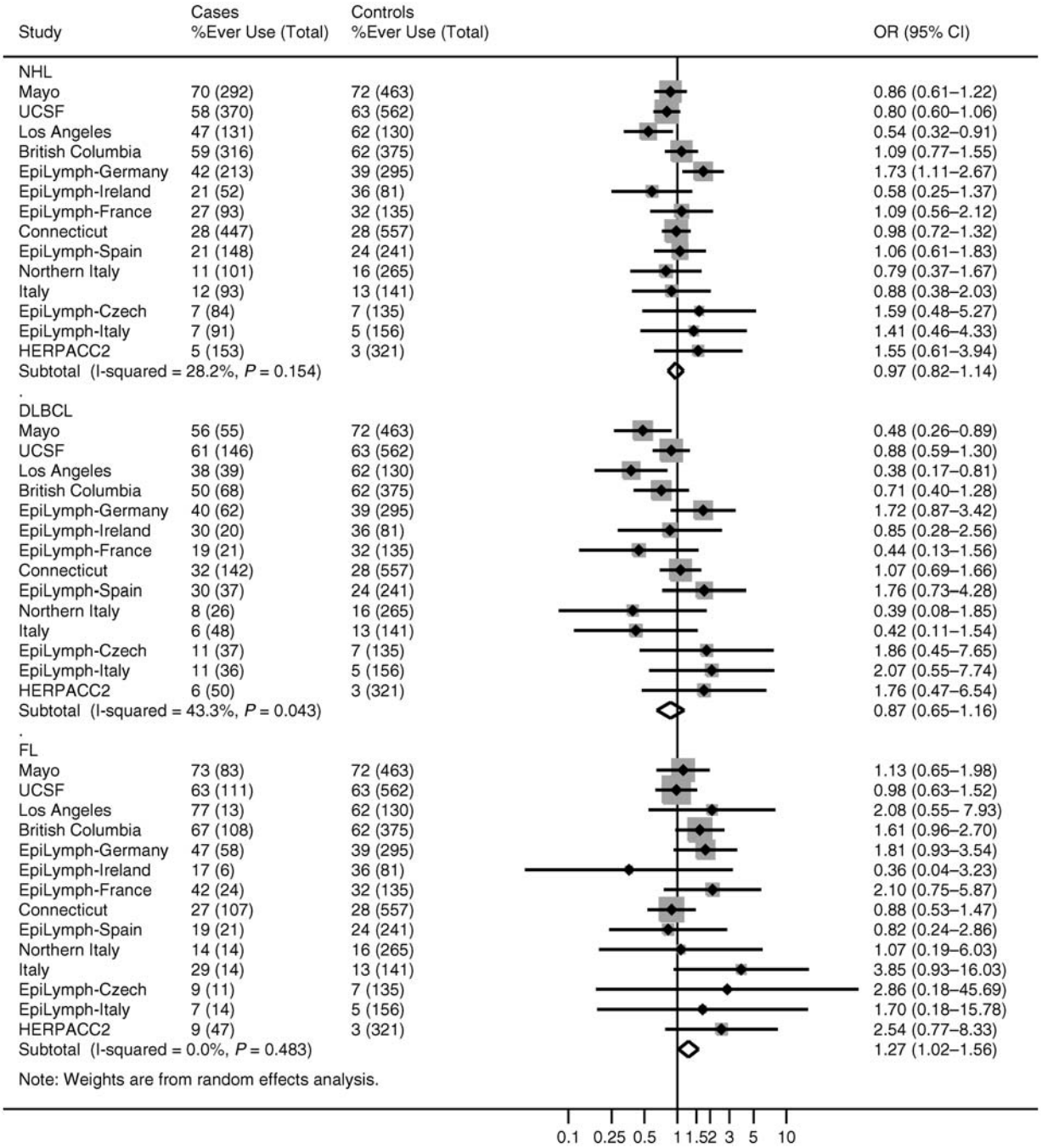

Figure 1. Study-specific associations between non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and hormonal contraception use among women born 1925 or later. Studies are ordered by the percentage of control women who had ever used hormonal contraceptives. NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

estrogen and progestogen rather than progestogen-only contraception. Hormonal contraception was also likely to be taken orally as contraception administered by other routes is rare in the countries of study [34]. As for investigating possible dose–response relationships, the time period of first use was chosen as a surrogate marker for hormone dose, although at around the same time, oral contraception changed from sequential administration of hormones to the combined pill. During the 1970s, estrogen and progestogen levels in the pill were reduced and our findings for FL are consistent with periods when hormone contraception doses were at their highest. Interestingly, we found that FL risk declined as time since last use got closer to diagnosis. As the studies included are contemporaneous, this finding may reflect use during the higher dose era. Nevertheless, to our knowledge, this is the first study of NHL that has considered the time before diagnosis that hormonal contraception was used. Its effect has been examined for breast cancer where a similar pattern has been reported among women diagnosed at ages akin to the majority of our FL cases (i.e. after the age of 50) [36].

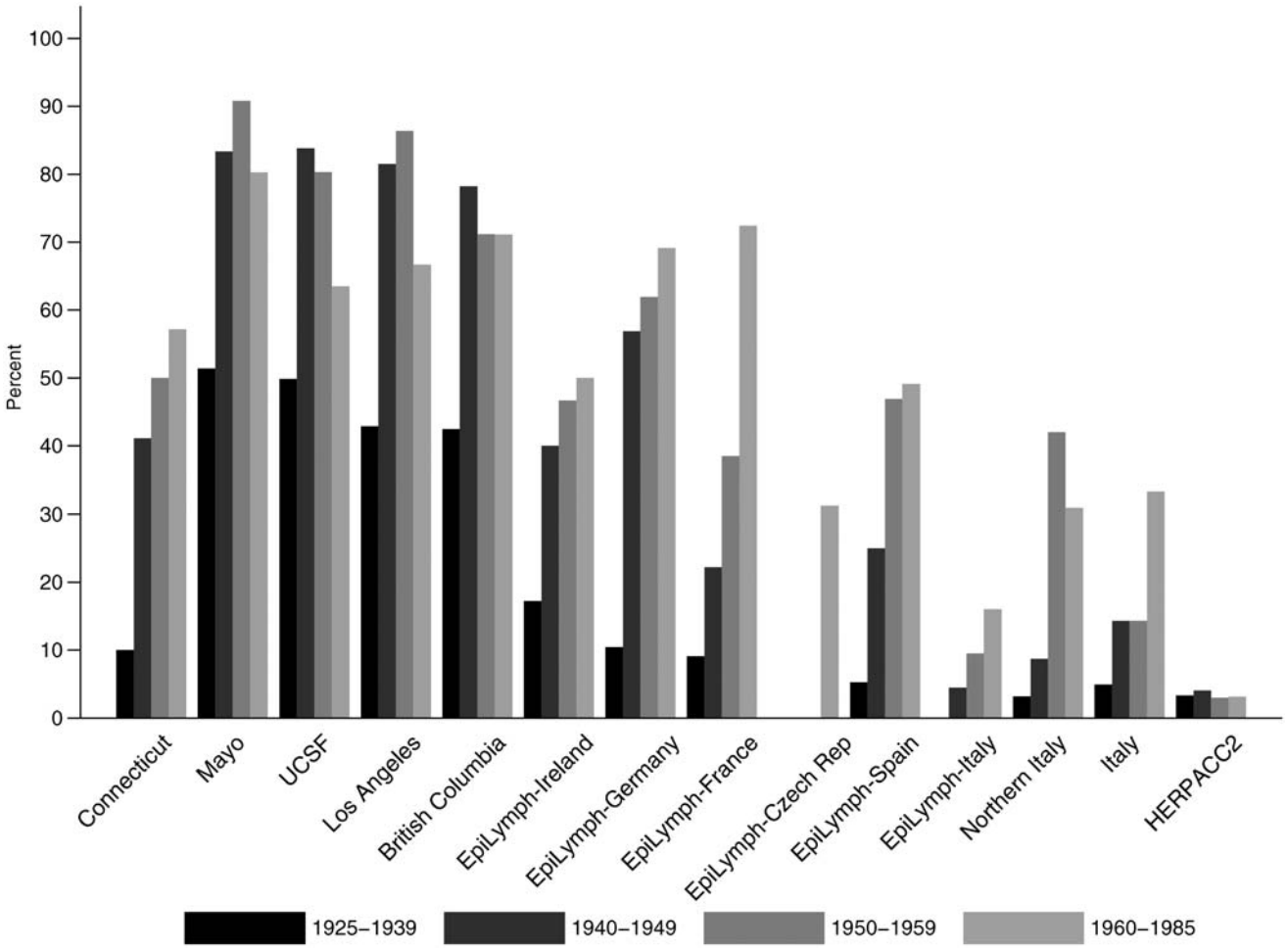

Figure 2. Percent of control women who had ever used hormonal contraception by study and birth cohort. Shading of the bars reflects the birth cohort distribution, where >40% of women were born before 1940, >25% in the 1940s and ∼15% in each of the other two time periods.

The mechanisms by which hormonal contraception may lead to FL are uncertain but may involve the effects estrogen has on the immune system. Sex hormones are known to affect B-cell development, cytokine production and cytokine receptor expression, for instance [2]. Estrogen at physiological levels increases the production of cytokines associated with innate immunity [e.g. interleukin-2 (IL-2), interferon-γ (IFN-γ)] and suppresses the humoral response. With the pharmacological intake of estrogen from hormonal contraceptives, the immune system switches more towards the humoral response with the production of cytokines such as IFN-γ being reduced and IL-6 and IL-10 increased [37]. This environment may increase the number of B lymphocyte subpopulations perhaps via estrogen receptors and the estrogen-induced expression of the *bcl-2* gene reducing B-cell apoptosis [38]. There is also the suggestion from mouse models that estrogen can increase sensitivity to prolactin and prolactin can cause more autoreactive B cells to mature to follicular B cells [39, 40]. However, estrogen effects vary between species and even strains of mice so the exact processes by which estrogen alters the immune system are not fully understood, and even less is known about its role in lymphomagenesis.

Oral contraception has been available in the United States since the early 1960s, from the mid to late 1960s in Europe and not until the 1990s in Japan. With regard to our investigation of NHL risk, the reliability of the findings depends on the accuracy of self-reported information—which for oral contraception has been shown to be high when compared with medical records [41–43]—and the representativeness of controls of the population from which cases arise. As a comparison, data on ever using oral contraception among 100 000 women participating as controls in studies of breast cancer were accessed [44]. Our control data were similar to the percentage of ever users among US, Canadian, German, French and Italian women born in 1925–1929 through to 1945–1949, and although not entirely consistent, differences may relate to factors such as region and socioeconomic status. Examination of data by study and birth cohort (Figure 2) indicates the variation in lifetime use of oral contraceptives among different generations of women living in a number of economically developed nations.

In conclusion, this study found little evidence of an association between reproductive factors and NHL overall or its two most common subtypes, DLBCL and FL. The results suggest that the risk of FL was increased among women who had used hormonal contraception but that hormonal contraception was not related to NHL overall or DLBCL. FL risk was highest for use many years before diagnosis and may

relate to oral contraceptives of higher hormone doses. This analysis has the advantage of a large sample size, detailed exposure information and information on potentially confounding factors and the consistency of NHL classification. One limitation, however, was it included women in economically developed nations and not other parts of the world where the incidence of FL may differ. In addition, since the majority of women studied were born before 1950, our findings may not be applicable to women of later birth cohorts and in particular, may not apply to lower dose contraceptives if a long latency is needed before FL onset. Future investigations among women of later birth cohorts may address whether lower dose contraceptives pose a risk to the development of FL.

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disclosures

The authors declare no conflicts of interest.

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Prognostic impact of meningeal dissemination in primary CNS lymphoma (PCNSL): experience from the G-PCNSL-SG1 trial

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